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The effect of partial hepatectomy on the strength of a conditioned taste aversion: A parametric study

Christopher Adam Duva

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THE EFFECT OF PARTIAL HEPATECTOMY ON THE
STRENGTH OF A CONDITIONED TASTE AVersion:
A PARAMETRIC STUDY

A Thesis
Presented to the
Faculty of
California State University,
San Bernardino

In Partial Fulfillment
of the Requirements for the Degree
Master of Arts
in
Psychology

by

Christopher Adam Duva
Spring 1990
THE EFFECT OF PARTIAL HEPATECTOMY ON THE
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Approved by:
Stuart R. Ellins, Chair, Psychology
David M. Riefer
Frederick A. Newton
ABSTRACT

The present study was designed to investigate the role of the liver as a possible homeostatic regulator in taste aversion learning. Ellins and Costantino (1987) showed that partial removal of the liver disrupts the establishment of a conditioned taste aversion. The present study examined how taste aversion conditioning may vary with the amount of liver present. It was hypothesized that rats that had been hepatectomized would develop attenuated aversions and that the strength of their aversions would vary as a function of the amount of liver regenerated over days post-hepatectomy. Rats were given a novel saccharin solution and were made ill by LiCl injections 1, 2, 3, 4, 5, 6, 7, and 13 days after receiving a partial hepatectomy. They were then tested for the strength of an aversion over four extinction trials. An analysis of variance revealed that there was no difference in the strength of an aversion between hepatectomized and control animals on the first extinction trial. Overall, however, hepatectomized animals did extinguish their aversions faster than controls (p < .01). Additionally, it was found that the strength of a taste aversion did not vary as a function of days-post hepatectomy. Results are discussed in terms of liver regeneration, homeostatic regulation, and general process learning theory. An integration with Garcia's (1989) unified theory of classical conditioning and taste aversion learning is also presented.
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Introduction

Organization of the Introduction

One of the fundamental questions that remains unanswered in the field of taste aversion learning (TAL) is whether or not a common factor exists between aversions induced by different methods. Early Pavlovian models of TAL proposed that stimulation of the brain's emetic center serves as the unconditioned stimulus (UCS). However, more recent research has shown that aversions can be conditioned by methods that do not activate emetic mechanisms, bringing into question the idea that emesis is a common factor in all TAL. The primary purpose of this paper is to examine the manner in which treatments come to act as UCS's and to explore the underlying physiological mechanisms that mediate them. The introduction begins with a brief discussion of the history and importance of TAL with primary emphasis on the adaptiveness of the behavior and the robustness of the paradigm itself. This will be followed by a detailed description of the Pavlovian conditioning model and the problems with interpreting TAL within the framework of classical conditioning. Next, the underlying physiological mechanisms that govern TAL will be examined. This section will focus on the viscera, neural pathways, and brain structures that are involved in TAL, primarily in relation to the emetic/UCS hypothesis. A description of the various chemical agents and processes that induce taste aversions
and their relation to the physiological mechanisms involved in aversion learning will also be included. While every effort will be made to keep these sections as distinct as possible, some overlap is unavoidable.

The final section of the introduction will consist of an integration of the aforementioned ideas into a theory of homeostatic regulation. It is posited that the common factor in TAL may be a generalized level of physiological arousal; a deviation from a homeostatic setpoint that may be brought about by a variety of emetic as well as non-emetic agents. Experimental and physiological evidence will be presented that suggests that the liver may play a mediating role in this process.

**Background**

The phenomenon of TAL was first elucidated by Garcia and his colleagues in the mid-1950's (Garcia, Kimeldorf, & Hunt, 1957; Garcia, Kimeldorf, & Koelling, 1955) when it was demonstrated that by pairing a novel sweet taste, such as that of saccharin, with illness experimentally induced through exposure to ionizing radiation, rats would come to associate the taste with the illness. On subsequent trials, when the animals were exposed to the taste, they would avoid it and consume less of the solution than did control animals. Further studies in the 1960's (Garcia, Ervin, & Koelling, 1966; Garcia & Koelling, 1966) established that rats are biologically predisposed to associate certain...
stimuli (i.e. auditory and visual cues) with certain outcomes and that learning can take place with long interstimulus intervals.

While these studies marked the beginning of the modern study of food aversion learning, the idea that learned avoidances help to guide dietary selection is over a century old. Wallace (1866) proposed that the gaudy color patterns exhibited by some caterpillars served as an outward sign to predators that they were unpalatable. A paper published by Poulton (1877) entitled "The Experimental Proof of the Protective Value of Color and Markings in Insects in Reference to their Vertebrate Enemies" also suggested the role of learned avoidance in the establishment of food preferences, as did works by Pavlov (1827) and Darwin (1871). Studies on poison avoidance behavior in rats by Richter (1953) and Rzoska (1953) are two modern examples of taste aversion work that preceded Garcia's now classic studies.

In the 35 years since the scientific investigation of TAL first began, it has been shown to be one of the most universally demonstrable and robust of all learning phenomena. Taste aversions have been conditioned in a wide variety of vertebrates, including rats (Galef & Osborne, 1978), red-tailed hawks (Brett, Hankins, & Garcia, 1976), Atlantic cod (Mackay, 1974), garter snakes (Burghardt, Wilcoxon, & Czaplicki, 1973), coyotes (Ellins, Thompson, &
Swanson, 1983), squirrel monkeys (Gorry & Ober, 1970), and humans (Garb & Stunkard, 1974), as well as invertebrate garden slugs (Sahley, Gelperin, & Rudy, 1981), praying manti (Berenbaum & Miliczky, 1983), and sea anemones (Haralson & Haralson, 1974).

Further attesting to the robustness of TAL are the diverse conditions under which aversions can be established. Aversions can be conditioned by both naturally occurring events as well as through a wide variety of experimental procedures. For example, cancer patients often develop food aversions as a result of nausea induced by the treatment. Bernstein (1978) presented children with novel flavored ice cream prior to their receiving chemotherapy. On later test trials when given a choice between the ice cream flavor eaten prior to the chemotherapy and another flavor, patients consumed significantly less of the flavor eaten before treatment. Bernstein (1980) has also extended these studies to adults with similar results. Additionally, ship passengers often acquire taste aversions to food consumed prior to boarding as a result of subsequent seasickness. Taste aversion are also readily formed when the consumption of an alcoholic beverage is followed by gastrointestinal upset. Logue, Ophir and Strauss (1981) have shown that one fourth of all food aversions reported by college students were to alcoholic beverages. Logue has also stated that
alcohol aversions are highly flavor specific and often times
do not generalize from one alcoholic beverage to another.

Experimentally, taste aversions have been conditioned
under a wide variety of conditions. Roll and Smith (1972)
first allowed rats to drink chocolate milk and then
anesthetized them. While still under anesthesia the rats
were made ill with an injection of an emetic drug. Upon
recovery from illness and anesthesia the animals were tested
for the acquisition of a taste aversion. Roll and Smith
found that taste aversions were formed even when the rats
were unconscious. No other type of learning has been
reported when the subject is under general anesthesia
(Kalat, 1977). This example is particularly interesting
when juxtaposed against the examples of seasick passengers
who avert to foods eaten prior to their voyage and cancer
patients who avert to foods eaten before chemotherapy. In
these scenarios aversions were formed even when it was known
that the food was not the cause of the illness (Garcia &
Hankins, 1977). In the anesthetized rats, aversions were
formed even when the rats apparently had no knowledge of the
illness. It appears then that the association of taste and
its consequences does not require cognitive awareness.

TAL has also been shown to be resistant to the amnesiac
effects of electroconvulsive shock (ECS). Nachman (1970)
presented rats with a novel saccharin solution and allowed
them to drink for 5, 10, or 30 sec. Upon completion of
drinking, the animals received ECS to the brain and were then made ill by LiCl injections. Rats that were allowed to drink for 30 sec showed no signs of an interruption of their learning and ECS given after 5 or 10 sec of drinking produced only a weak amnesiac effect. The limited amnesiac effects of ECS underscores the strength of food aversion learning.

In another preparation, Hunt, Carrol, and Kimeldorf (1965) demonstrated humoral transmission of a taste aversion in parabiont rat pairs united by vascular anastomosis. One member of the pair was irradiated while the other member was shielded and consumed a novel saccharin solution. The shielded animals developed a strong aversion even though they were not direct recipients of the aversive stimulus, suggesting blood-bourn mediation of the UCS. Similarly, transfusions of serum from irradiated donors has also been shown to induce a taste aversion (Garcia, Ervin, & Koelling, 1967). TAL has also been demonstrated in fetal rats. Stickrod, Kimbell and Smotherman (1982) injected the amniotic fluid of pregnant rats with apple juice and injected the fetuses intraperitoneally with LiCl. At 16 days of age the pups were tested for an aversion by giving them a choice of the mother's nipples coated either with apple juice or saline. Pups that were exposed to apple juice and made ill in utero preferred the saline coated nipples.
Taste aversion learning has also been used as a form of behavior modification to bring certain behaviors under control. Control of predation on livestock is a common example. A number of field studies (Ellins & Catalano, 1980; Ellins, Catalano, & Schechinger, 1977) have demonstrated that predation on domestic sheep and turkeys by coyotes can be reduced by employing a TAL procedure. In one such experiment (Ellins & Catalano, 1980), sheep carcasses laced with LiCl were presented to free ranging coyotes adjacent to sheep herds. This procedure significantly reduced coyote attacks on live sheep and the effects were quite long lasting. The suppression of these attacks is reportedly due to the non-gustatory stimuli of the sheep (i.e. odor) becoming associated with the illness through a potentiating taste. The potentiation phenomenon is discussed in greater detail later in this paper. Similar results have been reported for a number of other species and procedures (for a complete listing, see Gustavson, 1985).

Alcoholism has also been treated using chemically induced aversions, though with limited success. A strong illness and repeated taste-illness pairings are needed to produce the desired effect. The problem appears to be that while it is easy to condition an aversion to one particular type of alcoholic beverage, these aversions do not generalize and the alcoholic merely switches brands (Logue, Ophir, & Strauss, 1981).
One of the reasons for the phylogenetically and ecologically diverse number of species that exhibit TAL and the wide range of conditions under which TAL can occur is its apparent adaptive value. If an animal consumes a food and becomes ill and survives, it learns to avoid the food in the future, a behavior that is beneficial not only to the organism but also to the species. TAL, then, can be viewed as a biological toxin screen. The fact that the avoidance to the taste is learned with only a single taste-illness pairing (limiting the possibility that a toxin may be ingested more than once) and with a long delay between consumption and illness (a natural temporal characteristic of digestion), further demonstrates the adaptive nature of this screen (Riley & Tuck, 1985).

Theoretical Interpretations of TAL

The diversity and robustness of TAL has made it a popular field of investigation among scientists. One of the questions most often addressed is what learning model can best predict and explain the many phenomena observed in TAL. One explanation of the behavior seen in TAL is that it is not a result of associative learning but is actually enhanced neophobia. Barnett (1957) has demonstrated that wild rats show a pronounced hesitation in eating or drinking a novel substance. He suggested that this hesitation is an instinctive survival mechanism and termed the behavior "neophobia." In early studies on wild rats the introduction
of a novel food was sufficient to lower intake for several days (Richter, 1953). Evidence of this behavior in laboratory rats was first demonstrated by Carrol, Dinc, Levy, and Smith (1975) who showed a neophobic response to a .1% saccharin solution. These researchers also stated that this neophobia could be enhanced by pairing the novel taste with subsequent illness. Nachman and Ashe (1974) suggested that TAL may be a result of enhanced neophobia due to the fact that rats do not display strong taste aversions to substances that are not novel. If the rat is innately neophobic, then by pairing a novel substance with an aversive consequence one merely enhances what is already there.

In the studies that preceded Garcia's work, Richter (1953) and Rozska (1953) implied that TAL is simple conditioned operant avoidance. The organism makes a response (consumes a food), which is followed by an aversive consequence (illness). Subsequently, as predicted by the law of effect (Thorndike, 1911), the organism does not eat the food again.

The fact that TAL changes the taste quality of a stimulus has led most researchers to interpret it in terms of Pavlovian conditioning. In this interpretation, the novel taste of food or water is analogous to a CS that is paired with illness (either naturally occurring or experimentally induced) which is analogous to a UCS. After
becoming ill, the organism consumes little or none of the substance on future trials. However, several aspects of TAL do not fit comfortably into this paradigm. First, associations between the taste CS and the illness UCS are usually formed as a result of only one CS-UCS pairing. In contrast, in most classical conditioning procedures, such as that of the nictitating membrane response in rabbits (Gormezano, 1966) and the gill withdrawal response in the Aplysia (Kandell & Schwartz, 1982), repeated CS-UCS pairings are needed for learning to occur. However, one trial learning has been reported in some fear conditioning procedures (Domjan & Burkhard, 1986).

A second characteristic of TAL that distinguishes it from other types of classical conditioning is the fact that the CS and the UCS must not be temporally contiguous for robust learning to occur. The optimal interstimulus delay in most classical conditioning procedures is two sec or less (Domjan & Burkhard, 1986). If the time between the onset of the CS and the presentation of the UCS is delayed, learning the association between the two stimuli is weakened. In TAL long interstimulus delays are the rule rather than the exception. The organism is presented with the taste CS and, typically, does not experience the illness UCS for at least 30 min after ingestion. In fact, it has been shown that aversions can be conditioned with interstimulus delays of 4, 6, 12, and up to 24 hrs (Etscorn & Stevens, 1973).
Additionally, if the illness UCS is presented temporally contiguous with the taste CS the organism will not come to make the association between the two, a biological characteristic specific to TAL.

Another characteristic of TAL that distinguishes it from other types of classical conditioning is the fact that certain cues selectively associate with certain consequences. Early theorists (Pavlov, 1927) assumed that all stimuli were equally associable with all other stimuli. Garcia and Koelling (1966) demonstrated, however, that this is not the case with TAL. In their landmark experiment they showed that rats readily learned associations between taste and illness but not between taste and shock. Additionally, they demonstrated that associations between exteroceptive stimuli (visual and auditory) and shock were easily learned but associations between exteroceptive stimuli and taste were not. Garcia and Koelling (1966) referred to this as cue to consequence learning. Organisms are biologically predisposed to associating certain cues with certain outcomes.

An additional problem with the Pavlovian conditioning interpretation of TAL is the absence of an overshadowing effect (Pavlov, 1927). According to Pavlov, overshadowing occurs when two or more CS's are present in a learning situation and the organism learns only about the one that is most salient. The weaker CS is overshadowed by the stronger
one that the organism associates with the UCS. In TAL the opposite is true; a strong taste, the predominant cue in food aversion learning, will potentiate associations between weaker olfactory, auditory, or visual CS's and illness rather than overshadow them (Ellins, Cramer, & Whitmore, 1985; Galef & Osborne, 1978; Rusiniak, Palmerino, & Garcia, 1982). That is, if the two stimuli in the CS compound (taste and nongustatory cue) are followed by illness and are then tested independently of one another for an illness association, both are shown to produce aversions, and the aversion to the nongustatory cue is stronger than if a simple nongustatory cue-illness pairing was made. Potentiation can be viewed as an extension of cue to consequence learning and is highly adaptive. Taste potentiated associations between nongustatory stimuli and illness ensure that an organism need not taste something (and risk being poisoned) in order to avoid it.

Physiological Mechanisms in TAL

In addition to these anomalies, another fundamental problem with the Pavlovian model of TAL is determining the nature of the UCS. While much is known about the phenomenon of TAL, the mechanisms by which treatments come to act as UCS's is still poorly understood (Riley & Tuck, 1985). Garcia et al. (1961, p. 394) has stated that "the UCS may be closely related to the initiation of gastrointestinal dysfunction" and Wittlin and Brookshire (1968, p. 218) have
said that "conditioned taste aversions may occur when novel stimuli are associated with gastrointestinal upset." This has subsequently become known as the emetic/UCS hypothesis of TAL (Coil & Garcia, 1977). Thus, according to the Pavlovian model of TAL, the UCS is viewed as stimulation of the brain's emetic center following the introduction of a toxin into the gastrointestinal tract.

Recently, however, it has been shown that a variety of agents such as amphetamine and morphine, which produce no overt signs of emesis, will induce taste aversions. Many researchers now question whether the activation of emetic mechanisms is necessary to establish a taste aversion (Grant, 1987). While an in-depth discussion of the treatments that induce taste aversions will be presented later in this paper, it is first necessary to examine the physiological mechanisms underlying TAL primarily in regards to the emetic/UCS hypothesis.

The anatomical and neural substrates that underlie TAL are just beginning to be explored but the lack of consistent experimental methodologies among researchers makes the results of these studies difficult to interpret. Oftentimes it is necessary to compare results not only across experiments but across species as well (Grant, 1987). What is currently known (and most widely accepted) about the physiology of TAL can be broken down into three broad, and in many ways overlapping, categories; taste, emesis, and
neural integration (Kiefer, 1985). A diagram of the relevant viscera and neural structures is presented in Figure 1.

Taste. Taste can be classified dichotomously as either hedonically positive or hedonically negative (Grill & Norgren, 1978a). This can be determined by presenting an animal with a substance and comparing the amount consumed to a baseline level of consumption of a neutral substance, such as water. If the animal consumes more of the substance than baseline, then it is hedonically positive; if less than baseline is consumed then it is hedonically negative. Grill and Norgren (1978a) have also determined another method by which to judge the hedonic value of a taste. Rather than measure the amount of a substance consumed to determine it's hedonic value, they have proposed, instead, a taste reactivity test. In this test the animal's lingual, masticatory, and facial muscle responses to a taste are observed and recorded using a strategically placed mirror and a video camera. Grill and Norgren have shown that there are two characteristic fixed-action patterns, one displayed when the organism encounters something hedonically positive, and the other when a substance is hedonically negative. Oral presentation of a positive substance, such as sucrose or glucose, results in an ingestion sequence which includes rhythmic mouth movements, tongue protrusions, lateral tongue protrusions, and paw licking. Presentation of a negative
Figure 1. Schematic drawing outlining the gustatory and visceral pathways in the rat. Olfactory afferents are also included. Abbreviations: (AM) amygdala, (CB) cerebellum, (CTZ) chemoreceptor trigger zone, (CX) cortex, (GNC) gustatory neocortex, (IC) internal capsule, (LH) lateral hypothalamus, (LRF) lateral reticular formation, (ML) medial lemniscus, (NTS) solitary nucleus, (OB) olfactory bulb, (OFC) orbitofrontal neocortex, (PP) prepyriform cortex, (PTA) pontine taste area, (SI) substantia innominata, (ST) subthalamic nucleus, (VB) ventrobasal thalamic complex (Kiefer, 1985).
substance such as quinine or morphine results in an aversion sequence which is characterized by gapes, chin rubs, head shakes, paw wipes, forelimb flailing and locomotion. When a taste aversion is learned the animal avoids the substance because the hedonic quality of the taste is changed. If a substance such as saccharin, which initially elicits the ingestion sequence, is paired with LiCl induced illness, then on later presentations of saccharin it comes to elicit the aversion sequence. This is referred to as a "hedonic shift" in taste quality (Garcia, Hankins, & Rusiniak, 1974).

Taste is a chemical sense of which there are only four qualities; bitter, sour, sweet, and salty. Flavor, in contrast to taste, is a combination of both gustatory and olfactory stimuli. In order for a substance to be tasted, molecules of it must first be dissolved in saliva. These molecules then stimulate taste buds which are arranged around papillae on the tongue and soft palate (Carlson, 1986). Taste information is then relayed to the brainstem via two cranial nerves; the facial (VII) and the glossopharyngeal (IX). The vagus nerve (X) also makes a minor contribution to the relay of taste information (Kiefer, 1985). These fibers all converge at the anterior portion of the nucleus of the solitary tract (NTS) located in the brainstem. The vagus nerve, which innervates much of the gastrointestinal tract, also synapses at the NTS. Fibers from the NTS then project rostrally to the
parabrachial nucleus of the pons. Pontine fibers synapse at diffuse regions of the brain. One set of fibers projects to ventral forebrain structures which include the amygdala (which also receives fibers directly from the NTS), hypothalamus, and the substantia innominata. A second set of pontine fibers projects to the ventrobasal complex of the thalamus. Thalamic fibers then project to the gustatory neocortex.

The ability to discriminate between tastes is primarily a brainstem reflexive behavior. Grill and Norgren (1978b) have shown that decerebrate rats exhibit the same ingestive and aversive sequences as intact animals when presented with palatable and unpalatable tastes. These results indicate that higher cortical functioning is not necessary for taste discrimination and that the primary taste center is located within the brainstem.

Emesis. Emesis is also a brainstem reflexive behavior. Much of what is known about the emetic response is based on Borrison and Wang's work (1953) with reflexive vomiting in dogs. Borrison and Wang have demonstrated the existence of an emetic center, located in an area lateral to the reticular formation and adjacent to and overlapping the NTS. Stimulation (electrical or naturally occurring) of this area produces the emetic syndrome which includes nausea, retching, and vomiting. This emetic response is a threshold response which indicates that a substance must not only be
present but must be present in a certain quantity in order to trigger the emetic reflex. According to the Borrison and Wang model, the system that mediates the emetic syndrome consists of receptors that respond to various emetic treatments, afferent pathways which transmit information from the receptor sites to the emetic center, and the emetic center which coordinates the emetic syndrome (Grant, 1987).

Emetic receptors are located in both the peripheral and central nervous systems. The primary peripheral receptors are located in the gastrointestinal tract and transmit information to the brain via the vagus nerve and sympathetic afferents. The emetic response normally elicited by local gastric irritation with copper sulfate (CuSO₄) can be significantly reduced by vagotomy (Borrison & Wang, 1953) but not by sympathectomy. However, a combined vagotomy and sympathectomy eliminates emesis to all but very high doses of CuSO₄ (Grant, 1987). This indicates that the vagus nerve is the primary pathway involved in transmitting information about gastric distress to the brain's emetic center. While the vagus is the primary neural route by which the emetic center can be stimulated, other peripheral emetic receptors are located in the inner ear (Wang & Chin, 1956) and the vagal body (Borrison & Fairbanks, 1952; Borrison & Sampson, 1961).

Within the CNS, emetic receptor sites are located in the emetic chemoreceptor trigger zone in the area postrema
along the floor of the fourth ventricle. The area postrema is most probably involved in monitoring blood-borne toxins: it is highly vascularized and the blood-brain barrier is particularly weak at this point (Borrison, 1974). The fact that the area postrema and the fourth ventricle are proximally close suggests that cerebrospinal fluid is also monitored. The trigger zone receptors are presumed to communicate with the emetic center via the NTS (Borrison, 1974). Toxins detected by the area postrema trigger the emetic reflex. Borrison and Wang (1953) have shown that emesis resulting from blood-borne toxins no longer occurs when the area postrema is lesioned. Similarly, vagotomy eliminates emesis when CuSO₄ is administered intragastrically but not intraperitoneally (Wang & Borrison, 1952).

It appears that an emetic center exists within the brainstem and that this area can be stimulated by vagal afferents primarily from the gastrointestinal tract and by blood-borne toxins monitored by chemoreceptors in the area postrema. Based on this model of emesis, Coil and Garcia (1977) proposed that TAL results from the activation of emetic mechanisms and that the UCS is emesis. Coil, Rogers, Garcia, and Novin (1978, p. 510) stated that "stimulation of the emetic center may provide an effective UCS for the conditioning of a chronic taste aversion toward a flavor CS, for emesis and aversion are functionally related in defense
against poison; the vomiting reflex ejects the poisoned meal and the conditioned aversion inhibits ingestion of similar poisoned meals."

In a test of this idea, Coil et al. (1978) conducted a series of experiments designed to investigate the vagal and circulatory mediation of TAL. Rats received a subdiaphragmatic vagotomy and were put through a TAL procedure. In the first experiment rats received an intragastric infusion of CuSO$_4$ (which has been shown by Borrison and Wang to produce emesis through the vagus) as the aversion inducing agent. The acquisition of a taste aversion was disrupted in the vagotomized rats relative to sham controls. In a corollary to this experiment the aversion inducing abilities of blood-borne toxins in vagotomized rats was tested. Rats were vagotomized, presented with a novel taste, and then received an intraperitoneal or intravenous injection of copper CuSO$_4$. It was expected that a strong aversion would develop because the blood-borne CuSO$_4$ would bypass the disrupted vagal route. Rats that received intravenous injections displayed strong aversions, but those that received intraperitoneal injections displayed weak aversions. The results of these studies were interpreted to mean that similar afferent mechanisms mediate both reflexive vomiting and TAL. Aversions induced by other blood-borne toxins (i.e. ethanol) are also not disrupted by vagotomy (Kiefer, Cabral, &
Rusiniak, 1980). In addition to these findings, Greenberg, Dowdy, and Peacock (1977) found that subdiaphragmatic vagotomy disrupts the formation of aversions induced by LiCl, though they did not specify whether the LiCl was administered intragastrically or intraperitoneally.

Kiefer, Rusiniak, Garcia, and Coil (1981) have suggested that the vagus is not only involved in the establishment of a taste aversion, but also plays a role in its maintenance. Rats were first trained to avoid saccharin and then vagotomized. When later tested it was found that the aversion in vagotomized rats was severely attenuated and extinguished faster than intact controls. This indicates that there is a complex feedback system between the brain and abdominal viscera.

Not all studies have supported the notion of vagal mediation of the UCS. In contrast to Greenberg et al. (1977), Martin, Cheng, and Novin (1978) and Kiefer (1985) found that aversions induced by intragastric LiCl were not interrupted by subdiaphragmatic vagotomy but were reduced by area postrema lesions (Hartley, 1977), suggesting that LiCl may induce its effects vascularly. Rabin, Hunt, and Lee (1985), using similar procedures to Coil et al. (1978), found that CuSO₄ produced no aversion in intact rats and a significant aversion in vagotomized rats. The results of this study are questionable, however, due to the well documented use of CuSO₄ as an emetic. Why Rabin et al.
found no taste aversions in intact animals remains unanswered. Another piece of contradictory evidence is provided by Bernstein and Goehler (1981) who have shown that a subdiaphragmatic vagotomy can be used as an effective UCS in the acquisition of a taste aversion. This is a difficult paradox to resolve; the same procedure that has been shown to attenuate taste aversions can also be used to establish them.

Just as the area postrema has been shown to be involved in emesis, it has also been implicated in TAL. Coil and Norgren (1982) found that area postrema lesions disrupt the acquisition of taste aversions produced by blood-borne toxins but have no effect on toxins that operate through vagal afferents. This effect, however, appears to be specific to aversions induced by emetic methods. Berger, Wise, and Stein (1982) have reported that area postrema lesions have little or no effect on aversions induced by amphetamine.

Neural Integration. Another reason for the postulated relationship between emesis and TAL is that both gustatory and vagal afferents converge at the NTS. In addition, the emetic center is located in an area adjacent to and overlapping the NTS (Borrison & Wang, 1953) and the chemoreceptor trigger zone is also linked to the emetic center by the NTS. Mechanisms that mediate taste information, visceral information, and emesis are all
contained within an anatomically close portion of the brainstem.

While taste discrimination and emesis are brainstem reflexive behaviors, the association between the two cannot be accomplished by brainstem mechanisms alone. Grill and Norgren (1978c) demonstrated that decerebrate rats display the same ingestive and aversive sequences as normal rats when presented with palatable or unpalatable tastes. In contrast, decerebrate rats show no change in the ingestive sequence of saccharin after pairing it with LiCl induced illness, even after 12 taste-illness pairings.

It is apparent then that some rostral structures are involved in the formation of taste-illness associations. The hypothalamus, hippocampus, amygdala, and neocortex have all been implicated in some aspect of TAL. Of primary importance, however, is the gustatory neocortex, which is located in the anterolateral portion of the forebrain (Kiefer, 1985). Rats that have had the gustatory neocortex destroyed display two peculiar characteristics: a deficit in the learning of taste aversions to both preferred and non-preferred tastes, and a tendency to generalize taste aversions to other non-target tastes (Kiefer & Braun, 1979). Additionally, rats that were trained to avoid a taste and then received gustatory neocortex ablations displayed no aversions or severely attenuated aversions (Kiefer, Leach, & Braun, 1984).
Establishment of Taste Aversions

The main problem with the emetic/UCS hypothesis is its inability to explain the various conditions under which a taste aversion can or cannot be established. Specifically, there are three main paradoxes that exist: (1) certain drugs that are known to be toxic are ineffective in inducing taste aversions; (2) some drugs that are self-administered as reinforcers of motor behavior are capable of establishing taste aversions; (3) some treatments that produce no overt signs of illness can be used to induce taste aversions. For a detailed list of effective and ineffective aversion-inducing treatments see Appendix A.

Generally speaking, most drugs that produce toxicosis will condition a taste aversion. In their review, Riley and Tuck (1985) have listed over 50 toxins known to induce taste aversions. LiCl (Archer, Sodjen, & Carter, 1979), CuSO\(_4\) (Nachman & Hartley, 1975), methyl bromide (Miyagawa, 1982), and lead acetate (Dantzer, 1980) are agents that produce overt symptoms of toxicosis and induce taste aversions. However, Riley and Tuck have also listed 11 drugs, such as sodium cyanide (Nachman & Hartley, 1975), gallamine triethiodide (Ionescu & Buresova, 1977), and warfarin (Nachman & Hartley, 1975), which produce severe symptoms of toxicosis but are ineffective in conditioning a taste aversion. These findings are difficult to interpret,
particularly in regards to the idea that TAL serves as a natural toxic defense system.

Several explanations have been offered to resolve this intriguing anomaly. TAL has been shown to be a direct function of the dose of the drug administered (Nachman & Ashe, 1973). For example, LiCl, one of the most widely used aversion inducing agents, is ineffective at doses below .60 mEq. .15M. Many of the toxins reported not to induce aversions (gallamine, cyanide, warfarin) were examined at only one dose level, and it is possible that this dose was below the threshold necessary to condition an aversion (Riley & Tuck, 1985). Related to drug dose is drug duration, which has also been reported to be an important variable in TAL (Cappel & Leblanc, 1977). A possible reason for the ineffectiveness of a toxin in producing a taste aversion is its relatively short period of action (e.g. sodium cyanide). Methods which prolong the action of a drug have been shown to be effective in conditioning a taste aversion with drugs that were previously ineffective (Riley & Tuck, 1985).

Another factor that may influence a toxin's inability to induce a taste aversion is the number of conditioning trials. It has been shown that strychnine sulfate, a compound previously shown not to induce aversions, will produce aversions with repeated conditioning trials (Nachman & Hartley, 1975). Many of the toxins shown to be
ineffective in inducing taste aversions were tested with only one conditioning trial.

It has also been speculated by Riley and Tuck (1985) that some toxins may fail to produce aversions because they disrupt the neural mechanisms involved in learning taste-illness associations. This idea, however, remains largely untested.

Dose, duration of action, and number of conditioning trials obviously effects a substance's ability to condition a taste aversion and may be directly related to a toxin's inability to do so. However, Garcia (1974) has proposed that it is the physiology of the organism which dictates whether or not a toxin will induce a taste aversion. In a direct extension of cue to consequence learning, Garcia has stated that an organism contains two separate defense systems; one external, the other internal. The external system is designed to protect the organism from environmental dangers (i.e. predators) and hence the organism selectively associates peripheral insults with exteroceptive stimuli. Similarly, the internal defense system selectively associates taste with illness (Garcia, Lassiter, Bermudez-Rattoni, & Deems, 1985). This is referred to as skin-gut duality. Supposedly, the reason that toxins such as gallamine and cyanide do not induce aversions is that, rather than producing internal distress (illness), they produce peripheral distress (pain). Pain
according to skin-gut duality, is more readily associated with exteroceptive stimuli, not taste, and therefore, the association between the two is not formed. The pain-like effects of gallamine and cyanide should be associated with exteroceptive stimuli. In a test of this idea, Lett (1985) has shown that gallamine will produce strong place aversions and weak taste aversions.

The skin-gut duality model has also been used to explain why drugs such as morphine and amphetamine (which are self-administered by many species) can be used to induce a taste aversion. These drugs, when administered to the external system, may have a rewarding effect, however, when administered to the internal system the effects may be aversive. An event that functions as a positive reinforcer need not display that characteristic in all possible settings; the same is also true of negative reinforcers (Cappel & LeBlanc, 1977). In addition, Vogel (1976) has speculated that a drug may have rewarding properties if its administration is under control and aversive properties if its control is precluded. Support for this idea is provided by Steiner, Beer, and Schaffer's (1969) work with electrical self-stimulation of the brain. Steiner et al. found that rats that would previously work for a pattern of brain stimulation could also be trained to avoid the same pattern. To accomplish this it was only necessary to make the delivery of the stimulation independent of the rats
behavior. The problem with these interpretations is that drugs such as amphetamine and morphine, as well as many others (see Cappel & LeBlanc, 1977 for a complete listing), produce no overt signs of emesis, toxicosis, or distress, but are still capable of inducing taste aversions. It is obvious, then, that an animal need not display symptoms of sickness while experiencing an event which induces a taste aversion (Gamzu, Vincent, & Boff, 1985). Several explanations of this phenomenon have also been put forth. Pelchat, Grill, Rozin, and Jacobs (1983) have suggested that these compounds may induce aversions based on "danger," though their definition of danger and how it becomes associated with taste is not specified. A more plausible explanation is offered by Riley & Tuck (1985) who state that while no overt signs of toxicosis may be present, TAL may be a better index of toxicosis than casual observation.

Amit and Baum (1970) have proposed that non-emetic treatments may induce taste aversions through novelty. Drug treatments cause changes in many physiological systems resulting in a variety of uniquely novel internal stimuli (Gamzu, 1977). They argue that animals (which are innately neophobic to begin with) perceive all novel drug states as aversive. Some of the treatments that induce taste aversions may not be inherently aversive, but their effects may be difficult for the animal to assess (Gamzu, 1977). In the absence of any additional information the organism
interprets this novel internal state as potentially harmful, much the same way that they initially classify new foods as potentially dangerous (Gamzu, 1977).

A related phenomenon can be observed in human interpretations of drug affect. People often report negative reactions to the physiological and psychological states induced by prescription drugs. These negative reactions, however, can be reduced by informing the patient of the possible effects of the drug. Similarly, people often report very negative experiences related to first time use of recreational drugs such as marijuana and heroin (Gamzu, 1977). Results of Schacter and Singer's classic (1962) experiment with epinephrine also support this idea. College students were given an injection of epinephrine and were not informed of its pharmacological effects. It was found that the behavior and mood of the subjects was strongly influenced by a confederate's behavior. If the confederate was euphoric so was the subject; if the confederate was irritable the subject behaved in a similar manner. These examples demonstrate that it is difficult to classify the effects of a drug if one does not know what to expect.

Drug preexposure experiments also illustrate the importance of novelty in TAL. Gamzu (1974) gave rats three preexposure trials to chlordiazepoxide (CDAP) and apomorphine. The rats were then put through a TAL procedure
in which CDAP or apomorphine served as the UCS, respective to the preexposure treatments. Gamzu found that the formation of a taste aversion by CDAP was completely blocked and that rats preexposed to apomorphine developed severely attenuated aversions. Gamzu added that the number of preexposures, the time between preexposure and testing, and the magnitude of preexposure are important variables in this phenomenon. Not all researchers, however, have demonstrated this preexposure effect (e.g. Elsmore, 1972).

In another attempt to distinguish a non-specific mechanism common to all TAL, Braveman (1977) suggested that the aversive property underlying all treatments is more general than sickness, novelty, or lack of control. He has proposed that the "general aversive property is the stress that results from the application of aversion-inducing treatments." The common factor, he argues, is the stress related physiological changes common to and produced by a wide variety of aversion-inducing agents, particularly changes in the blood level of corticosterone, or its precursor ACTH. Braveman cites an unpublished study by Riley and another by Ader in which it was demonstrated that rats exhibited an increase in blood corticosterone levels following injections of various emetic agents. Similarly, pretreatments with ACTH antagonists (which deplete the system of corticosterone) have been shown to attenuate taste aversions (Hennessy, Smotherman, & Levine, 1976) and
treatments with ACTH agonists block the extinction of conditioned taste aversions (Rigter & Poppings, 1976). Braveman states that the preexposure crossover effect also supports the idea of a single common stress related factor. It has been demonstrated that preexposure to one type of UCS will reduce TAL not only to that stimulus but also to other non-specific UCS's. Preexposure to LiCl has been shown to attenuate motion induced aversions (Gamzu, 1975) and preexposure to methylscopolamine attenuates LiCl induced aversions (Braveman, 1975). Braveman believes it is the preexposure to the general level of stress that is responsible for the observed attenuations. Cappel and LeBlanc (1975), however, have pointed out some problems with this interpretation. In some experiments preexposure to treatment A will block or attenuate aversions induced by treatment B, but when the order is reversed and B is used as the preexposure agent, the ability of A to induce a taste aversion is not affected. Findings such as this suggest that there is a not a single factor common to all treatments.

Experimentally, taste aversions can be induced by treatments other than drugs, some of which also produce no signs of illness. Ionizing radiation, for example, can be used to establish a conditioned taste aversion. In fact, the phenomenon of TAL was serendipitously discovered by Garcia, Kimeldorf, and Hunt (1955) while investigating the
effects of radiation on rats when they noticed that rats
would not consume food eaten prior to radiation treatment.
Radiation can produce taste aversions at doses large enough
to produce emesis as well as at doses below the emetic
threshold. This aversion appears to be mediated by the area
postrema. Area postrema lesions reduced radiation induced
taste aversions in cats (Rabin, Hunt, Chedester, & Lee,
1986) and in rats (Ossenkopp, 1983). On the other hand,
vagotomy has no effect on radiation induced aversions
(Rabin, Hunt, & Lee, 1983). Additionally, motion has also
been used successfully to induce taste aversions and appears
to operate through emetic mechanisms. If the vestibular
apparatus is dissociated from the brain via bilateral
labyrinthectomy, motion induced aversions are reduced
(Hartley, 1977). In another manipulation Bernstein and
Sigmundi (1980) have shown that the toxic effects of Leydig
tumors can also be used to establish a taste aversion.

Statement of the Problem

A wide variety of treatments can be used to establish a
taste aversion, many of which do not conform to the
emetic/UCS hypothesis. The use of a single word such as
nausea, emesis, or toxicosis to describe the UCS in food
aversion learning is hopelessly inadequate (Garcia et al.,
1985). Illness may be viewed as a sufficient but not a
necessary cause in the establishment of a taste aversion.
The control, novelty, and stress hypothesis are also
inadequate in describing many of the conditions under which a taste aversion can be established. This has lead some researchers (Gamzu et al., 1985; Grant, 1987; Riley & Tuck, 1985) to speculate that there is no common factor in TAL, and that there may be a number of different types of taste aversions mediated by different mechanisms. In this view a taste aversion that is conditioned by LiCl would, perhaps, involve the emetic center of the brain as well as neural or vascular communication from the gastrointestinal tract, whereas aversions induced by drugs such as amphetamine or morphine would be governed by separate physiological mechanisms.

While this idea does have some surface appeal it really does not answer the question nor does it solve the problem of the nature of UCS. While a large percentage of taste aversions do conform to the emetic/UCS hypothesis, many do not. Are we to hypothesize a different type of TAL and a different mechanism of action for each of the remaining treatments? And what would happen when the inevitable occurred and a new treatment that induced a taste aversion was found? It would then be necessary to create a new type of TAL every time a new method was discovered and did not fit into one of the existing models. Seligman (1970) warned against developing specific models of learning in favor of more general theories: "inherent in the emphasis on arbitrary events, however, is a danger: that the laws so
found will not be general but peculiar to arbitrary events" (Seligman, 1970, p. 514). A similar problem would occur if we begin to hypothesize different types of taste aversions mediated by different mechanisms.

From an evolutionary standpoint, it is more logical to assume that a learning phenomenon as phylogenetically diverse as TAL is mediated by similar physiological and neural structures, regardless of the conditions under which it was acquired. How then can we integrate the wide range of drugs and treatments that induce taste aversions into a single framework? Garcia et al. (1985, p. 12) has stated that "the UCS in taste aversion learning is a complex homeostatic process that is impossible to describe in one word." Gamzu et al. (1985) and Riley and Tuck (1985) have also suggested the possible role of homeostasis in TAL. Therefore, if one interprets the UCS not as illness but as a generalized level of physiological arousal, such as the disruption of the homeostatic mechanism of the organism, then it is not necessary to hypothesize different types of aversions mediated by different mechanisms. Viewed in this way, the introduction of both emetic and non-emetic agents into an organism results in a deviation from a homeostatic setpoint, which is inherently aversive. The taste then becomes associated with this internal arousal and the organism learns to avoid it. Thus, by hypothesizing a single homeostatic mechanism that may play a role in many
types of aversions, we can generate a more parsimonious explanation of what the UCS may be.

If indeed the common factor in TAL is some type of homeostatic disruption, then what mechanisms may be involved? Physiological evidence exists that suggests that the liver may play a role in TAL. Food intake is controlled primarily through glucoreceptors in the liver, a process which, until recently, was thought to be governed by glucoreceptors in the hypothalamus (Carlson, 1986). Russek (1971) demonstrated that intravenous injections of glucose had little effect on food intake, while intraperitoneal injections suppressed food intake. Russek hypothesized that the intraperitoneal glucose was taken up by the liver and that the liver sends signals that control food consumption to the brain. Electrophysiological studies (Niijima, 1982) have detected glucoreceptors in the liver that convey information to the brain via vagal afferents. Lautt (1983) has provided a comprehensive summary of both the efferent and afferent pathways involved in hepatic function.

It is also a well documented fact that the liver plays a central role in maintaining the homeostatic balance of an organism through its many detoxification, hormone inactivation, and storage functions (Sawchenko & Friedman, 1979). Sawchenko and Friedman have also suggested that the liver and its vasculature contain neural receptors which, "appear to activate a number of physiological and behavioral
responses that help to correct homeostatic imbalances, many of which are associated with the consequences of ingestion" (Sawchenko & Friedman, 1979, p. 21). These researchers also state that metabolic receptors in the liver may influence food intake by modulating reactivity to taste. A compelling piece of evidence in support of this is provided by Rogers, Novin, and Butcher (1979) who have shown that gustatory response neurons in the parabrachial complex respond to electrical and chemical stimulation of the hepatic branch of the vagus nerve, indicating that the liver communicates neurally with a portion of the brain involved in processing taste information. In light of this finding, it is interesting to note that people suffering from liver disease often report diminished taste acuity (Smith, Henkins, & Dell, 1976). The apparent role of the vagus nerve in the hepatic modulation of taste reactivity is consistent with the convergence of visceral and gustatory afferents at the NTS (Sawchenko & Friedman, 1979).

Another piece of evidence that serendipitously implicates the liver in TAL is the previously mentioned work of Coil et al. (1978) who demonstrated that subdiaphragmatic vagotomies block the development of taste aversions, and Kiefer et al. (1981) who showed that subdiaphragmatic vagotomies attenuate previously conditioned taste aversions. It was believed that these deficits in learning occurred because the gut could no longer communicate neurally with
the brain and could, therefore, no longer communicate the UCS. The subdiaphragmatic vagotomy, however, does not only dissociate the gut from the brain but also the liver, which is innervated by the hepatic branch of the vagus nerve (Lautt, 1983). Therefore, when researchers demonstrated an attenuated taste aversion following subdiaphragmatic vagotomy, it may have been due to the disruption of the UCS signal to the brain, not from the gut, but from the liver.

There is also experimental evidence that implicates the liver in TAL. Ellins and Costantino (1987) attempted to taste avert ten rats that had undergone a partial hepatectomy. In this procedure 70% of the animals liver is removed (median and left lateral lobes) leaving the vagus nerve intact. Rats then experience complete liver regeneration within 21 days post-surgery (Higgins & Anderson, 1931). At thirteen days post-surgery the rats drank a novel saccharin solution and were made ill by intragastric infusions of LiCl. It was found that the taste aversion in the partially hepatectomized rats was attenuated and extinguished faster relative to that of intact controls. Furthermore, once the livers had completely regenerated, the rats were again put through a TAL procedure. The rats that were previously hepatectomized behaved like naive subjects. In order to establish the necessary control groups, Costantino, Duva, Hooks, Van Norman, and Ellins (1990) conducted a partial replication of this study. The method
used for the establishment and testing for aversions was almost identical to that used in the previous experiment. However, in this experiment animals received the same dose and molarity of LiCl intraperitoneally rather than intragastrically. The results indicated that the hepatectomized animals extinguished their aversions faster than control and sham animals. However, no significant attenuation was found on the first test trial.

The results of these two experiments suggests that the liver in some way mediates TAL and that the partial hepatectomy disrupts the establishment of a taste aversion. The liver may do this directly or by transmitting visceral information to the brain. The present study is designed to further implicate the liver as a possible homeostatic regulator in TAL which may mediate both emetic and non-emetically induced taste aversions, as described by Ellins and Costantino (1987) and Costantino et al. (1990).

Specifically, the purposes to the present experiment are:

1) To demonstrate the significant first trial attenuations that Ellins and Costantino (1987) found in their first experiment but were not replicated by Costantino et al (1990). These inconsistent findings could be the result of a floor effect in the second experiment; that is, the animals were made so sick by the LiCl that any attenuation of an aversion was masked by the intensity of the illness. This could be due to the procedural difference of using
intraperitoneal injections instead of intragastric infusions. To alleviate this floor effect rats in the present study were given a smaller dosage of LiCl (i.e. .06% of body weight in contrast to .12%) intraperitoneally. According to Nachman and Ashe (1973), this dose is sufficient to condition a taste aversion; and 2) to determine to what degree the disruption of a taste aversion may vary as a function of liver regeneration. Higgins and Anderson (1931) have shown that liver regeneration in the rat is a biphasic process with the majority of regeneration occurring within the first seven days post-surgery. Ellins and Costantino (1987) and Costantino et al. (1990) tested their subjects at 13 days post-surgery, a point arbitrarily chosen and at which time the majority of the liver had regenerated. In the present study the relative strength of a taste aversion was examined at 1, 2, 3, 4, 5, 6, and 7 days post-surgery. Additionally, a 13 day post-hepatectomy group was included as a reference point to previous work. It was hypothesized that the strength of a taste aversion would vary as a function of liver regeneration. That is, if indeed the liver is involved in TAL, then those animals tested early in the regeneration phase (i.e. 1, 2, 3 days post surgery) should display stronger attenuations than those tested later in the regeneration phase due to the fact that less liver is present.
Method

Subjects

The subjects were 128 male Sprague-Dawley rats (Simonsen Labs, Gilroy, California). They were 60 days old at the beginning of the experiment and were housed individually in 18 x 21 x 24 cm-high stainless steel cages. The animals were maintained on a 12 hr light/dark cycle and were provided with ad lib Purina rat chow and water throughout the experiment, except where noted. All animals were checked daily for the condition of their health. A protocol for the use of the animals in this experiment was approved by the University's Institutional Animal Care and Use Committee.

Apparatus

The apparatus consisted of five sound-attenuated isolation chambers (Colbourn Instruments E10-1020) outfitted with a small ventilation fan and a low wattage light. Contained within each isolation chamber was a plastic test box. Each box measured 27.5 x 18 x 18 cm-high and was constructed of clear Plexiglas 3 mm thick (see Figure 2). On one side of the test box was a sliding door 25 x 12.5 cm-high that allowed access to the inside of the box. On an adjacent side of the box there was a 3.5 cm diameter hole that allowed rats access to a drinking tube that was positioned 1.5 cm from the outside of the box. The floor was constructed of a stainless steel grid 15 x 13 cm-wide.
Figure 2. Experimental chamber.
with grid spacings of approximately 1.5 cm. Attached to the outside of each test box was a glass 150 ml drinking bottle with a rubber stopper, inserted into which was a glass drinking tube. A brass wire was inserted through the rubber stopper into the water of each bottle and was connected to a drinkometer (Lafayette Instruments 5808). When a rat stood on the metal grid and touched its tongue to the drinking tube an electrical circuit was completed. Each drinkometer was wired to an electronic counter (Colbourn Instruments R11-25) which recorded lick time in milliseconds.

**Procedures**

**Assignments.** The rats were randomly assigned to one of eight hepatectomized (H) groups (n=8), eight intact control (IC) groups (n=7) and one sham control (SC) group (n=8). They were then assigned into five groups in such a manner that each group contained approximately an equal number of animals from each experimental condition. Each of these group was then randomly assigned to one of the five isolation chambers. So as to maintain consistency among the deprivation times, each animal was assigned to a drinking schedule that was utilized throughout the experiment.

**Habituation.** Fifteen days prior to illness training all animals were habituated to drinking tap water in the isolation chambers. Animals were water deprived for 12 hrs preceding the start of habituation. Each animal received four, 7 min habituation sessions over two consecutive days.
On the first day each subject received two sessions, separated by 4 hrs, in the morning; then an 8 hr break and two identical sessions in the evening. The schedule for the second day was the same except that the final evening session was omitted.

**Surgical Procedure.** The rat liver is comprised of four separate and distinct lobes; the right lateral, left lateral, median, and caudate (see Figure 3). In the partial hepatectomy procedure used, the left lateral and median lobes are excised, which represents a removal of approximately 70% of the total liver mass. Surgeries were performed in the University's physiological psychology laboratory under aseptic conditions and followed procedures outlined by Higgins and Anderson (1931) and Waynforth (1982) for partial hepatectomy.

Surgeries were performed on the H groups for 13 days such that all rats in the experiment received illness training and testing on the same days. Thus, the first group of H rats received surgery 13 days prior to illness training, the second group received surgery 7 days prior to illness training, the third group 6 days, and so on. Each H group had its own IC group against which to compare the strength of the aversion and to evaluate the effects of the anesthesia. In addition, the group hepatectomized 1 day before illness training had an SC group. This group was
Figure 3. Dorsal view of the rat liver (Waynforth, 1962).
necessary to establish if any attenuation of an aversion in the rats that received illness training 1 day post-surgery was, in fact, due to the hepatectomy and not lack of recovery from illness due to the short post-operative recovery period.

Animals scheduled to receive partial hepatectomies were anesthetized with intraperitoneal injections of Nembutal (50 mg/kg). The surgical area was then shaved and cleansed with betadine solution. The rat was laid on its back with its tail towards the investigator and a midline ventral abdominal skin incision was made from the xiphoid to the umbilicus. The skin was retracted and a similar incision was made in the body wall. The body wall was then clamped with hemostats and retracted, exposing the peritoneal cavity. A small cotton bolster was placed under the thorax which caused the liver to fall slightly away from the diaphragm. Suspensory ligaments that attached the liver to the diaphragm were then cut. A dry piece of gauze was laid along the edge of the incision onto which the median and left lateral lobes of the liver were laid. Extrusion of the liver from the peritoneal cavity was accomplished by the investigator placing both hands around the incision and pushing the gut just posterior to the liver forwards and upwards in a concave semicircle with a light compression of the abdominal cavity (Waynforth, 1982). The median and left lobes of the liver were then placed on their ventral surface.
on the gauze. Two other suspensory ligaments that attached the liver to the peritoneum and other viscera were now exposed and were also severed. The lobes of the liver were gently lifted vertically away from the peritoneal cavity and the blood vessels at the base of these lobes were securely ligated with suture near the hilus. The lobes were then laid back onto the gauze and several small cuts were made around each of the lobes allowing them to bleed onto the gauze and not back into the peritoneal cavity. The lobes of the liver were then wrapped in the gauze, lifted away from the peritoneal cavity, and excised with a cut just above the ligature. A 0.9% solution of injectable saline heated to the rats body temperature was used to irrigate the peritoneal cavity throughout the surgical procedure. The incision was then closed with sutures to the body wall and stainless steel Autoclips to the skin. The procedure for the sham hepatectomy was similar except that the lobes were loosely ligated and then the ligation was removed. No excision of liver tissue took place. The control rats were anesthetized, shaved, and allowed to recover, but received no surgical manipulation.

Immediately following surgery the rats were returned to their home cages and allowed to recover. Ad lib food and water was made available to them 4 hrs after waking up from anesthesia. Overall survival rate was above 92%.
Illness Training. Prior to illness training the rats were 12 hrs food and water deprived and then presented with a novel solution of 0.2% sodium saccharin in distilled water. Initially, however, the animals drank very little or none of the sodium saccharin solution. Illness training was then halted and an additional 4 hrs of food and water deprivation was given. Upon resumption of illness training (now 16 hrs food and water deprived) the animals still consumed little or none of the saccharin water. Four more hrs of water deprivation was then given to the remaining animals and they were provided with ad lib food for 1 hr. These animals were then placed in the test apparatus (21 hrs water deprived) at which time they consumed the sodium saccharin solution readily.

The rats lick time with the novel solution was recorded and served as a baseline measure of consumption. Immediately following this session the H and IC groups received a 0.6% of body weight solution of 0.15 M LiCl (Nachman & Ashe, 1973) in sterile water. SC control animals received an equivalent injection of 0.9% sterile saline solution. All injections were administered intraperitoneally using a 26 gauge x 1/2 in. needle attached to a 5cc plastic syringe. The rats were then returned to their home cages and deprived of food and water for 6 hrs following injections to prevent spurious associations.
between the illness and non-target tastes other than saccharin.

Within 30 min of receiving the LiCl injection the animals experienced gastrointestinal malaise which was indicated by piloerection and a decrease in overall activity. Animals that received injections of sterile saline displayed no overt signs of illness. Upon recovery from illness the rats were provided with ad lib food and water for 24 hrs.

**Extinction.** Prior to the first extinction session all animals were 12 hrs water deprived; additionally ad lib water was not available in the home cages throughout extinction testing. Rats received four, 7 min extinction trials each separated by 12 hrs. Immediately following each of these sessions the rats were allowed 10 min free access to tap water in their home cages.

**Results**

The mean lick times in seconds for the H and IC groups (taste averted 1-7 and 13 days post-surgery) and the SC group (taste averted 1 day post-surgery) are presented in Figures 4-8. Rats that consumed more than 50% of their baseline score on the first extinction trial were considered not to have been averted and were not included in the figures or data analysis. Figure 4 shows the mean level of consumption of the saccharin solution at baseline. As can
Figure 4. Mean lick times at baseline for groups of rats that received illness training at different days post-hepatectomy and their respective control groups.
be seen there was little difference in the lick times between groups. The exception to this is the day 7 IC group whose mean level of consumption was the highest of all the groups (but was not significantly different.

Figures 5-8 compare the mean lick times of the groups across the four extinction trials. On the first extinction trial there was little difference in the mean consumption levels between the H and IC groups at 1, 2, 3, and 7 days post-surgery. However, in relation to the other IC groups, the day 7 IC group demonstrated an unusually elevated level of consumption, similar to the high lick times exhibited at baseline. There was a much larger difference in the consumption between the H and IC groups for days 4, 5, 6, and 13. In addition, the SC animals (who received saline instead of LiCl and were not made ill) had the highest mean lick times of all of the groups for the first extinction trial. A general pattern of consumption is demonstrated across the remaining three extinction trials. Overall, the H animals had higher mean lick times as compared to their relative IC groups, with the possible exception of the day 7 IC group that consistently showed elevated mean lick times. The SC animals had the highest level of consumption across all four extinction trials. For the exact means and standard deviations for each group, see Appendix B.
Figure 5. Mean lick times on extinction trial #1 for groups of rats that received illness training at different days post-hepatectomy and their respective control groups.
Figure 6. Mean lick times on extinction trial #2 for groups of rats that received illness training at different days post-hepatectomy and their respective control groups.
Figure 7. Mean lick times on extinction trial #3 for groups of rats that received illness training at different days post-hepatectomy and their respective control groups.
Figure 8. Mean lick times on extinction trial #4 for groups of rats that received illness training at different days post-hepatectomy and their respective control groups.
Statistical analyses were conducted on the rats' lick time scores with the novel saccharin solution. A 2 (H vs. IC) x 8 (days) x 5 (trials) mixed analysis of variance (ANOVA) showed a significant main effect for treatments (H vs. IC), $F (1, 84) = 7.33, p < .01$, indicating that the H animals had significantly higher mean lick times than the IC animals. The main effect for trials was also significant $F (4, 336) = 139.42, p < .01$, demonstrating that the aversions for both groups extinguished over the four extinction trials. These results should be interpreted in terms of the significant treatment x trials interaction which was also found, $F (4, 336) = 5.61, p < .001$. This interaction can be seen in Figure 9, which shows the mean lick times for the H (n=52) and IC groups (n=48), collapsed across days, for baseline and the four extinction trials. The graph shows that the H group appears to extinguish their aversion faster than the IC group. Post hoc Fisher's LSD tests showed that these groups did not differ significantly on consumption at baseline, indicating that H animals do not drink more than IC animals as a result of having their livers removed. Further tests revealed that the difference between the H group means from baseline to the first extinction trial (71.08) was significant, $p < .001$. Similarly, the difference between the IC groups means from baseline to the first extinction trial (65.9) was significant, $p < .001$. These results indicate that both groups had formed a taste
Figure 9. Mean lick times for the hepatectomized and control animals, collapsed across days, for baseline and the four extinction trials.
aversion as a result of the LiCl induced illness. No significant differences between the H and IC group means were found on the first extinction trial. However, the differences between the H and IC groups means (10.37) approached significance for the second extinction trial, \( p < .08 \), and were significant on extinction trial three (31.68), \( p < .01 \), and extinction trial four (39.73), \( p < .01 \), indicating that the H group extinguished its aversion significantly faster than the IC group.

The overall ANOVA further revealed that there were no effect for days, \( F (7, 84) = 1.33, p > .05 \). In addition, the treatment x day interaction, \( F < 1 \), the day x trial interaction, \( F (28, 336) = 1.44, p > .05 \), and the treatment x trial x day interaction \( F < 1 \), were also found to be nonsignificant.

Due to the fact that SC animals were used only at 1 day post-surgery, they were compared to H and IC groups only for day 1 and were analyzed with a separate 3 (H vs. IC vs. SC) x 5 (trials) ANOVA. Significant main effects for treatments (H vs. IC vs. SC), \( F (2, 17) = 9.28, p < .001 \), and trials, \( F (4, 68) = 19.71, p < .001 \) were found. The treatments x trials interaction was also found to be significant \( F (8, 68) = 4.84, p < .001 \). These strong effects were driven by the high lick times of the SC group, who received saline instead of LiCl and were not averted.
The mean liver weights for each H group as well as a control group (which contained one animal from each of the IC groups and one SC animal) were calculated (see Appendix C). This was done to draw a possible correlation between liver weight and the strength of an aversion. However, in light of the fact that the mean liver weights between H groups and the control group varied by less than three grams and that the trend was not linear, such an analysis would appear to be fruitless.

Discussion

The findings of the present study suggest that the liver does play a mediating role in TAL. With respect to the initial hypotheses, the results must be interpreted in terms of: a) the strength of taste aversion conditioning on the first extinction trial, b) the strength of taste aversion conditioning as a function of the number of days post-hepatectomy (amount of liver regeneration), and c) the overall effect of partial hepatectomy on TAL.

Compared to their respective IC groups, none of the H groups displayed significantly attenuated taste aversions on the first extinction trial, which contradicts the findings of Ellins and Costantino (1987). The major procedural difference of using intraperitoneal injections in the present study as compared to intragastric infusions used by Ellins and Costantino could be the reason for this
discrepancy. It has been demonstrated that route of administration is a critical factor when investigating the physiological mechanisms involved in TAL. There are four common methods by which taste aversion inducing drugs are administered; intravenously (usually through tail vein injections), intragastrically, intraperitoneally, and subcutaneously. The results of many physiological studies have demonstrated that different disruptive procedures do not necessarily attenuate taste aversions induced through different routes of administration. For example, subdiaphragmatic vagotomy will attenuate aversions if the agent is given intraperitoneally, but not if it is given intravenously (Coil et al., 1978). Similarly, area postrema ablations attenuate aversions induced intravenously and intraperitoneally, but have only a weak effect on aversions induced intragastrically (Grant, 1987; Kiefer, 1985). It is possible that partial hepatectomy is a procedure that is most effective in disrupting TAL when the aversion inducing agent is administered intragastrically.

These results are, however, similar to that of Costantino et al. (1990) who, using intraperitoneal injections of LiCl, found that hepatectomized animals did not display significantly attenuated aversions on the first extinction trial but did extinguish their aversion faster than control animals. The consistency of results between Costantino et al. (1990) and the present experiment are
further evidence suggesting that the attenuated aversions on
the first extinction trial (demonstrated by Ellins &
Costantino, 1987) may be a result of the different route of
administration that was used.

The overall pattern of results, while nonsignificant,
is suggestive. Some attenuation of an aversion was shown in
the rats that received illness training 4, 5, 6, and 13 days
post-hepatectomy. The group of animals hepatectomized 7
days prior to illness training consumed saccharin water at
approximately the same rate as the H 1, 2, and 3 day groups.
However, due to the fact that their IC group exhibited
extremely high mean lick times, the aversion for the 7 day H
group could not be said to have been attenuated (see Figure
5). The H and IC groups at 1, 2, and 3 days post-surgery
did not show any significant difference in the strength of
their aversions. The weakly attenuated aversions, however,
suggest that the liver may play at least a small role in
aversions induced through intraperitoneal injections. The
fact that the partial hepatectomy does not remove the entire
liver and that some liver is always present to mediate TAL
may also be a possible reason for the weakly attenuated
aversions.

The fact that significant attenuations of an aversion
were not found on the first trial must be further
interpreted in terms of the prediction that the strength of
conditioning would vary as a function of number of days
post-hepatectomy (amount of liver regenerated). It was hypothesized that rats who were taste averted early in the regeneration process (i.e., 1, 2, 3 days post-hepatectomy) would display more severely attenuated aversions than rats tested later during the regeneration process because they would have less liver, which in turn would produce an attenuated signal to the brain. However, the pattern of results are the opposite of what was predicted; taste aversions were the strongest shortly after hepatectomy and were attenuated later in the regeneration phase (albeit, nonsignificantly).

There are two possible explanations for this trend. First, the animals that were taste averted shortly after hepatectomy may still have been ill as a result of surgery. It has been shown by Nachman and Ashe (1973) that the strength of a taste aversion is directly related to the magnitude of the UCS. Animals who receive larger doses of LiCl as the UCS, and are made sicker, develop stronger taste aversions than animals that receive smaller doses and are made less ill. A similar process may be occurring in the H 1, 2, and 3 day groups. If, in fact, these animals are still ill as a result of surgery and are then made ill further by the LiCl injections, then the magnitude of the UCS is compounded. This means that the intensity of the UCS may not be equal for all groups. Thus, these animals (1, 2, and 3 days post-hepatectomy) are actually made sicker than
those rats given illness training at a later time and would, according to Nachman and Ashe (1973), develop stronger taste aversions. Any attenuation of an aversion as a result of partial hepatectomy may be masked by the intensity of the illness.

The SC group was initially implemented to evaluate this possible confound. The SC group received saline instead of LiCl; thus, if any aversion developed it could be attributed to the surgical manipulation and not the saline. Results show that the SC animals did not develop an aversion and consumed the saccharin solution readily throughout extinction. The fact that the SC control animals received illness training 1 day post-hepatectomy and did not develop aversions would lead one to believe that illness resulting from surgery is not a sufficient explanation for the strong aversions found in the rats at days 1, 2, 3, post-hepatectomy. However, this is not necessarily the case. There is a qualitative difference between a partial hepatectomy and a sham procedure. The hepatectomized animals required much more time to recover from anesthesia as compared to the shams. Typically, hepatectomized animals were under anesthesia anywhere from 5-10 hrs, whereas the shams often recovered in 2 hrs or less. In addition, the physiological disruption brought about by the removal of a major organ such as the liver is in no way equivocal to a sham procedure. Any attenuation of an aversion due to
partial hepatectomy may be obscured by the gross level of physiological disruption caused by the surgical procedure itself. This may be true not only of the animals tested shortly after surgery, but may also be true of those tested later, who demonstrated some, but nonsignificant, attenuations.

A second explanation for the nonsignificant differences (between aversions in rats that received illness training at different times post-hepatectomy) is that there really is a days effect but it is obscured by variance in the data, such as the anomalous performances by the H7 and IC7 groups. The pattern of aversions that were found may be related to the liver regeneration process itself. Higgins and Anderson (1931) have stated that the majority of liver regeneration takes place very shortly after partial hepatectomy. In the first 1, 2, and 3 days after hepatectomy the liver may be producing some chemicals (as a result of regeneration) that may in some way mimic or be similar to the chemicals that are involved in learning a taste aversion. As the rate of regeneration and the chemical processes subside around the fourth or fifth day, the true effect of partial hepatectomy on TAL may begin to be seen.

While the present experiment produced only weak evidence that the total amount of liver present is a factor in the strength of a taste aversion, it has shown that the overall effect of a partial hepatectomy does influence TAL.
Collapsing across days, hepatectomized animals extinguished their aversions faster than intact control animals. The differences between the two groups approached significance on the second extinction trial and were significant on the third and fourth extinction trials. The hepatectomized animals had fully extinguished their aversion by the third trial while the control animals did not extinguish their aversion until the fourth trial. These results are similar to those of Ellins and Costantino (1987) and Costantino et al. (1990) who found that partial hepatectomy facilitates the extinction of a conditioned taste aversion.

The consistency of these findings across the three experiments is strong evidence implicating the liver in TAL. The reliability of these results can be judged in terms of other studies that have shown that severing the vagus nerve effects TAL. The subdiaphragmatic vagotomy procedure has been shown to produce a variety of results; it leads to attenuation of taste aversions (Coil et al., 1978), facilitation of the extinction of taste aversions (Kiefer, et al., 1985), has no effect on taste aversions (Rabin et al., 1980), and, paradoxically, it has even been shown to induce taste aversions (Bernstein & Goehler, 1981). Although most researchers have focused on various brain structures and the gut itself when investigating the physiological mechanisms involved in TAL (with the possible exception of Hartley, 1977, who looked at the emetic
receptors in the ear and their relation to motion-induced taste aversions) the present study, as well as the previous work of Ellins and Costantino (1987) and Costantino et al. (1990) represents the only research which has implicated abdominal viscera other than the stomach as contributing to TAL.

The possible role of the liver as a homeostatic regulator, and the notion that deviation from homeostasis is a factor common to all taste aversions, is still unclear. While it has been shown that the liver does play a role in TAL it has yet to be determined if this is related to homeostasis or is the result of another factor. It is possible that the liver is not involved physiologically in TAL but, in fact, is involved more so in taste acuity. As shown by Smith, Henkin, and Dell (1979), people with liver disease often demonstrate disordered taste acuity. The rapid extinction shown by the hepatectomized animals may not be due to interruption of the physiological mechanisms involved in TAL, but may be due to the fact that the rats do not discriminate as well between tastes. In order to test this idea it would be necessary to hepatectomize some animals and then put them through a procedure that would test their taste acuity relative to intact controls.

In addition, to further support the notion of the liver as a homeostatic regulator, it would be necessary to examine the liver's role in taste aversions induced by other
methods, specifically those that do not produce emesis. This may prove beneficial because, despite almost a decade of research and dozens of articles dealing with the subject, a factor common to all TAL has not yet been elucidated. Many researchers have stated that there may be a number of different types of aversions mediated by different mechanisms. However, to this author's knowledge no research has been done to determine what these mechanisms may be. Many studies have been done showing that intrusive procedures (i.e. brain ablations, subdiaphragmatic vagotomy) will disrupt emetically induced aversions. However, similar studies with non-emetic treatments are lacking.

Seigel (1985) suggests that indeed there may be at least two fundamentally different types of aversions. Rats that are averted to a specific taste as a result of LiCL induced illness display gapes and chin rubs, indicating unpalatability. Aversions induced by amphetamine or lactose do not elicit gapes or chin rubs. The fact that different treatments manifest themselves differently behaviorally implies mediation by separate physiological pathways (Berger, Wise, & Stein, 1973). Further investigation may demonstrate that the liver is involved in many different aversions, supporting the homeostasis model.

Future studies should employ other experimental and surgical techniques when studying the liver, not only to use a procedure that is less intrusive than the partial
hepatectomy, but also to investigate the precise mechanism of action through which the liver mediates TAL. One such procedure is a hepatic vagotomy. This procedure is similar to a subdiaphragmatic vagotomy in that the liver is isolated neurally from the brain. Rather than cutting the vagus nerve below the diaphragm, denervating the entire gastrointestinal tract, the hepatic branch of the vagus nerve is severed or chemically denervated with phenol. This procedure isolates the liver from the brain but spares the connections with other abdominal viscera and is much less physiologically disruptive. In addition to these important differences, by using the hepatic vagotomy procedure it may be possible to determine if the liver mediates TAL vascularly, neurally, or both. Plans are currently underway in our laboratory to conduct such a study.

There are two more points to consider when addressing the possibility of a factor common to all TAL. One is the problem of the semantics itself. Many researchers refer to the UCS as toxicosis, illness, emesis, or gastrointestinal malaise. The meanings of these terms are often poorly defined, and in cases where they are discussed, the authors usually state some type of disclaimer regarding their definition. Another point of contention is the fact the many aversion inducing treatments produce no visible signs of illness. But what they do produce is not specified. If the animals are not getting sick then what are they doing?
What behavioral responses are occurring? Virtually no articles detail the responses observed when a taste aversion is induced by a non-emetic method.

**TAL and General Process Learning Theory**

A large portion of this paper has been devoted to a discussion of the nature of the UCS in TAL and the many paradoxes that exist between aversion inducing treatments. In addition, the anomalies of one trial learning, selective associations, long interstimulus intervals, overshadowing, and potentiation have also been examined. The fact that these phenomena do not appear to adhere to the general laws has been the genesis for much empirical work and ethological speculation.

When I speak of the general laws of learning I am referring to them as they apply to classical conditioning; though similar ideas may be applied to instrumental learning. In light of this, there are two somewhat opposing positions prevalent in the literature today. One position holds that general process learning theory can be applied to TAL and that the differences observed between TAL and other traditional learning paradigms are quantitative rather than qualitative (Logue, 1979). In contrast, the other position holds that the existing general laws of learning must be modified to incorporate the species-specific (Bolles, 1970) and task-specific (Seligman, 1970) differences in learning that have been largely ignored.
Many attempts have been made to integrate TAL into the framework of general process learning theory (Revusky, Taukaulis, & Parker, 1979; Spiker, 1977; Testa & Ternes, 1977). Logue (1979) is a staunch proponent for interpreting taste aversion conditioning within the traditional laws of learning. She states, however, that there are two problems inherent in this task. First, the traditional laws of learning are not clearly specified. "No list of equations presently exists that accurately describes all that we know about the learning process" (Logue, 1979, p. 277). And, secondly, it is difficult to determine what constitutes an exception to a general law of learning.

Take, for example, the phenomenon of one trial learning that is frequently documented in taste aversion conditioning; a characteristic assumed to make TAL an exception to general process learning theory. On the surface this would appear to be the case, but a closer examination of the taste aversion literature, as well as the literature pertaining to other more conventional (supposedly) types of learning, reveals this not to be so. Some drugs, such as strychnine sulfate (Nachman & Hartley, 1975), require repeated conditioning trials to condition a taste aversion. In fact, some drugs thought to be previously ineffective in inducing taste aversions will do so with several taste-drug pairings (Riley & Tuck, 1985). Similarly, one trial learning can occur in many conditioned
avoidance paradigms, particularly when the response is a species-specific-defense-reaction (Bolles, 1970). It would appear then that the one trial learning frequently observed in TAL is not outside of the parameters of traditional learning theory. At most, it seems, taste aversions are relatively easy to acquire, a difference in quality not quantity (Logue, 1979). Examples similar to this can be found for selective associations, long interstimulus intervals, and overshadowing (Logue, 1979).

Other researchers, however, believe that general process learning theory is inadequate, not only in describing TAL but also in reference to the fact that it fails to characterize other types of Pavlovian conditioning as well. Traditional descriptions of conditioning fail to address the circumstances that produce learning, the content of that learning, and how that learning affects the behavior of an organism (Rescorla, 1987). While none of these researchers suggests a total abandonment of general process theory, they do stress the necessity of modifying or removing existing general laws to accommodate adaptive specializations in learning (Logue, 1979).

One of the major assumptions about classical conditioning that has been called into question is the principle of equivalence of associability (Seligman, 1970); the idea that any neutral CS can become associated with any UCS, and that a set of universal laws governs the formation
of these associations. The fact that rats selectively associate taste with illness and exteroceptive stimuli with pain begs this point. In response to selective learning, Seligman (1970) has proposed a continuum of preparedness that mediates the associability of stimuli. An organism can be either prepared, unprepared, or contraprepared to learn about a situation. If an organism learns a response after only a few pairings of the stimuli then the organism is said to be prepared. If many pairings are needed for an association to be formed the organism is unprepared. If the response emerges only after very many pairings, or not at all, the organism is said to be contraprepared. The relative preparedness of an organism for learning about a situation is defined by the amount of input (e.g. number of trials, number of pairings) which must occur before the output (response) is reliably elicited (Seligman, 1970). In regards to TAL, a rat is prepared to associate taste with illness. Unprepared to associated exteroceptive stimuli with illness, and contraprepared to associate taste with shock. Seligman points out two interesting implications to this theory. First, the actual laws of learning may vary among the different dimensions of preparedness. Laws governing acquisition, extinction and inhibition might very well change as a function of an organism's place on the preparedness continuum. Second, different neural structures may underlie differently prepared learning. Elaborate
neural prewiring may mediate prepared associations, while unprepared and contraprepared associations may be mediated by more malleable structures.

Another concept fundamental to Pavlovian conditioning that may require modification is the notion of CS-UCS contiguity. Traditional views hold that the CS and the UCS must be presented together temporally for learning to occur. We have already seen that TAL violates this assumption, but several other classical conditioning procedures fail to adhere to the parameters of temporal contiguity as well (Rescorla, 1987). Rescorla has proposed that contiguity is neither necessary nor sufficient to establish learning. Conditioning depends not on the temporal relations between stimuli, but on the information the CS provides about the UCS. An organism learns relations between events in its environment, not in response to contiguity but in order to represent the structure of its world (Rescorla, 1987). An example of the importance of the information value of a stimulus in the formation of associations has been illustrated by Ellins et al. (1985). It had previously been shown by Garcia et al. (1966) that rats would not associate an auditory cue (a tone emanating from a speaker placed on a wall of the apparatus) with illness. However, Ellins et al. found that a noise-illness association can be formed if two criteria are met. First, the auditory cue must be presented in compound with a potentiating taste. Second, the noise
must be part of the food. Ellins et al. termed this phenomenon "spatial contiguity." Non-gustatory cues can become associated with illness if they are perceived as attributes of the ingesta. This demonstrates the importance of the information value of a stimulus in the formation of an association. In Garcia et al.'s experiment the tone was displaced from the water and therefore provided no information about the water. An association was not formed even though the two were presented together temporarily. Conversely, the tone in Ellins et al.'s experiment came from a speaker embedded in the food. In this case, the noise did provide information about the food and, hence, an association was formed.

In any classical conditioning situation an organism learns not only about the primary CS-UCS relationship, but also about the context in which they are presented; organisms form a broad range of associations among a wide variety of stimuli (Rescorla, 1987). The multiple CS-UCS associations may represent what is occurring with potentiation. The rat forms associations not only between the primary CS (taste) and the UCS, but also between features of the stimulus situation, such as the other olfactory, auditory and visual CS's.

Some New Ideas

While the aforementioned ideas of Seligman and Rescorla would require certain (perhaps extensive) modifications to
general process learning theory, an even more radical departure from the traditional Pavlovian models of TAL has been proposed by Garcia (1989). Garcia attempts to unify classical conditioning and conditioned taste aversions into a "single explanation of feeding behavior" (p. 46). He proposes that we adopt two major changes in our conceptualization of learning and, more specifically, taste aversions conditioning.

Garcia's model is based on Tolman's (1949) distinction of two different types of learning, "field expectancies" or "cognitions" and "cathexis." According to the views shared by Garcia and Tolman, CS's are distal stimuli in the environment guiding organisms toward goals and away from dangers. UCS's are the pleasant or unpleasant stimuli that result from contact with goal objects or disturbance objects, respectively. Feedback (FB) "stems from the internal homeostatic regulatory system following the consummatory bout which usually ends a behavioral sequence, as when food consumed brings about satiation or nausea" (Garcia, 1989, p. 49). CS's and UCS's are associated cognitively which results in a change in behavior. The organism then utilizes environmental information to form field expectancies and cognitive maps that represent CS-UCS relations that help to guide future behavior. This cognitive map appears to be similar to the multiple association schema proposed by Rescorla (1987). Thus,
according to Garcia (1989), when Pavlov's dogs salivated to a tone it was because they "expected" the taste to follow.

Cathexis is a process by which the incentive value of a stimulus is modified according to homeostatic FB. Taste quality, for example, can be modified by FB. If a taste is paired with beneficial internal consequences, it becomes hedonically positive. Paired with detrimental internal consequences, it becomes hedonically negative. These hedonic shifts are well documented by Grill and Norgren (1978a; 1978b). Cognitive awareness of the FB is not necessary for this hedonic shift to take place (Garcia, 1989).

Garcia believes that in order to fit TAL into the framework of classical conditioning we must change the labeling of the CS's and the UCS's. In this new model, CS's are stimuli associated with the eating environment (i.e. contextual cues). Taste is the UCS for two reasons: 1) it was Pavlov's original UCS, and 2) tastes are not neutral. The definition of a CS is that it, initially, elicits only an orienting response. Tastes are either hedonically positive or hedonically negative and elicit either an ingestive sequence or an aversive sequence (Grill & Norgren, 1978a; 1978b). The homeostatic consequences of consuming the ingesta are the FB, which modulate the hedonic quality of the UCS. Thus, TAL can be explained in terms of a synthesis between field expectancies and cathexis. Taste
serves as a UCS whose hedonic quality is modified through FB. At the same time an organism develops a cognitive map of the cues in the eating environment. These expectancies guide an organism's behavior in the approach or avoidance of a stimulus object. A comparison between the traditional Pavlovian model of TAL and Garcia's unified model is presented in Figure 10.

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**Figure 10**

**A Comparison of the Pavlovian and Unified Models of TAL**

Traditional Pavlovian Model:

Taste $\rightarrow$ Illness
CS $\rightarrow$ UCS

Garcia's Unified Model:

Cues $\rightarrow$ Taste $\rightarrow$ Homeostatic Disruption
CS $\rightarrow$ UCS $\rightarrow$ FB

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This model helps to eliminate the confusion surrounding the nature of the UCS (for it is now taste). The illness UCS is now viewed as a disruption of homeostasis and is termed an FB, not a UCS. Garcia states that there may be a variety of different types of FB's depending upon which systems are involved in learning. The definitions of FB among these systems and the physiological mechanisms that may mediate them are, at best, vague. It is possible that the liver may play a role in some type of homeostatic FB related to the consequences of ingestion (Sawchenko &
Freidman, 1979). The fact that the liver communicates with the brain's taste center (Rogers, Novin, & Butcher, 1979), and that people suffering from liver disease report disordered gustatory acuity (Smith, Henkin, & Dell, 1979), suggest that there may be a feedback system between the liver and the brain. This system may be responsible for modulating the hedonic quality of the taste UCS. It would be interesting to see if isolation of the liver from the brain would result in altered mimetic responses. The fact that the present study has shown that the liver is involved in TAL is further support for this idea.

This model is not without severe problems. First, and most considerable, it would require that we assume that there are different types of learning, which is in direct contrast to the widely accepted general process theory. Second, 35 years of taste aversion work would need to be reinterpreted and reevaluated in terms of this new model. It is not surprising then, that this model has not met with widespread acceptance. Besides the fact that it has yet to be empirically tested, many researchers are reluctant to speculate on more than one type of learning and to disregard three decades of scientific inquiry.

It appears that the ways in which classical conditioning and TAL are interpreted are changing. Many of the new theories are in direct response to the failures of general process learning theory to adequately explain a
large number of phenomena. Strict behaviorism is on the decline. Organisms are no longer viewed as merely responding to stimuli irrespective of biological constraints and environmental influences. The "black box" is slowly being replaced by theories that emphasize cognition, field expectancies, and multiples associations. Learning is no longer being defined in terms of a single uniformed entity but as an adaptive specialization of which there can be many types.
APPENDIX A

Table 1A.
Toxins that are Effective in Inducing Taste Aversions (Riley & Tuck, 1985).

<table>
<thead>
<tr>
<th>Toxin</th>
<th>Toxin</th>
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<tbody>
<tr>
<td>Arsenic</td>
<td>Mesurol</td>
</tr>
<tr>
<td>Barium carbonate</td>
<td>Methyl bromide</td>
</tr>
<tr>
<td>Cadmium chloride</td>
<td>Metrazol</td>
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<tr>
<td>Chloral hydrate</td>
<td>Monosodium glutamate</td>
</tr>
<tr>
<td>Cobalt chloride</td>
<td>Ozone</td>
</tr>
<tr>
<td>Cobra venom</td>
<td>Paraquat</td>
</tr>
<tr>
<td>Copper sulfate</td>
<td>Red squill</td>
</tr>
<tr>
<td>Deltamethrin</td>
<td>Scorpion venom</td>
</tr>
<tr>
<td>DMSA</td>
<td>Sodium fluoride</td>
</tr>
<tr>
<td>Endosulfan</td>
<td>Strychnine sulfate</td>
</tr>
<tr>
<td>Lithium carbonate</td>
<td>Thallium sulfate</td>
</tr>
<tr>
<td>Lithium chloride</td>
<td>Triethyltin</td>
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<tr>
<td>Mercuric chloride</td>
<td>Viper venom</td>
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Table 2A.

**Toxins that are Ineffective in Inducing Taste Aversions**

*(Riley & Tuck, 1985).*

<table>
<thead>
<tr>
<th>Toxin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aluminum chloride</td>
</tr>
<tr>
<td>Baygon</td>
</tr>
<tr>
<td>Chloraphacinone</td>
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<tr>
<td>Diphacinone</td>
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<tr>
<td>Gallamine triethiodide</td>
</tr>
<tr>
<td>Methylchlorophenoxyacetic</td>
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<tr>
<td>Propoxur</td>
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<tr>
<td>Pyrrolopyrimidine</td>
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<tr>
<td>Sodium cyanide</td>
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<tr>
<td>Sodium malonate</td>
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<tr>
<td>Warfarin</td>
</tr>
</tbody>
</table>
Table 3A.

Agents that are Effective in Inducing Taste Aversions (Riley & Tuck, 1985).

<table>
<thead>
<tr>
<th>Agent</th>
<th>Agent</th>
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<tbody>
<tr>
<td>Acetaldehyde</td>
<td>Ethanol</td>
</tr>
<tr>
<td>Amobarbital</td>
<td>Ether</td>
</tr>
<tr>
<td>Bombesin</td>
<td>Fenfluramine</td>
</tr>
<tr>
<td>Cannabichrome</td>
<td>Hashish</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>Histamine diphosphate</td>
</tr>
<tr>
<td>Cocaine</td>
<td>Insulin</td>
</tr>
<tr>
<td>Cortical spreading depression</td>
<td>Irradiation</td>
</tr>
<tr>
<td>d-amphetamine</td>
<td>Isotonic procaine</td>
</tr>
<tr>
<td>Delta-8-THC</td>
<td>Leydig tumors</td>
</tr>
<tr>
<td>Desipramine</td>
<td>Lorezapam</td>
</tr>
<tr>
<td>Diazepam</td>
<td>Mercuric chloride</td>
</tr>
<tr>
<td>Dichlorovus</td>
<td>Mescaline</td>
</tr>
<tr>
<td>Diethyldithiocarbamate</td>
<td>Methamphetamine</td>
</tr>
<tr>
<td>Emetine</td>
<td>Morphine</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>Nicotine</td>
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Table 4A.

Agents Ineffective in Inducing Taste Aversions (Riley & Tuck, 1985).

<table>
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<tbody>
<tr>
<td>Ammonia</td>
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<td>Ammonium sulfate</td>
</tr>
<tr>
<td>Arginine</td>
</tr>
<tr>
<td>Cytosine</td>
</tr>
<tr>
<td>Electroconvulsive shock</td>
</tr>
<tr>
<td>Glucose</td>
</tr>
<tr>
<td>Haloperidol</td>
</tr>
<tr>
<td>Heat</td>
</tr>
<tr>
<td>Hot mustard</td>
</tr>
<tr>
<td>Imipramine</td>
</tr>
<tr>
<td>Melatonin</td>
</tr>
<tr>
<td>Methaqualone</td>
</tr>
<tr>
<td>Pimozide</td>
</tr>
<tr>
<td>Propranolol</td>
</tr>
<tr>
<td>Quinine</td>
</tr>
<tr>
<td>Saccharin</td>
</tr>
<tr>
<td>Sodium chloride</td>
</tr>
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<td>Walker tumors</td>
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APPENDIX B

Table 1B.

Mean Lick Times and Standard Deviations for the H, IC and SC groups.

<table>
<thead>
<tr>
<th>Trials</th>
<th>Baseline</th>
<th>Ext 1</th>
<th>Ext 2</th>
<th>Ext 3</th>
<th>Ext 4</th>
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<tbody>
<tr>
<td><strong>Day 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hep</td>
<td>80.008</td>
<td>3.262</td>
<td>15.995</td>
<td>60.367</td>
<td>120.013</td>
</tr>
<tr>
<td>(n=6)</td>
<td>33.426</td>
<td>3.167</td>
<td>23.035</td>
<td>66.804</td>
<td>111.993</td>
</tr>
<tr>
<td>Icon</td>
<td>63.790</td>
<td>3.167</td>
<td>7.6820</td>
<td>30.340</td>
<td>80.4550</td>
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<tr>
<td>(n=6)</td>
<td>35.553</td>
<td>4.724</td>
<td>8.1070</td>
<td>32.131</td>
<td>67.9600</td>
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<td>SCon</td>
<td>69.166</td>
<td>67.320</td>
<td>138.10</td>
<td>166.99</td>
<td>179.795</td>
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<tr>
<td>(n=8)</td>
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<td>46.026</td>
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<td>60.963</td>
<td>53.3420</td>
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<td><strong>Day 2</strong></td>
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<tr>
<td>Hep</td>
<td>58.384</td>
<td>3.026</td>
<td>19.117</td>
<td>65.829</td>
<td>117.716</td>
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<tr>
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<td>29.349</td>
<td>2.348</td>
<td>19.603</td>
<td>57.793</td>
<td>78.1670</td>
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<td>Icon</td>
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<td>3.674</td>
<td>19.026</td>
<td>41.126</td>
<td>82.3970</td>
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<tr>
<td>(n=7)</td>
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<td>2.838</td>
<td>19.334</td>
<td>34.471</td>
<td>71.8820</td>
</tr>
<tr>
<td><strong>Day 3</strong></td>
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<td></td>
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<td></td>
<td></td>
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<tr>
<td>Hep</td>
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<td>5.164</td>
<td>23.314</td>
<td>67.063</td>
<td>96.9560</td>
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<tr>
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<td>5.538</td>
<td>31.119</td>
<td>73.794</td>
<td>82.6760</td>
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<td>Icon</td>
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<td>3.793</td>
<td>15.445</td>
<td>42.992</td>
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<tr>
<td>(n=6)</td>
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<td>2.002</td>
<td>15.246</td>
<td>51.501</td>
<td>53.8620</td>
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Table 1B. cont.

Mean Lick Times and Standard Deviations for the H, IC and SC groups.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
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<th>Ext 2</th>
<th>Ext 3</th>
<th>Ext 4</th>
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<tr>
<td>Hep</td>
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<td>9.404</td>
<td>42.854</td>
<td>101.42</td>
<td>165.889</td>
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<td>(n=7)</td>
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<td>11.07</td>
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<td>74.864</td>
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<tr>
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<td>2.421</td>
<td>23.561</td>
<td>64.797</td>
<td>122.184</td>
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<tr>
<td>(n=7)</td>
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<td>1.036</td>
<td>19.796</td>
<td>38.971</td>
<td>35.9830</td>
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<td><strong>Day 5</strong></td>
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<td>Hep</td>
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<td>29.791</td>
<td>81.647</td>
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<td><strong>Day 6</strong></td>
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<tr>
<td>Hep</td>
<td>74.482</td>
<td>8.438</td>
<td>35.620</td>
<td>131.89</td>
<td>180.562</td>
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<td>15.360</td>
<td>28.241</td>
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<tr>
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<td>3.719</td>
<td>8.7480</td>
<td>15.718</td>
<td>45.6330</td>
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<td><strong>Day 7</strong></td>
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<tr>
<td>Hep</td>
<td>95.948</td>
<td>9.332</td>
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<td><strong>Day 13</strong></td>
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<tr>
<td>Hep</td>
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<td>(n=4)</td>
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<td>5.761</td>
<td>2.9360</td>
<td>16.713</td>
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Table 1C.

Mean Liver Weights in Grams

<table>
<thead>
<tr>
<th>Day</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
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</tr>
<tr>
<td>Hep 2</td>
<td>12.1</td>
</tr>
<tr>
<td>Hep 3</td>
<td>12.8</td>
</tr>
<tr>
<td>Hep 4</td>
<td>12.2</td>
</tr>
<tr>
<td>Hep 5</td>
<td>12.2</td>
</tr>
<tr>
<td>Hep 6</td>
<td>11.3</td>
</tr>
<tr>
<td>Hep 7</td>
<td>12.3</td>
</tr>
<tr>
<td>Hep 13</td>
<td>10.9</td>
</tr>
<tr>
<td>Control</td>
<td>13.9</td>
</tr>
</tbody>
</table>

**Note 1:** The livers were not weighed until several days after extinction, thus the weights presented here are not representative of the actual weights at different days post-hepatectomy.

**Note 2:** The control group was comprised of one animal from each of the intact control groups and one animal from the sham control group.
References


