EFFECTS OF A CATION EXCHANGE RESIN ON COMPENSATORY NaCl DRINKING IN ADRENALECTOMIZED RATS

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EFFECTS OF A CATION EXCHANGE RESIN ON COMPENSATORY NaCl DRINKING IN ADRENALECTOMIZED RATS

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CHAPTER I

INTRODUCTION

Removal of the adrenal glands results in excessive excretion of sodium in rats and other mammals. If left untreated, these animals die within a short period of time. Treatment with mineralocorticoid hormones and/or sodium chloride (NaCl) leads to a prolongation of life. Further, if protected from stressful stimulation, an adrenalectomized animal so treated will live in a relatively healthy state for an indefinite period. Richter (1936) found also that adrenalectomized rats given access to solutions containing NaCl will ingest sufficient quantities of sodium to insure survival. This appetite appears to be specific for the Na^+ ion (Richter & Eckert, 1938).

Interest in this homeostatic behavior pattern has been generally directed toward determining the influence of taste, need and experiential factors. Possible physiological substrates are also being investigated (for recent review see Finger & Mook, 1971).

In order to further elucidate the controlling variables, some recent work has centered around experiential factors which delay or disrupt the response. For example, aversion to NaCl produced by either LiCl poisoning (Cullen, 1970b) or gamma-ray irradiation (Cullen, 1969) has been shown to modify the salt-seeking behavior of the adrenalectomized rat. A preference for one of a number of sugar solutions developed preoperatively may also result in inadequate salt intake (Cullen, 1970a;

Harriman, 1955, 1971). The present study utilized another manipulation in order to interfere with the compensatory response.

Physiological Effects of Adrenalectomy

The adrenal glands are two small organs, richly supplied with blood, located rostral to the kidneys. Each adrenal has two functional portions: the medulla and the cortex. The medulla (inner portion) is composed of two types of specialized sympathetic ganglion cells. Upon stimulation by preganglionic cholinergic autonomic nerve fibers, these cells secrete the catecholamines epinephrine and norepinephrine, respectively, into the blood stream (Williams, 1963). Epinephrine elicits constriction of the blood vessels associated with the digestive system, kidneys and skin, while dilating those in the skeletal muscles and lungs and increasing cardiac output. Norepinephrine has an overall constriction effect and decreases cardiac output. Large amounts of these products are generally secreted in response to intensive stimulation of the organism (Grossman, 1967).

The adrenal cortex, surrounding the medulla, is composed of three distinct cellular layers and is capable of functional regeneration (Grossman, 1967). The various steroids secreted by the cortex are involved predominantly in organic metabolism and water-electrolyte balance. The major classes of these steroids include glucocorticoids (e.g., cortisol), involved in liver glycogen storage and blood sugar maintenance, and mineralocorticoids (e.g., aldosterone) which mediate electrolyte balance.

Aldosterone, a mineralocorticoid product of the adrenal cortex, is the most potent regulator of electrolyte balance. Body water is

separated into two compartments: that inside the cells (intracellular) and that contained in blood plasma and interstitial fluid surrounding the cells (extracellular). The electrolyte content of these compartments, predominantly potassium intracellularly and sodium extracellularly, determines the amount of water contained therein. Changes in electrolyte balance producing osmotic gradients cause water to move across cellular membranes in order to reduce the gradient and reestablish osmotic equilibrium. If extracellular sodium chloride concentration is low, aldosterone stimulates the reabsorption of sodium ions by the kidney, sweat and salivary glands, and gastrointestinal tract (Lauler, 1969). Potassium, hydrogen, and ammonium ions are concomitantly excreted by the kidney. An increase in plasma sodium chloride concentration raising the osmolality of the extracellular fluid decreases aldosterone production and stimulates the secretion of pituitary antidiuretic hormone (ADH) which enhances renal conservation of water. By these mechanisms the correct amount and distribution of body water are maintained (Williams, 1963).

Adrenocorticotropic hormone (ACTH), a product of the anterior pituitary, controls to a large extent the activity of the adrenal cortex, especially the secretion of the glucocorticoids. Release of aldosterone, however, appears to be controlled by at least three mechanisms of which ACTH is only one. A second mechanism involves the kidney's release of renin (a proteolytic enzyme) in response to volume depletion and decreased sodium load. By a series of steps renin produces angiotensin II which stimulates the production and release of aldosterone by the adrenal cortex. Independent of the foregoing mechanisms is the potassium mediated control system: raised plasma potassium levels lead to increased

secretion of aldosterone by adrenal cortical cells (Denton, 1965; Lauler, 1969).

Extirpation of the adrenal medulla is not fatal; however, complete removal of the cortical portion of the adrenal glands can result in death among rats within five to 15 days (Grossman, 1967). Following bilateral adrenalectomy (and during adrenocortical insufficiency - Addison's disease) there is a drop in food and water intake, steady weight loss, and development of a critical susceptibility to stressful conditions. In addition, blood glucose levels fall (hypoglycemia) and sodium retention by the kidney is halted while potassium is retained. The decrease in concentration of sodium salts in the blood and concomitant lowering of osmotic pressure induces excess excretion of water by the kidneys. This eventually leads to hemoconcentration, a fall in blood pressure, renal failure and death (Langley & Cheraskin, 1965; see Appendix A). Administration of cortisol or cortisone along with a sodium-retaining hormone (e.g., aldosterone) will alleviate these symptoms and prolong life indefinitely (Williams, 1963).

Behavioral Effects of Adrenalectomy

Early research leading to the study of the behavioral effects of adrenalectomy began, in 1925, when Stewart & Rogoff found that the injection of a salt solution greatly prolonged the lives of adrenalectomized dogs. These results were confirmed by Rubin & Krick (1933) who were able to keep white rats alive indefinitely through oral administration of a salt solution. Loeb (1932) reported that large doses of sodium chloride effected clinical improvement in Addisonian patients and led to the establishment of near normal plasma electrolyte levels.

Gaunt, Tobin & Gaunt (1935) explored the effects of salt-treatment in 30-day-old (mean weight, 58g) and adult (weight range, 170-211g) adrenalectomized rats. In the untreated animals, 94% of the 30-day-olds and 75% of the adults died within 30 days of adrenalectomy. With salt-treatment, only 44% of the 30-day animals and 22% of the adults died within that period. Although salt-treatment prolonged the lives of many of these animals, the quality of life was not normal, especially in the younger rats. These animals were relatively inactive and showed depressed growth rates when compared with nonadrenalectomized controls of the same age. When salt-treatment was discontinued, many of the remaining animals died but some subjects in each group survived indefinitely: four and seven percent of the 30-day-olds, controls and salt-treated, respectively, and 12 and 52 percent of the control and salt-treated adults. All of these animals showed accessory adrenal tissue at autopsy. In another experiment (Gaunt & Gaunt, 1934), 50% of the adrenalectomized subjects which had been maintained on adrenocortical extract survived for at least 30 days after the hormone was withdrawn. Accessory adrenal tissue was found in all but one of these animals. The survival rate of untreated adrenalectomized subjects was five percent or less. It appears that if life is maintained, by whatever means, for a period following adrenalectomy, accessory adrenal tissue may hypertrophy and produce the adrenal hormones necessary for the maintenance of life.

Richter (1936) found that when given the choice between either a one percent or three percent salt solution and tap water, rats will significantly increase salt intake following adrenalectomy. The amount of salt ingested by these animals was enough to increase the period of postoperative survival, in most cases to the indefinite level. In addition,

Richter found that the average taste threshold (in actuality, a drinking preference threshold) of adrenalectomized rats for sodium chloride (NaCl) solutions was about 15 times lower than normal rats (Richter, 1939).

Richter & Eckert (1938) used several sodium and nonsodium solutions in testing adrenalectomized rats. Their results indicate that the increased intake following adrenalectomy is highly specific for the sodium ion (Na^+) and not for the chloride ion (Cl^-). Pfaffmann (1964) confirmed this specificity of choice.

In an attempt to explain these results, Richter (1942-43) hypothesized that the increase in salt appetite is due to an automatic internal regulatory mechanism--a specific increase in salt receptor sensitivity--activated by the state of physiological need. He excluded the possibility that beneficial aftereffects experienced by the animal following sodium ingestion may be of importance. In order to test this contention, Richter (1947) denervated the taste receptors through bilateral section of the lingual, chorda tympani and glossopharyngeal nerves. In line with the experimental prediction, no increase in sodium intake was exhibited by those rats after adrenalectomy. The denervation procedure, however, along with causing impairment of chewing and swallowing (Denton, 1965) might prevent the development of any preference (or aversion) based on taste, regardless of the mechanism.

It has been found, however, that rats can accurately regulate food (Epstein & Teitlebaum, 1962) and water (Epstein, 1960) intake when feeding themselves through direct intragastric self-injections, a method which eliminates oropharyngeal cues. Rats are also able to regulate NaCl solution intake while sham-drinking (esophagostimized and fitted with a gastric cannula). Both thirsty (Mook, 1963) and nondeprived (Mook &

Kozub, 1968) animals appear to utilize postingestional, rather than taste, cues in effecting the regulation. Specifically, the normal preference for saline is eliminated when water reaches the stomach rather than the saline that the animal tastes.

Pfaffmann & Bare (1950) directly tested Richter's hypothesis by electrophysiologically recording the discharges of the chorda tympani nerve. The receptor thresholds of the adrenalectomized rats were the same as those of normals even though the adrenalectomized animals preferred NaCl solutions of lower concentrations than did the normal animals (see also Nachman & Pfaffmann, 1963). That adrenalectomy elicits a lower preference threshold in rats without changing the sensitivity of the taste receptor was corroborated by Harriman & MacLeod (1953). Through the use of reward and punishment these investigators were able to obtain, in normal rats, finer discriminations between distilled water and very low concentrations of NaCl than those reported by either Richter or Pfaffmann & Bare for adrenalectomized animals. This level of discrimination was not improved following adrenalectomy. Carr (1952) obtained similar results.

Some investigators hold that bodily need per se is the important determinant of salt intake. Lewis (1960) found that response strength, as measured by volume intake of 1% NaCl in 15 minutes, increased with increasing hours of NaCl deprivation in adrenalectomized rats. Epstein & Stellar (1955) reported increased intake of a 3% NaCl solution that was related to increased need. The conclusion drawn from these studies was that the adrenalectomized animal will drink the amount necessary to provide itself internally with a constant amount of NaCl.

That neither taste nor need factors operate alone is the conclusion

drawn from other studies. Bare (1949) reported that in a two-choice preference situation, normal rats drank significantly more NaCl than tap water in increasing amounts from the preference threshold concentration (0.06%) up to 0.9%. Further increases in concentration led to decreases in intake until, at 1.5%, there was no preference exhibited. Beyond that point, a marked preference was shown for the tap water. Adrenalectomized animals exhibited the same form of preference-aversion function; however, the preference threshold was lower, and the amount of NaCl solution ingested at each concentration was greater, than that of the normal rats. Interesting in itself is the increased intake at the very low concentrations where the amount of salt taken in is too small to be of more than minimal benefit to the adrenalectomized rat.

Young & Chaplin (1949) confirmed the finding that rats do not ingest constant amounts of NaCl in a free choice situation, but that the amount ingested depends upon the concentration at which the NaCl solution is presented. The authors conclude that since adrenalectomy does not change this relative preference, but does change the amount consumed of all the concentrations, that need factors (appetite) and taste factors (palability) should be considered separately when analysing the intake of salt or other food items (see also Young, 1966).

In order to identify better the influence of these two factors, Harriman (1967) performed extended (45-day) two-bottle preference tests in sodium-depleted adrenalectomized rats and sodium-repleted sham-operated rats. Each adrenalectomized rat was deprived of all sodium except that contained in solution in one of the drinking tubes attached to the living cage (the other tube contained distilled water). The diet of the sham-operated animals contained in addition 1% NaCl. Six NaCl

concentrations, varying from 1.2% to 2.7%, were used in the drinking tests, with one adrenalectomized and one sham group receiving each concentration. During the first 5-day period of the drinking tests, the mean total daily intake of NaCl (in milligrams - mg) by the adrenalectomized rats was the same as the sham-operated animals. The adrenalectomized animals maintained this same level of intake throughout the 45 days of tests. The milligram-NaCl intake of the sham-operated rats, on the other hand, decreased by approximately 40% during the first 15 days and remained at the low level for the remainder of the experiment. During the first 5-day block again, the mg-NaCl intake by the adrenalectomized rats was similar to that of the sham-operates at a given concentration. For days 41-45, however, this pattern was different. While mg-NaCl intake by the control subjects varied with the concentration of the NaCl solution, the mg-NaCl intake of the adrenalectomized animals appeared to be independent of concentration (see also Cullen, 1970a). Harriman explained this apparent inconsistency with the results of Bare (1949) and Young & Chaplin (1949) by pointing out that the former investigator used fewer subjects and briefer test periods, while the latter researchers allowed their adrenalectomized animals access to 4% sodium phosphate. The adrenalectomized rats in Bare's study also had access to an additional source of sodium: a commercial lab chow containing 1% NaCl. It is possible, therefore, that the animals in Harriman's study were more severely depleted than those in the above studies and that this fact accounts for the discrepancy. If true, this suggests that palatability factors regulate sodium intake in repleted and mildly depleted animals, but that they are overridden by bodily need factors in the severely depleted.

Harriman's results are compatible with those of Jalowiec & Stricker (1973) who measured various blood and urine parameters in adrenalectomized rats following periods of sodium deprivation and access to 0.51M NaCl. Adrenalectomized animals permitted continuous access to a sodium-replete diet and the relatively unpalatable 0.51M NaCl (approximately 3.0%) solution nevertheless evidenced symptoms of sodium deficiency: plasma sodium and plasma potassium levels which were significantly lower and higher than normal, respectively. Adrenalectomized animals deprived of sodium for up to eight hours showed this same level of deficiency. This small but chronic deficiency appeared to be due to ingestion of saline in small amounts at intervals of 1-3 hours. Since significant amounts of sodium were being lost in the urine almost continuously, this intake procedure replaced the deficits only temporarily. The authors speculated that the availability of a more palatable solution probably would have enabled the animals better to maintain sodium balance through more frequent drinking of larger quantities.

Adrenalectomized animals which were more severely depleted through maintenance on a sodium-deficient diet and not allowed access to the NaCl solution for several hours quickly drank more than enough sodium to replace their losses (as measured by urine sodium). The degree of this overcompensation increased as the sodium deficit was increased. The authors note, and indeed it is interesting, that the behavioral overcompensation did not lead to above normal plasma sodium concentrations or volumes. In light of these results, it appears that an experiment exploring the effects of various degrees of deprivation on the intake of several concentrations of NaCl in conjunction with measuring several physiological variables would elucidate greatly the separate and combined

effects of palatability and level of need.

The critical physiological changes which operate to stimulate sodium appetite during sodium deficiency have been the subject of much research and speculation. The mineralocorticoids have naturally been implicated since both aldosterone secretions and sodium intake are increased during sodium deficiency in the intact rat (Denton, 1965). It has been shown that selected doses of both aldosterone (Fregly & Waters, 1966; Wolf, 1964b; Wolf & Handal, 1966) and deoxycorticosterone (Wolf, 1965) are capable of eliciting sodium appetite in rats. While the mineralocorticoids may be involved somehow in saline ingestion in intact rats, it is obvious that they are not responsible for the adrenalectomized rat's ability to replace sodium losses through intake (Jalowiec & Stricker, 1973). Other endocrine systems have been studied, but the overall conclusion drawn seems to be that none has a direct effect on sodium appetite (Jalowiec & Stricker, 1973).

Richter (1956) proposed a natrorexigenic (sodium appetite stimulating) function to lowered plasma sodium levels (hyponatremia). The evidence against this hypothesis is strong, however. Stricker & Wolf (1966) induced low plasma sodium levels by hydration and found no increase in sodium appetite. In addition, the adrenalectomized rats in the Jalowiec & Stricker (1973) study exhibited increasing sodium appetite without changes in plasma sodium during lenthening sodium deprivation periods from 24 to 48 hours.

The natrorexigenic effect of hypovolemia (low blood volume), in contrast, has received some support. Hypovolemia produced by both subcutaneous injection of a colloidal substance in intact and adrenalectomized rats and concurrent water and sodium deprivation in adrenalectomized

animals is sufficient to elicit sodium appetite in the absence of plasma sodium concentration changes (Smith & Stricker, 1969; Wolf & Stricker, 1967).

Stricker & Wolf (1969) proposed the existence of a reservoir whose sodium content fluctuates with changes in certain hemodynamic factors. Critical loss of sodium from this reservoir directly stimulates sodium appetite. Clear support for this hypothesis has not yet been obtained (Jalowiec & Stricker, 1973). Denton (1965) suggested the presence of a receptor cell which responds to relative changes between intracellular and extracellular sodium ion concentrations. Denton (1972) proposed that it is a neuronal population which reacts to intracellular sodium content to initiate "a strong goal directed drive". In connection with this, it has recently been found that lesions of the lateral hypothalamus eliminate the increased NaCl intake in sodium-deficient rats without affecting the preference-aversion responses normally seen (Wolf, 1964a; Wolf & Quartermain, 1967). The search for a neural substrate of salt preference has not produced conclusive results as yet; however, there seems to be considerable research activity in the area (for references, see Finger & Mook, 1971).

The search for a physiological substrate for sodium appetite has at its base the assumption that the mechanisms controlling the behavior do not require experiential influences to operate adaptively. Indeed, it appears that this "innateness" assumption is no longer seriously questioned (Denton, 1972; Richter, 1956; Rozin & Kalat, 1971; Wolf, 1969). The behavioral evidence usually cited in support of this position includes the observations that sodium-deficient rats (a) show an immediate preference and increased appetite specifically for sodium containing

fluid (Handal, 1965; Nachman, 1962) and food (Bolles, Sulzbacher & Arant, 1964; Grimsley, 1973) at their first encounter with these items; (b) work harder for salt in a manner related to their deficiency (Lewis, 1960); (c) drink salty-tasting fluids which they had learned to avoid when replete (Stricker & Wilson, 1970); and, (d) gradually increase NaCl solution intake as a function of physiological need rather than experience (Epstein & Stellar, 1955).

More specifically, it is presently thought that increased sodium appetite during sodium deficiency is a behavioral homeostatic response mediated by a centrally activated change in responsiveness to salt taste (Denton, 1972; Finger and Mook, 1971; Richter, 1956). Two additional lines of evidence, along with the neurophysiological data, support this view: (1) in situations designed to minimize or eliminate feedback from the postingestional consequences of sodium ingestion, sodium deficient rats still show increased preference for sodium-containing substances (Falk & Herman, 1961; Mook, 1969; Smith, Holman & Fortune, 1968; Smith, Stricker & Morrison, 1969); and, (2) a lack of demonstrated change in receptor sensitivity due to sodium deficiency (Nachman & Pfaffmann, 1963; Pfaffmann & Bare, 1950). Mook (1969) presents provocative preliminary results on a study designed to test the role of the state of the internal state on the response to taste. In a 24-hour procedure, the esophagostomized rat was allowed ad lib access to water and 0.5M NaCl. No matter which substance the animal tasted, however, only water was delivered to his stomach through the indwelling tube, thus equalizing the postingestional consequences. Before adrenalectomy, the animal drank very small quantities of the unpalatable NaCl solution, as does a normal rat. Following adrenalectomy, the animal drank increasing amounts of the saline

even though only water was reaching his stomach and his increasing sodium deficits were not being replaced. The animal continued this drinking pattern until it died ten days after surgery.

While taste is obviously important, the possibility that postingestional cues may be necessary for the maintenance of NaCl consumption has not been ruled out (Smith, 1972; Smith, Holman, & Fortune, 1968). Mook (1969) reported that nondeficient rats select the substance to be ingested on the basis of taste, but that the amount actually consumed is determined by postingestional consequences. In a single-choice situation, the normal rat will drink more when isotonic saline is available than when water is available ("preference" for saline). If only water reaches the animal's stomach, the amount ingested from each solution will be equal (no "preference"). On the other hand, if only hypertonic saline is intubed, the intake when saline is present is much below that when water is available ("preference" for water). If isotonic saline is intubed when water is tasted and vice versa, the animals demonstrated the normal "preference" for saline will be made on the basis of postingestional cues. That is, when the rats were tasting saline but receiving water, they drank only as much as when they were tasting and receiving water (normal drinking). This level of intake was much less that that under the conditions of normal saline drinking or tasting water and receiving saline, which produced equal intakes (Mook & Kozub, 1968).

When animals are made sodium-deficient through adrenalectomy, factors of internal need are added to those of taste and postingestional consequences. In a study by Epstein & Stellar (1955), adrenalectomized rats maintained through access to 3% NaCl and water increased their NaCl intake when part of the sodium tasted was prevented from being absorbed

through binding with an ion exchange resin in the intestine. The degree of increase was roughly proportional to the amount estimated to be bound by the resin. The intact animals showed no increase in NaCl intake when the exchanger was added to the diet. In this situation, with palatability held constant, level of need and postingestional cues presumably interacted to produce a change in NaCl intake rate.

A study showing the interaction of the source of the need and postingestional consequences was performed by Smith & Stricker (1969). Normal animals given continuous access to isotonic saline and water preferred saline in response to hypovolemia produced by subcutaneously injected polyethylene glycol (intravascular dehydration), but chose water to drink when intracellularly dehydrated. This demonstrated not only that hypovolemia is sufficient to induce saline appetite, but also that the rat is capable of selecting the available solution which will more efficiently reverse the specific dehydration.

It is generally considered that all specific hungers so far studied, except that for sodium, are learned (although agreement over what exactly is learned by the animal has not been reached) (Rozin & Kalat, 1971). Nevertheless, experiential influences have been demonstrated for sodium appetite as well. As noted above, postingestional consequences do exert some control over NaCl intake. Further, Smith, Pool & Weinberg (1958) showed that esophageal-fistulated sham-drinking rats failed to demonstrate need-related preferences for NaCl. The findings were interpreted in terms of learning as follows: Since the postingestional effects of NaCl ingestion were not experienced, the sham-drinking animals failed to associate the taste of NaCl with its beneficial consequences. It must be noted, however, that the sodium-deficient animals did drink more of the

NaCl solution, in absolute terms, than did the non-deficient animals.

Clearer experience-related influences were demonstrated in a study by Smith, Holman & Fortune (1968) who used an esophagostomy-catheter system in rats in an approach similar to that used by Mook (1963). Sodium-deprived animals given experience with tasting and receiving saline reversed a previously demonstrated preference between two non-sodium solutions when the taste of the less-preferred substance was paired with glucose. Animals lacking the experience failed to show the reversal.

McCutcheon (1971) demonstrated sensory adaptation and incentive contrast effects on NaCl drinking by normal and adrenalectomized rats in short-term preference situations. Essentially, he found that the number of times an animal licked a given NaCl concentration varied with the concentration of the NaCl solution to which the animal had been exposed (for the duration of 60 licks) immediately prior. It was also found that the concentration of the adapting solution affected the preference relationship demonstrated between two NaCl solutions immediately following.

In another study (Devenport, 1973) normal rats given access to either hypertonic or isotonic saline only for 24 hours subsequently reversed a preference shown for isotonic saline over water (two-bottle test) before such exposure. This reversal occurred even when a period (seven days) of exclusive access to water intervened between the saline-access period and preference testing. It would be interesting to see if adrenalectomized animals also reversed preferences using these procedures.

Certain types of experience interfere with compensatory sodium ingestion. The behavior produced by these manipulations has been labelled "anhomeostatic" by Falk (1961), in reference to its nonregulatory nature. One procedure which appears to modify sodium hunger in adrenalectomized

rats is lithium chloride (LiCl) poisoning. Although lithium and sodium elicit similar electrophysiological responses from the chorda tympani nerve (Beidler, 1953), and discrimination between them by normal and adrenalectomized rats alike is poor in short-term preference tests (Harriman & Kare, 1964; Nachman, 1962, 1963b), rats are able to discriminate if allowed to experience the toxic effects of lithium in repeated or prolonged preference tests (Fregly, 1958; Nachman, 1963b). Harriman & Kare (1964) found that one 12-hour period of exposure to LiCl vs. water in a two-bottle test was enough to facilitate the adrenalectomized rat's ability to discriminate between equimolar NaCl and LiCl solutions. Adrenalectomized animals without this experience and sham-operated animals with or without LiCl experience were able to make the discrimination only after several exposures to the test situation.

Nachman (1963a) demonstrated that the aversion which develops to LiCl generalized to other solutions in a manner proportional to the degree to which their chemical properties are similar to LiCl. In confirmation, Cullen (1970b) found prolonged exposure to LiCl and either water or 0.15M NaCl did lead to subsequent aversion to NaCl. The aversion was strong enough to interfere with compensatory NaCl intake by adrenalectomized subjects, some of which showed protracted weight loss and a small percentage of which died. Using different procedures, Frumkin (1971) was able to demonstrate only a small and transient decrease in NaCl intake attributable to generalization of a LiCl aversion in adrenalectomized rats. Aversion to NaCl produced more directly by contingent gamma-ray irradiation was shown to reduce NaCl intake following adrenalectomy (Cullen, 1969).

Interference with compensatory NaCl drinking by adrenalectomized

rats has been demonstrated in certain cases where a preoperative preference for a highly palatable non-sodium solution was established. Rats given preoperative experience with 8% sucrose opposite 1.2% NaCl continued to prefer the sucrose following adrenalectomy to the extent that they all lost weight and 20% died (Harriman, 1955). Similar studies utilizing sucrose preference did not yield the same results (Cullen & Scarborough, 1969; Grimsley, 1970; Grimsley & Cullen, 1968). Similarly, no evidence of interference was found by Grimsley & Fisher (1967) as a result of preoperative saccharine preference. Cullen (1970a) reported, however, that preoperative saccharine-glucose polydipsia led to decreased post-adrenalectomy intakes of a relatively unpalatable (2%) NaCl solution and weight loss. Identically experienced adrenalectomized rats offered the highly palatable 0.9% NaCl vs. saccharine-glucose did not show this effect. In another study, dextri-maltose (20%) preference led to a decreased preference for 1.5% NaCl by adrenalectomized rats (Harriman, 1971).

As Cullen (1970b) points out, the procedures cited above produce only temporary reduction in NaCl intake. It is obvious, though, that given the right conditions the behavioral homeostatic response can be modified. This modification is of long enough duration to lead to weight loss and even death in some cases.

Ion Exchange Resins

Dock, in 1946, first proposed the use of ion exchange resins *in vivo* for the purpose of controlling the extent of absorption of electrolytes. His study of sodium depletion by means of a cation exchanger introduced a new tool by which edema, caused by sodium retention, could be alleviated.

Subsequently, various medical applications of ion exchange resins were developed. For example, cation exchangers have been used for the treatment of edema associated with congestive heart failure, cirrhosis of the liver, and hypertension. Anion exchangers found utility in cases of peptic ulcer, gastritis, heartburn and in some forms of colitis (Martin, 1955). Goodman and Gilman, writing in 1970, reported that these applications are no longer practiced, but that cation exchangers are used in cases of acute hyperkalemia.

Ion exchange resins are synthetic high molecular weight polymers containing ionizable groups, the nature of which affects the chemical behavior of the resin. The mobile ions of these groups are capable of reversibly exchanging with other ions without physically changing the resin itself. Generally, this exchange takes place on an equivalent basis: One gram equivalent of an ion replaces one gram equivalent of another ion. The two major types of ion exchange resin are cationic (weak- and strong-acid) and anionic (weak- and strong-base). This designation refers to the sign of the charge on the ions which are released and adsorbed by the ionizable groups on the resin, e.g., a cation exchange resin exchanges positive ions. The cycle of the resin refers to the identity of the ions attached to the ionizable group when it is introduced into the exchange medium (hydrogen cycle, ammonium cycle, etc.).

The polymer portion of the resin molecule is usually made up of polystyrene chains linked at various intervals by such groups as divinylbenzene. The degree of crosslinkage confers various properties to a given ion exchanger. For example, as crosslinkage increases, solubility and permeability decrease along with the tendency to swell

when wet. In addition, wet volume capacity and selectivity of the resin increase while equilibrium rate decreases. Particle or mesh size is another important variable for determining the behavior of a resin. Particles of small size reach equilibrium with their surroundings faster than large particles and are more efficient (in terms of percent exchange per unit of resin) (Bio-Rad Laboratories, 1970). In choosing an exchange resin for a specific purpose, both of these variables must be considered. The best balance for physiological applications is one of small particle size, for a maximum availability of ion-reactive groups, combined with a degree of crosslinkage which would allow a sufficient diffusion rate without unmanageable swelling (Martin, 1955). The exchanger used in the present study (Dowex 50W - X8) contained 8% crosslinkage and was mixed in the diet so that one-half the resin content was 100-200 mesh and the other half was 200-400 mesh.

The following discussion will be limited to the cation type because the present interest concerns removal of sodium ions. The major cation reactive groups used for physiological purposes are carboxylic and sulfonic. Because these are acidic types, respectively weak and strong, they are most efficient in alkaline surroundings such as the gastrointestinal tract. As the resin passes through the gastrointestinal tract (not digested and unabsorbed), the mobile ions are exchanged for cations in the intestinal fluid. The affinity characteristics of a given resin in part determine which cations it will bind. Generally, the higher the valence of the cation the more firmly it will be bound. The affinity rankings of cations within a valence group is such that bonding strength increases with increasing atomic weight. As an example, the decreasing affinity series for Dowex 50W (in vitro determination) is as follows (Dow

Chemical, 1964; see Appendix B):

$$Ba^{++} > Pb^{++} > Sr^{++} > Ca^{++} > Ni^{++} > Cd^{++} > Cu^{++} > Co^{++} > Zn^{++} > Mg^{++} > Be^{++}$$

$$Ag^{+} > Ti^{+} > Cs^{+} > Rb^{+} > K^{+} > NH_4^{+} > Na^{+} > H^{+} > Li^{+}$$

The availability of an ion in the exchange medium is also important in determining its bonding potential. Thus, the greater relative concentration of sodium in the intestinal fluids offsets, at least in part, the greater bonding strength of calcium, magnesium and potassium (Ch'en & Freeman, 1950; Martin, 1955; see Appendix C).

The position that the hydrogen ion (H^+) occupies in the exchange series of a resin determines to a large extent the exchange capacity of that resin at a given pH. Carboxylic-type exchangers have a high affinity for H^+ and, therefore, will release other ions in exchange for H^+ in acid pH situations. On the other hand, H^+ falls below the metallic cations in the sulfonic series and can be exchanged for these ions even at the stomach pH of 1.5. That is, the exchange capacity of the sulfonic resins is much less affected by pH than is that of the carboxylic type (Martin, 1955; McChesney, 1951).

Toxicity studies indicate that cation exchange resins are fairly safe for animal consumption. Flanagan, et al. (1951) studied the effects of ammonium and ammonium-potassium cycle carboxylic resins, fed at 10% of both normal and low sodium diets, for periods from one week to six months in rats and dogs. Abnormalities were found neither in growth rate, hematology, reproduction, tissue electrolyte content, endocrine gland weights nor principle organ histology. These results led the investigators to conclude that the resins caused no interference with the absorption of either vitamins, amino acids or other essential nutrients.

In support of this conclusion, McChesney (1952b) found no loss of amino acid, thiamine or riboflavin as a result of either sulfonic or carboxylic resin feeding at the 10% dietary level in rats. A nine-month chronic toxicity study utilizing an ammonium sulfonate resin also yielded no toxic effects below the 15% dietary level (McChesney, 1952a).

In contrast to the above studies, Danowski, et al. (1951) reported that decreased serum sodium, increased serum chloride and metabolic acidosis (decreased serum carbon dioxide and pH) accompanied the feeding of hydrogen cycle carboxylic resins for 7 to 11 days. Martin (1955) concluded that the discrepancies here could be due to differences in composition of the diets used by the different sets of investigators. He does report that acidosis is a frequently cited accompaniment of cation exchange therapy in humans, but it is usually of the nontoxic, compensated form (i.e., neither symptoms nor pathological changes are evident).

A prime intention in the present study was to remove ingested sodium before it was absorbed into the animal's system. In selecting a cation exchange resin for this purpose, a variety of types and combinations were evaluated in order to find the one which would maximize the desired effect. After comparing several ion exchangers McChesney & McAuliff (1950) reported that generally only 20-25% of a resin's theoretical capacity was utilized in vivo. All of the exchangers tested did bind sodium and potassium in the intestine in the ratio of about 2:1 even though the dietary ratio of these cations was either 3:2 or 2:2. Fecal sodium and potassium content was increased by the resin while urine content was decreased. These results were substantiated by Ch'en & Freeman (1950) who found additionally that a high calcium diet interfered with the uptake of both sodium and potassium by the resin. Martin, et al. (1953) used

ethylenediaminetetraacetic acid (EDTA), a polyvalent cation chelator, in an attempt to overcome this interference effect. Fed at the 1% dietary level, EDTA increased significantly the monovalent cation-removing capacity of a carboxylic cation exchanger.

Several investigators (McChesney, et al., 1953; Root, 1953) have explored the concomitant use of an anion exchanger in attempting to increase the sodium removing efficiency of cation resins in vivo. Their results indicate that significant amounts of anions were not removed and that the sodium binding capacity of the resin was not increased in rats.

Ch'en & Freeman (1950) studied the effect of diet-sodium level on cation removal capacity of sulfonic exchangers. When the level of sodium in the diet was high (1% NaCl), these resins increased the percentage of ingested sodium normally found in the feces of rats by 14 to 25%. With a low sodium diet, this measure increased to 29 to 45%. Fecal potassium levels were not appreciably affected by the sodium content of the diet. In the salt-free diet case, negative balances of sodium, potassium and calcium were elicited in both resin and control animals. The amount of sodium and potassium found in the feces of the resin-fed animals, however, was approximately 26 and 14 times that of controls, respectively. Root (1953) also found that decreasing diet sodium content, while decreasing the amount of sodium bound by a carboxylic resin, increased the percentage of ingested sodium removed.

Several investigators (McChesney & McAuliff, 1950; McChesney, 1951, 1952b; McChesney, et al., 1951, 1953; Root, 1953) have compared the capacities of sulfonic vs. carboxylic exchangers. The in vitro capacity of carboxylic resins to bind cations is approximately twice that of the sulfonic resins. Nevertheless, McChesney, et al. (1953) found the

sulfonic types were more efficient *in vivo* (in terms of percentage of theoretical capacity). Conversely, Root (1953) reported *in vivo* sodium-binding capacities of some carboxylic resins which were two to three times greater than those of some of the sulfonic resins tested. In another study, approximately equal sodium-binding capacities were found for the two types (with the sulfonic holding a slight edge) (McChesney, 1952b). McChesney, *et al.* (1953) compared the *in vivo* sodium- and potassium-binding powers of three sulfonic and three carboxylic resins fed at the 10% level. The results indicate the average capacity of the sulfonic resins (1.52 mEq/g) was greater than that of the carboxylic (1.27 mEq/g). Further, although potassium removal capacity was approximately equal, the sulfonic types demonstrated a greater selectivity for sodium. In addition, the work of the McChesney group seems to indicate that the sulfonic types tend to lose less of their capacity than the carboxylic types when used in conjunction with a low sodium diet (Martin, 1955).

It is extremely difficult to derive generalizations from the work of these various researchers because there is little consistency among them with respect to brand (e.g., Dowex 50, Win 300), cycle (e.g., H^+, NH_3^+, K^+, or combinations) and dietary level used. This is sometimes the situation even within a given experiment (see especially McChesney & McAuliff, 1950, and Root, 1953). Conflicting evidence exists as to the effect of percent dietary level of resin, at least within the 5% to 15% range (McChesney & McAuliff, 1950; McChesney, *et al.*, 1953). The particular cycle in which a resin is fed, however, does appear to be an important parameter in determining the capacity of the resin. Martin (1955) states that it is generally agreed that hydrogen cycle forms are of higher

capacity than the metallic cation forms.

A sulfonic resin (Dowex 50W - X8, H^+ cycle) was chosen for use in the present study because of the primary interest in removing ingested sodium. Sulfonic types begin the exchange process in the stomach before appreciable absorption occurs while carboxylic types must wait until they are passed to the more alkaline environment of the intestine (McChesney, 1951; McChesney, et al., 1953; Martin, 1955).

McChesney, et al. (1953) determined the in vivo bulking tendencies of resins by measuring the stool weights of patients both on and off diet resins. While all the resins tested caused some bulking and swelling, the sulfonic types caused only one fourth that of the carboxylic. Even though (or, perhaps, especially because) the effects of bulking have not been directly investigated in laboratory in vivo exchange studies, it would seem reasonable to control for them by having control animals ingest non-nutritive, non-exchanging bulk (e.g., cellulose) in place of resin. However, only two of the papers treated in the present review reported use of controls for bulk in the diet (see Ch'en & Freeman, 1950, and Martin, et al., 1953). Although sulfonic exchangers were used in one study and carboxylic in the other, both reported that equal quantities of roughage or resin were fed in the control and experimental diets, respectively. This procedure was also followed in the present experiments.

Statement of the Problem

It is obvious that under certain circumstances compensatory sodium chloride (NaCl) drinking can be delayed by the development of an aversion to NaCl or a preference for a more palatable solution than NaCl. It is possible that other manipulations are also effective in this regard.

Epstein & Stellar (1955) introduced a cation exchange resin into the diet of adrenalectomized rats in order to reduce absorption of ingested sodium. Thus, the palatability of the NaCl solution (3%) remained the same, while the need-alleviating capacity (reinforcement value) of a given quantity of ingested NaCl was reduced. The adrenalectomized rats so treated promptly increased their intake of NaCl so that approximately the same amount of sodium was absorbed by the body (as determined by estimates of the resin's sodium-binding capacity) as occurred before the resin was added to the diet. Presumably, the animals drank to supply themselves with a constant amount of sodium. Similarly, Harriman (1967) found that sodium-deprived adrenalectomized rats took in a given amount of sodium regardless of the concentration of the available NaCl solution.

Epstein & Stellar's (1955) adrenalectomized rats had experience with the need-alleviating quality of NaCl ingestion for several days prior to the introduction of the resin. In light of Mook's (1969) finding that volume intake is primarily determined by postingestional (feedback) effects, it is conceivable that this experience was necessary for the increased NaCl intake following resin ingestion. The present study was designed to test the hypothesis that sodium appetite may develop inadequately for an available sodium source when rats are depleted of sodium through (1) adrenalectomy and (2) a Na-free diet under the conditions of greatly reduced need alleviation resulting from addition of a cation exchange resin to the diet immediately following surgery.

CHAPTER II

METHOD

0.25M NaCl Experiment

Subjects

Fifty-three naive male Holtzman rats, 50 days of age, were randomly assigned to five groups such that each experimental group contained 10 subjects (Ss) and the remaining made up a pool of supplemental animals. Subjects were maintained in a Percival environmental chamber and were housed individually in cages measuring either 20.3 X 27.3 X 20.3 cm or 22.9 X 38.1 X 19.7 cm in inside dimensions. (The proportion of animals in each type of cage was the same for all groups.) Food and fluid were available ad libitum. The ambient temperature and humidity averaged 25°C and 51%, respectively, and the chamber was lighted from 8:00 am to 8:00 pm daily.

Procedures

Pretest Period. During 10 Pretest days, all Ss were given a basic mash derived on the basis of Harriman's (1969) study of self-selection of diet in the laboratory (Holtzman) rat (see Table Ia). A metal cup with a 1 1/2 inch hole in the lid held the food in each cage. Distilled water and a 0.25M NaCl solution were presented in a pair of 140ml calibrated Richter-type drinkers attached to the front of each cage. The relative

TABLE I

CONSTITUENT COMPOSITION OF THE PRETEST DIET (BASIC) AND TWO TEST DIETS (RESIN AND CELLULOSE)

Component	Percentage Composition		
	a. Basic	b. Resin	c. Cellulose
[1]NBC "vitamin free" casein	27.0	22.0	22.0
Sucrose	57.0	50.0	50.0
Wesson oil	12.0	11.0	11.0
[1]NBC vitamin diet fortification mixture	2.0	2.0	2.0
[2]GBI Na-deficient salt mix + 0.4% NaCl	2.0	-	-
[3]Dowex 50W-X8 (H^+ cycle; 1/2 100-200 mesh, 1/2 200-400 mesh)	-	14.0	-
[4]EDTA acid	-	1.0	-
[2]GBI non-nutritive fiber (cellulose type)	-	-	15.0

[1]Nutritional Biochemical Corporation.

[2]General Biochemicals.

[3]J. T. Baker Chemical Company.

[4]Fisher Scientific.

position of tubes was alternated every 24 hours to distribute the effects of possible position habits across the two solutions. Clean tubes containing fresh fluids were provided every 48 hours.

Body weight and 24-hour intake data were recorded at approximately 3:25 pm daily. Body weights were measured to the nearest 0.5g, and food intakes (corrected for spillage) were determined to the nearest 0.1g. Fluids were measured in ml, and control drinkers were used to correct for evaporation.

After the data were collected on the 10th Pretest day, all Ss were subjected to either bilateral adrenalectomy (two Adx groups) or sham-operation (two Sham groups) under ether anesthesia. The surgical procedure followed that of Bare (1949). Subjects were then returned to the individual cages. Experimental Ss which died during surgery or within the 48 hours following were replaced from the pool of supplemental Ss.

Test Period. Following surgery, the animals were entered into an additional 10-day period of Richter-type drinking tests. The diet fed to the rats was changed from that used in the Pretest. Other elements of the procedure were the same as those followed in the Pretest. The diet fed to one Adx group and to one Sham group contained 14.0% hydrogen cycle cation exchange resin and 1.0% EDTA (ethylenediaminetetraacetic acid) (see Resin Diet, Table Ib). The diet fed to the remaining Adx and Sham groups contained 15.0% nonnutritive bulk in lieu of the ion exchanger and EDTA (see Cellulose Diet, Table Ic). Also, both diets lacked the mineral mix present in the food fed during Pretest.

Posttest Period. Following testing, a bioassay was performed to

measure completeness of the adrenalectomies. In the bioassay, all Ss were fed only the original diet used in the Pretest plus distilled water ad libitum. Body weights only were recorded daily for seven days. An S was considered to have been completely adrenalectomized if body weight on the 7th Posttest day was at least 0.5g below the last preoperative weight (i.e., weight on Pretest Day 10). Subjects failing to meet this criterion were discarded, and rats from the supplemental pool were used as replacements.

Elemental Determinations

In order to determine whether the diet containing the ion exchange resin was effective in binding Na^+ ions in the rats' intestines, feces samples were collected from the cage of each animal on the seventh Test day and analysed for Na concentration. The concentrations of potassium (K), calcium (Ca), and magnesium (Mg) were also determined.

Samples were prepared according to the procedure of Black (1965), with one exception: sulfuric acid was eliminated from the digestion mixture (see Appendix D for specific procedures used here). After preparation, the samples were diluted with distilled, demineralized water and analysed for the presence of the elements under consideration by means of the Perkin-Elmer Atomic Absorption Spectrophotometer 303. The results of each analysis were then expressed in terms of mEq per g of feces.

Statistical Analysis

Each phase of the experiment was analysed separately as a three-factor experiment with repeated measures on one factor--Winer's Case II (Winer, 1971, pp. 559-571) (see Appendix E for the model and analysis of

variance summary table underlying the design). This model requires that the order of presentation of the levels of the repeated factor, in this case Days, be randomized separately for each S. Because it was impossible to randomize the order of presentation of Days and, therefore, to meet this requirement, heterogeneity of the variance-covariance matrices possibly resulted. Such heterogeneity violates the model's compound symmetry assumption and lends a positive bias to the F tests of both the repeated factor and interactions involving this factor. To overcome the bias, the Greenhouse-Geisser conservative procedure was used for the purpose of modifying the critical values (by lowering the degrees of freedom) for those F tests (Appendix E; see also Winer, 1971, pp. 523-524, and Kirk, 1968, pp. 287-288).

Biomedical Computer Program No. BMD01D (Dixon, 1970, pp. 42-48) was used for computation of means and standard deviations. Biomedical Computer Program No. BMD02V (Dixon, 1970, pp. 495-510), modified according to Clifford (1968) for this design, was used for the analyses of variance. Significant interactions were explored using simple effects and Newman-Keuls procedures.

0.50M NaCl Experiment

Subjects

Fifty-eight naive male Holtzman rats, 50 days old, were assigned to groups in the same manner as in the 0.25M NaCl experiment.

Procedures

The concentration of the NaCl solution used in this experiment was 0.50M. Other procedures were identical to those followed in the 0.25M NaCl experiment.

CHAPTER III

RESULTS

Elemental Determinations

Table II contains the group mean concentrations (in mEq/g) of each of the elements determined from the fecal samples on Day 7 of Test. (The mean scores for the Adx-Resin group were used as the scores for the animal in that group which died after the fourth Test day in the 0.50M NaCl experiment.) Two X two analyses of variance (ANOVA's) were used to an analyse the data on each element.

0.25M NaCl Experiment

Significant Diet effects were found in the ANOVA's on each element (Tables III-VI). From Table II it can be seen that the level of Na was higher than the other elements in all groups, and this concentration difference was greatly magnified in the Resin groups. The fecal concentrations of K, Ca and Mg were also greater in the Resin groups than in the Cellulose groups. In addition, K levels were found to be significantly higher in Adx animals than in the Sham-operates ($p < .05$).

0.50M NaCl Experiment

As in the 0.25M NaCl experiment, levels of all elements were higher in feces of animals fed the Resin diet (Tables VII-X), and Na was the element with the highest concentration in all groups (Table II).

TABLE II

FECAL ELEMENTS (mEq/g FECES) ON TEST DAY SEVEN

Experiment	Group	Na		K		Ca		Mg	
		M	SD	M	SD	M	SD	M	SD
0.25M NaCl	Adx-Resin	1.70	0.47	0.32	0.09	0.30	0.14	0.21	0.07
	Adx-Cellulose	0.18	0.06	0.02	0.01	0.02	0.01	0.02	0.01
	Sham-Resin	1.67	0.49	0.21	0.15	0.24	0.14	0.22	0.07
	Sham-Cellulose	0.21	0.10	0.01	0.00	0.01	0.01	0.02	0.00
0.50M NaCl	Adx-Resin	1.48	0.26	0.27	0.06	0.35	0.11	0.25	0.04
	Adx-Cellulose	0.14	0.08	0.02	0.02	0.03	0.01	0.02	0.00
	Sham-Resin	1.46	0.44	0.38	0.12	0.30	0.11	0.35	0.12
	Sham-Cellulose	0.14	0.06	0.02	0.00	0.01	0.00	0.03	0.00

TABLE III

SUMMARY OF THE ANALYSIS OF VARIANCE ON FECAL Na (mEq/g FECES) ON TEST DAY SEVEN - 0.25M NaCl EXPERIMENT

Source	Degrees of Freedom	SS	MS	F	p
Surgery	1	0.000	0.000	0.000	
Diet	1	22.255	22.255	199.174	.01
Surgery X Diet	1	0.010	0.010	0.088	
Within Cell	36	4.224	0.117		
Total	39	26.489			

TABLE IV

SUMMARY OF THE ANALYSIS OF VARIANCE ON FECAL K (mEq/g FECES) ON TEST DAY SEVEN - 0.25M NaCl EXPERIMENT

Source	Degrees of Freedom	SS	MS	F	p
Surgery	1	0.035	0.035	4.64	.05
Diet	1	0.597	0.597	79.26	.01
Surgery X Diet	1	0.026	0.026	3.44	.10
Within Cell	36	0.271	0.008		
Total	39	0.929			

TABLE V

SUMMARY OF THE ANALYSIS OF VARIANCE ON FECAL Ca (mEq/g FECES) ON TEST DAY SEVEN - 0.25M NaCl EXPERIMENT

Source	Degrees of Freedom	SS	MS	F	p
Surgery	1	0.010	0.010	1.07	
Diet	1	0.643	0.643	65.04	.01
Surgery X Diet	1	0.007	0.007	0.74	
Within Cell	36	0.356	0.010		
Total	39	1.016			

TABLE VI

SUMMARY OF THE ANALYSIS OF VARIANCE ON FECAL Mg (mEq/g FECES) ON TEST DAY SEVEN - 0.25M NaCl EXPERIMENT

Source	Degrees of Freedom	SS	MS	F	p
Surgery	1	0.000	0.000	0.23	
Diet	1	0.393	0.393	154.21	.01
Surgery X Diet	1	0.000	0.000	0.216	
Within Cell	36	0.0092	0.002		
Total	39	0.486			

TABLE VII

SUMMARY OF THE ANALYSIS OF VARIANCE ON FECAL Na (mEq/g FECES) ON TEST DAY SEVEN - 0.50M NaCl EXPERIMENT

Source	Degrees of Freedom	SS	MS	F	p
Surgery	1	0.001	0.001	0.01	
Diet	1	17.788	17.788	260.01	.01
Surgery X Diet	1	0.001	0.001	0.01	
Within Cell	36	2.463	0.068		
Total	39	20.252			

TABLE VIII

SUMMARY OF THE ANALYSIS OF VARIANCE ON FECAL K (mEq/g FECES) ON TEST DAY SEVEN - 0.50M NaCl EXPERIMENT

Source	Degrees of Freedom	SS	MS	F	p
Surgery	1	0.028	0.028	6.42	.05
Diet	1	0.953	0.953	218.00	.01
Surgery X Diet	1	0.035	0.035	7.95	.01
Within Cell	36	0.157	0.004		
Total	39	1.173			

TABLE IX

SUMMARY OF THE ANALYSIS OF VARIANCE ON FECAL Ca (mEq/g FECES) ON TEST DAY SEVEN - 0.50M NaCl EXPERIMENT

Source	Degrees of Freedom	SS	MS	F	p
Surgery	1	0.009	0.009	1.52	
Diet	1	0.949	0.949	159.27	.01
Surgery X Diet	1	0.002	0.002	0.27	
Within Cell	36	0.215	0.006		
Total	39	1.174			

TABLE X

SUMMARY OF THE ANALYSIS OF VARIANCE ON FECAL Mg (mEq/g FECES) ON TEST DAY SEVEN - 0.50M NaCl EXPERIMENT

Source	Degrees of Freedom	SS	MS	F	p
Surgery	1	0.028	0.028	7.15	.05
Diet	1	0.735	0.735	186.13	.01
Surgery X Diet	1	0.023	0.023	5.89	.05
Within Cell	36	0.142	0.004		
Total	39	0.929			

Significant Surgery and Surgery X Diet interaction effects were found for both K and Mg in this experiment. Simple effects on the interaction in the K data reveal that K levels were significantly higher in the Sham-Resin animals than in the Adx-Resin animals (Table XI). The K levels in the two Cellulose groups were the same. Similarly, a higher Mg concentration was found in the Sham-Resin as opposed to the Adx-Resin groups (Table XII).

Body Weights

0.25M NaCl Experiment

Pretest. At the beginning of the experiment, the average body weight of all the rats (50 days of age) was 206.0g (range, 108.5 - 245.5). The ANOVA indicated no significant differences between the groups on any of the days during this period (Table XLII, Appendix F). The F value for the repeated factor, Days, was significant at the 0.01 probability level, indicating a significant gain in weight by all groups. The average weight on the last day of the period was 272.4g (range 187.5 - 310.0).

Test. Figure 1 shows the average body weight for each group on the last day of the Pretest period, the ten days of Test, and the seven Post-test days. From Figure 1, it appears that the Sham-operated animals were heavier than the Adx animals during Test; however, the F test for this factor was not significant (Table XIII). The Surgery X Days interaction was significant, and simple effects tests were performed in order to isolate the source of the interaction (Table XIV). The simple effects between Surgery conditions were not signficant for even the day on which the largest difference in body weight was obtained (Day 10). For each

TABLE XI

AOV: SIMPLE EFFECTS OF THE SURGERY X DIET INTERACTION ON FECAL K (mEq/g FECES) ON TEST DAY SEVEN - 0.50M NaCl EXPERIMENT

Source	Degrees of Freedom	MS	F	p
Between Surgery W. Diet - Resin	1	0.063	14.33	.01
Between Surgery W. Diet - Cellulose	1	0.000	0.04	
Between Diet W. Surgery - Adrenalectomy	1	0.312	71.34	.01
Between Diet W. Surgery - Sham-Operation	1	0.676	154.61	.01

TABLE XII

AOV: SIMPLE EFFECTS OF THE SURGERY X DIET INTERACTION ON FECAL Mg (mEq/g FECES) ON TEST DAY SEVEN - 0.50M NaCl EXPERIMENT

Source	Degrees of Freedom	MS	F	p
Between Surgery W. Diet - Resin	1	0.051	13.02	.01
Between Surgery W. Diet - Cellulose	1	0.000	0.03	
Between Diet W. Surgery - Adrenalectomy	1	0.248	62.89	.01
Between Diet W. Surgery - Sham-Operation	1	0.510	129.135	.01

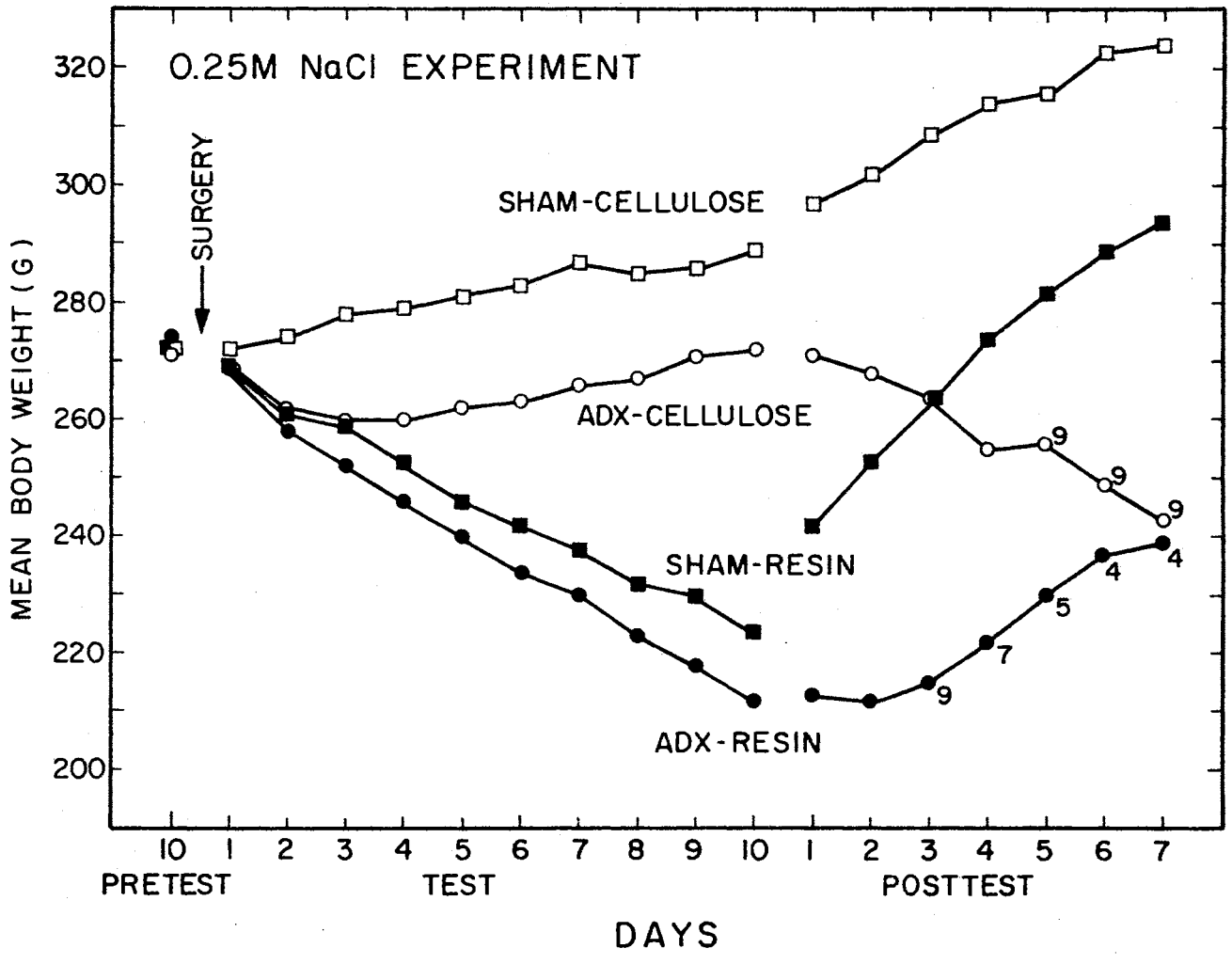

Figure 1. Mean Daily Body Weight on the Last Day of Pretest and on Each Test and Posttest Day in the 0.25M NaCl Experiment. n = 10, unless otherwise indicated.

TABLE XIII

SUMMARY OF THE ANALYSIS OF VARIANCE ON BODY WEIGHT (g)
DURING TEST - 0.25M NaCl EXPERIMENT

Source	Degrees of Freedom		SS	MS	F	p
Between Subjects	39		393,919.765			
Surgery	1		13,688.995	13,688.995	1.76	
Diet	1		98,000.295	98,000.295	12.59	.01
Surgery X Diet	1		2,052.124	2,052.124	0.26	
Subj. W. Groups	36		280,178.351	7,782.732		
	Conventional	Conservative				Conservative
Within Subjects	360		64,016.066			
Days	9	1	14,106.050	1,567.339	49.06	.01
Surgery X Days	9	1	1,372.106	152.456	4.77	.05
Diet X Days	9	1	37,857.202	4,206.355	131.66	.01
Surgery X Diet X Days	9	1	329.131	36.570	1.14	
Days X Subj. W. Groups	324	36	10,351.577	31.949		
Total	399		457,935.831			

TABLE XIV

AOV: SIMPLE EFFECTS OF THE SURGERY X DAYS INTERACTION ON BODY WEIGHT (g) DURING TEST - 0.25M NaCl EXPERIMENT

Source	Degrees of Freedom		MS	F	p (conservative)
Between Surgery W. Day 2	1		490.000	0.61	
Between Surgery W. Day 3	1		1,464.100	1.81	
Between Surgery W. Day 6	1		1,896.138	2.35	
Between Surgery W. Day 10	1		2,196.324	2.72	
	Conventional	Conservative			
Between Days W. Surgery - Adrenalectomy	9	1	1,278.952	40.03	.01
Between Days W. Surgery - Sham-Operation	9	1	428.894	13.424	.01

Surgery condition there was a significant ($p < .01$) difference between Days. For the Adx rats, a Newman-Keuls multiple comparison test revealed a significant drop in weight daily from Day 1 through Day 3. Thereafter, the weight loss was more gradual (Table XV). On the other hand, the Sham Ss maintained the same weight for the first four postoperative days and then slowly lost weight (Table XVI).

Simple effects tests exploring the Diet X Days interaction revealed that the Cellulose animals were significantly heavier than were the Resin animals after Day 4 (Table XVII). Each diet produced a significant ($p < .01$) change in body weight over days (i.e., the Cellulose groups gained weight while the Resin rats lost weight).

Posttest. Seven days after the removal of the NaCl solution and return to the basic diet (the conditions which define this period), five Adx-Cellulose rats were discarded for failure to meet the weight-loss criterion. No Adx-Resin animals were discarded for this reason.

Animals in the Adx-Resin group began dying after the second day of this period (Figure 1). Because of this, and in order to simplify the statistical procedures, the three-way ANOVA was performed on only the first two days (Table XVIII). Overall, the Sham groups were significantly heavier than the Adx groups (by approximately 30g), and the Cellulose animals were heavier than those receiving the Resin (by approximately 50g). In addition, the Sham animals gained a significant amount of weight from Posttest Day 1 to Day 2 (approximately 7g), while the Adx animals lost weight (approximately 2g) (simple effects for Surgery X Days interaction, Table XIX). The Resin animals gained weight during these two days ($p < .01$); however, the weight of those animals receiving Cellulose remained the same (Table XX).

TABLE XV

NEWMAN-KEULS TEST ON MEAN BODY WEIGHT (g) OF THE ADX RATS DURING THE TEN TEST DAYS - 0.25M NaCl EXPERIMENT

Days	10	9	8	7	6	5	4	3	2	1	r	$q_{.95}(r,36)$	$s_{\bar{b}}\, q_{.95}(r,36)$
Means	241.80	244.42	245.58	248.18	248.85	251.08	253.45	256.05	260.48	268.20			
10		2.62	3.78	*6.38	*7.05	*9.28	*11.65	*14.25	*18.68	*26.40	10	4.83	6.10
9			1.16	3.76	4.43	*6.66	*9.03	*11.63	*16.06	*23.78	9	4.72	5.97
8				2.60	3.27	*5.50	*7.87	*10.47	*14.90	*22.62	8	4.60	5.81
7					0.67	2.90	*5.27	*7.87	*12.30	*30.02	7	4.46	5.64
6						2.23	*4.60	*7.20	*11.63	*19.35	6	4.30	5.44
5							2.37	*4.97	*9.40	*17.12	5	4.10	5.18
4								2.60	*7.03	*14.74	4	3.84	4.85
3									*4.43	*12.15	3	3.49	4.41
2										* 7.72	2	2.89	3.65

$s_{\bar{b}} = 1.264$.

*$p < .05$, conservative test.

TABLE XVI

NEWMAN-KEULS TEST ON MEAN BODY WEIGHT (g) OF THE SHAM RATS DURING THE TEN TEST DAYS - 0.25M NaCl EXPERIMENT

Days	10	9	8	7	6	5	4	2	3	1	r	$q_{.95}(r,36)$	$s_{\bar{q}}{}_{\bar{b}.95}(r,36)$
Means	256.62	258.48	258.78	262.32	262.62	263.88	266.12	267.48	268.15	270.68			
10		1.86	2.16	*5.70	*6.00	*7.26	*9.50	*10.86	*11.53	*14.06	10	4.83	6.10
9			0.30	3.84	4.14	*5.40	*7.64	*9.00	*9.67	*12.20	9	4.72	5.97
8				3.54	3.84	*5.10	*7.34	*8.70	*9.37	*11.30	8	4.60	5.81
7					0.30	1.56	3.80	5.16	*5.83	*8.36	7	4.46	5.64
6						1.26	3.50	4.86	*5.53	*8.08	6	4.30	5.44
5							2.24	3.60	4.27	*6.80	5	4.10	5.18
4								1.36	2.03	4.56	4	3.84	4.85
2									0.67	3.20	3	3.49	4.41
3										2.53	2	2.89	3.65

$s_{\bar{b}} = 1.264$.

$p < .05$, conservative test.

TABLE XVII

AOV: SIMPLE EFFECTS OF THE DIET X DAYS INTERACTION ON BODY WEIGHT (g) DURING TEST - 0.25M NaCl EXPERIMENT

Source	Degrees of Freedom		MS	F	p (conservative)
Between Diet W. Day 2	1		714.030	0.88	
Between Diet W. Day 3	1		1,806.336	2.24	
Between Diet W. Day 4	1		4,008.008	4.97	.05
Between Diet W. Day 5	1		7,980.630	9.89	.01
	Conventional	Conservative			
Between Days W. Diet - Resin	9	1	5,478.372	171.47	.01
Between Days W. Diet - Cellulose	9	1	346.68	10.85	.01

TABLE XVIII

SUMMARY OF THE ANALYSIS OF VARIANCE ON BODY WEIGHT (g) DURING THE FIRST TWO DAYS OF POSTTEST - 0.25M NaCl EXPERIMENT

Source	Degrees of Freedom		SS	MS	F	p
Between Subjects	39		146,110.158			
Surgery	1		20,817.376	20,817.376	11.32	.01
Diet	1		58,996.925	58,996.925	32.08	.01
Surgery X Diet	1		87.231	87.231	0.05	
Subj. W. Groups	36		66,208.626	1,839.128		
	Conventional	Conservative				Conservative
Within Subjects	40		1,126.749			
Days	1	1	133.903	133.903	11.30	.01
Surgery X Days	1	1	458.403	458.403	38.68	.01
Diet X Days	1	1	73.179	73.179	6.17	.05
Surgery X Diet X Days	1	1	34.572	34.572	2.92	.10
Days X Subj. W. Groups	36	36	426.692	11.852		
Total	79		147,236.907			

TABLE XIX

AOV: SIMPLE EFFECTS OF THE SURGERY X DAYS INTERACTION ON BODY WEIGHT (g) DURING THE FIRST TWO DAYS OF POSTTEST - 0.25M NaCl EXPERIMENT

Source	Degrees of Freedom		MS	F	p (conservative)
Between Surgery W. Day 1	1		7,551.508	7.93	.01
Between Surgery W. Day 2	1		13,727.030	14.41	.01
	Conventional	Conservative			
Between Days W. Surgery - Adrenalectomy	9	1	49.000	4.13	.05
Between Days W. Surgery - Sham-Operation	9	1	543.178	45.83	.01

TABLE XX

AOV: SIMPLE EFFECTS OF THE DIET X DAYS INTERACTION ON BODY WEIGHT (g) DURING THE FIRST TWO DAYS OF POSTTEST - 0.25M NaCl EXPERIMENT

Source	Degrees of Freedom		MS	F	p (conservative)
Between Diet W. Day 1	1		13,418.129	14.09	.01
Between Diet W. Day 2	1		27,457.606	28.83	.01
	Conventional	Conservative			
Between Days W. Diet - Resin	1	1	202.500	17.08	.01
Between Days W. Diet - Cellulose	1	1	4.498	0.38	

0.50M NaCl Experiment

Pretest. At the beginning of this experiment, the average body weight of all the rats was 178.0g (range, 117.5 - 235.5). The ANOVA on body weight during this period revealed that although all Ss were treated identically during this period a significant ($p < .05$) Diet effect was obtained (Table XXI). That is, the animals which were designated to receive the Resin diet during Test were lighter than those due to receive the Cellulose diet. Since there was no Diet X Days interaction indicating a change in the relationship between the Diet groups over days, it appears that by chance lighter animals were assigned to the Resin groups than to the Cellulose diet. The significant Days effect suggests that, regardless of starting weight, all Ss gained during Pretest, the average body weight on the last day (Day 10) being 243.9 (range, 176.5 - 319.0). The Cellulose animals weighed approximately 22g more than the Resin animals on the average at the end of this period.

Test. During the 0.50M NaCl experiment, analyses on body weight, and all other measures, utilized data from only the first seven days of Test. The reason for this was that after Day 7, animals in the Adx-Resin group started dying at a fairly regular rate thereby yielding an unequal number of subjects in each group. Since the trends in the data were well established by the end of the seventh day (see figures to follow), it was decided that in order to simplify statistical procedures, only data through Day 7 would be analysed.

An additional complication in this experiment was caused by the death of one Adx-Resin animal following Test Day 4. To avoid the statistical complexity caused by unequal groups, scores on all measures were

TABLE XXI

SUMMARY OF THE ANALYSIS OF VARIANCE ON BODY WEIGHT (g)
DURING PRETEST - 0.50M NaCl EXPERIMENT

Source	Degrees of Freedom		SS	MS	F	p
Between Subjects	39		455,890.341			
Surgery	1		7,160.454	7,160.454	0.64	
Diet	1		46,534.745	46,534,745	4.17	.05
Surgery X Diet	1		563.922	563.922	0.05	
Subj. W. Groups	36		401,631.220	11,156.423		
	Conventional	Conservative				Conservative
Within Subjects	400		195,327.670			
Days	10	1	182,643.061	18,264.306	545.60	.01
Surgery X Days	10	1	403.194	40.319	1.20	
Diet X Days	10	1	160.419	16.042	0.48	
Surgery X Diet X Days	10	1	71.569	7.157	0.21	
Days X Subj. W. Groups	360	36	12,049.427	33.471		
Total	439		651,218.001			

estimated for this animal on Days 4-7. These data were derived such that this animal's scores changed at the same rate and in the same direction as the mean of the scores from the remaining animals in the group changed. Even though S was still alive on Day 4, data on this day was estimated in order to avoid biasing the group mean with the abnormally low intake levels typical of dying animals.

Due to the significant difference in body weight between the Diet conditions at the end of Pretest, prior to any differential treatment, an analysis of covariance was performed on body weight during Test, using weight on the last day of Pretest as the covariate (Table XXII). Significant differences in body weight due to Diet, Surgery, Days and all interactions with Days were revealed. The direction of the differences were the same as those in the 0.25M NaCl experiment (Figure 2).

Posttest. Three Adx-Resin rats and eight Adx-Cellulose animals were discarded for failure to meet the weight-loss criterion.

Food(g)/100g Body Weight

0.25M NaCl Experiment

Pretest. Food intake, corrected for body weight, was not significantly different among groups (Table XLIII, Appendix F). The average daily amount, however, did decrease from 8.5g/100g on Day 1 to 5.9g/100g on Day 10 (Days, $p < .01$).

Test. During the Test period, the Adx animals ate significantly less than did the Sham animals ($p < .01$; Table XXIII). Similarly, the animals receiving the Resin diet ate significantly less on a g/100g basis than did those receiving the Cellulose diet ($p < .01$). The F test for

TABLE XXII

SUMMARY OF THE ANALYSIS OF VARIANCE AND COVARIANCE ON BODY WEIGHT (g) DURING THE FIRST SEVEN DAYS OF TEST - 0.50M NaCl EXPERIMENT

Source	Degrees of Freedom		SS	MS	F	p
Between Subjects	39		397,585.438			
Surgery	1		29,388.557	29,388.557	3.93	.10
Diet	1		97,299.714	97,299.714	13.03	.01
Surgery X Diet	1		2,027.536	2,027.536	0.27	
Subj. W. Groups	36		268,869.631	7,468.601		
	Conventional	Conservative				Conservative
Within Subjects	240		20,073.285			
Days	6	1	7,036.435	1,172.739	63.81	.01
Surgery X Days	6	1	1,599.302	266.550	14.50	.01
Diet X Days	6	1	6,701.784	1,116.964	60.99	.01
Surgery X Diet X Days	6	1	765.864	127.644	6.94	.05
Days X Subj. W. Groups	216	36	3,969.900	18.379		
Total			417,658.732			
Surgery (Adjusted)	1		7,516.640	7,516.640	28.18	.01
Diet (Adjusted)	1		16,155.720	16,155.720	60.56	.01
Surgery X Diet (Adjusted)	1		4,642.640	4,642.640	17.40	.01
Sub. W. Groups (Adjusted)	35		9,336.360	266.753		

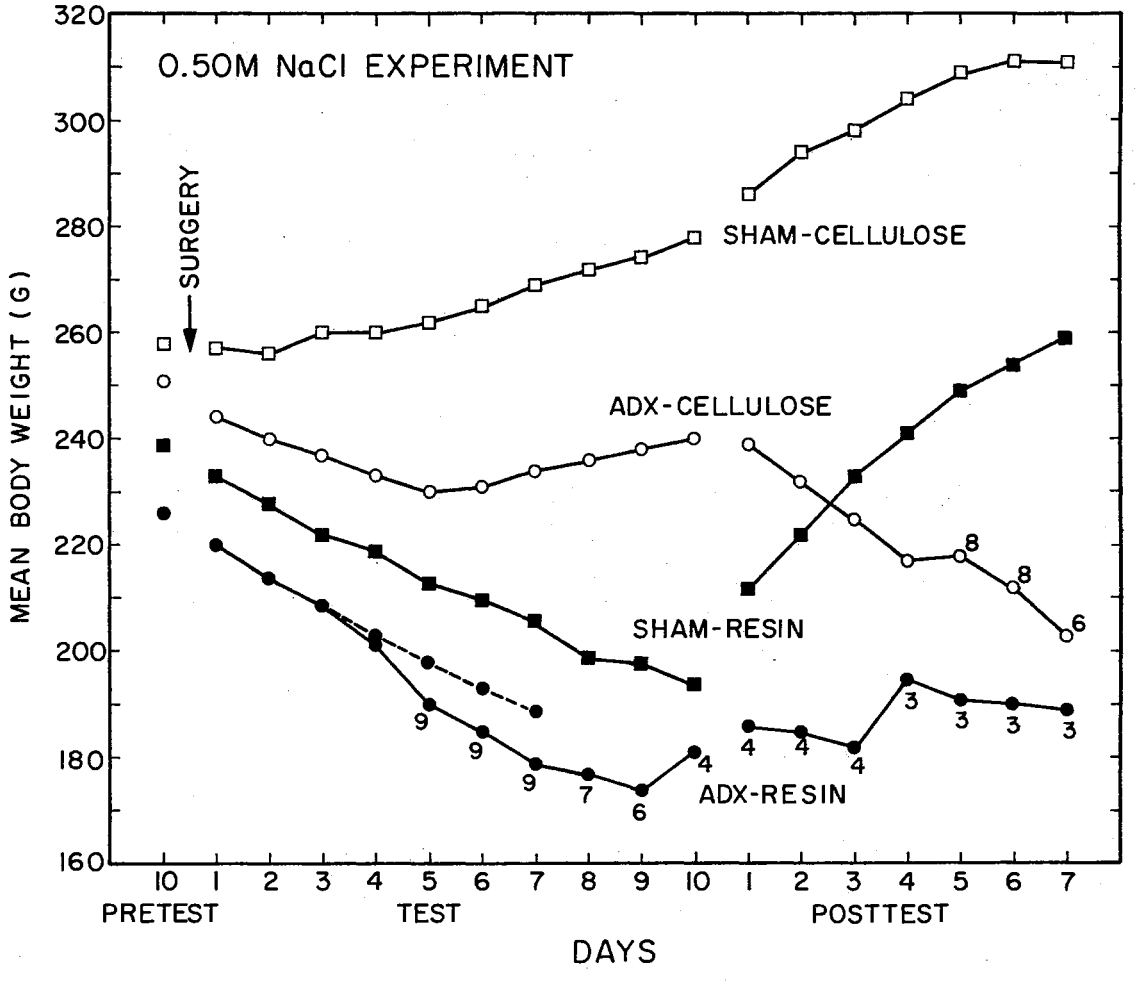

Figure 2. Mean Daily Body Weight on the Last Day of Pretest and on Each Test and Posttest Day in the 0.50M NaCl Experiment. n = 10, unless otherwise indicated; ●--●, points containing estimated data for one Adx-Resin S.

TABLE XXIII

SUMMARY OF THE ANALYSIS OF VARIANCE ON FOOD(g)/100g BODY WEIGHT DURING TEST - 0.25M NaCl EXPERIMENT

Source	Degrees of Freedom		SS	MS	F	p
Between Subjects	39		856.843			
Surgery	1		242.191	242.191	74.02	.01
Diet	1		496.722	496.722	151.81	.01
Surgery X Diet	1		0.120	0.120	0.04	
Subj. W. Groups	36		117.810	3.272		
	Conventional	Conservative				Conservative
Within Subjects	360		794.928			
Days	9	1	198.486	22.054	15.70	.01
Surgery X Days	9	1	58.140	6.460	4.60	.05
Diet X Days	9	1	49.882	5.542	3.94	.10
Surgery X Diet X Days	9	1	33.076	3.675	2.62	
Days X Subj. W. Groups	324	36	455.344	1.405		
Total	399		1,651.771			

Days was also significant, reflecting, perhaps, the small amount of food eaten by all Ss on the first day following surgery (Figure 3). Simple effects tests of the Surgery X Days interaction indicated that only on Day 7 were the Surgery groups not different (Table XXIV).

0.50M NaCl Experiment

Pretest. The average daily amount of food ingested decreased from 9.0g/100g on Day 1 to 6.3g/100g on Day 10 (Days, $p < .01$). No other tests in the ANOVA were significant (Table XLIV, Appendix F).

Test. Over the first seven days of the Test period, the Adx animals ate less than did the Shams, and the Resin groups ate less than did both Cellulose groups (Table XXV). In addition, a Surgery X Diet interaction existed, with the greatest difference in food intake between the Surgery groups being in those animals receiving the Cellulose diet (Table XXVI). As in the 0.25M NaCl experiment, only a small amount of food was eaten by all groups on the day following surgery (Days, $p < .01$; Figure 4). Simple effects tests of the Diet X Days interaction yielded significant differences between the Diet groups on all but Day 1 (Table XXVII).

Food Spillage

Rozin (1967) has pointed out that rats may spill unpalatable diets. Because of this, it was hoped that differential spillage might indicate the relative palatability of the diets. However, no significant treatment or interaction effects resulted from the analysis of the spillage data from either period of either experiment (Tables XLV-XLVIII, Appendix E). Nevertheless, the Ss in both experiments did spill more during the Test period than during Pretest.

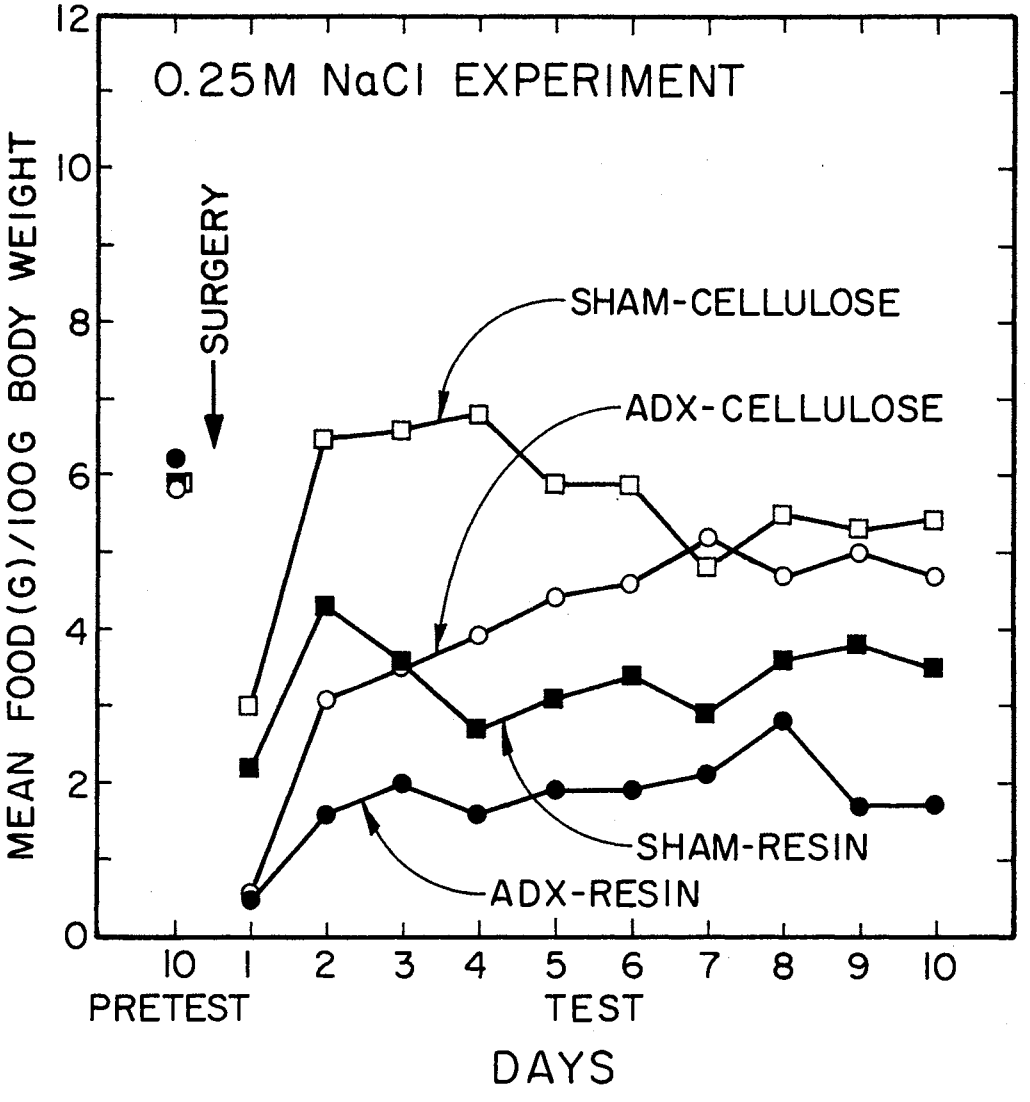

Figure 3. Mean Daily Food Intake on the Last Day of Pretest and on Each Test Day in the 0.25M NaCl Experiment. $\underline{n}$ = 10.

TABLE XXIV

AOV: SIMPLE EFFECTS OF THE SURGERY X DAYS INTERACTION ON FOOD(g)/100g BODY WEIGHT DURING TEST - 0.25M NaCl EXPERIMENT

Source	Degrees of Freedom	MS	F	p (conservative)
Between Surgery W. Day 1	1	41.616	25.50	.01
Between Surgery W. Day 4	1	36.864	22.59	.01
Between Surgery W. Day 7	1	0.484	0.30	
Between Surgery W. Day 8	1	7.056	4.32	.05
Between Surgery W. Day 9	1	14.161	8.68	.01

TABLE XXV

SUMMARY OF THE ANALYSIS OF VARIANCE ON FOOD(g)/100g BODY WEIGHT DURING THE FIRST SEVEN DAYS OF TEST - 0.50M NaCl EXPERIMENT

Source	Degrees of Freedom		SS	MS	F	p
Between Subjects	39		740.237			
Surgery	1		313.130	313.130	125.55	.01
Diet	1		287.883	287.883	115.43	.01
Surgery X Diet	1		49.438	49.438	19.82	.01
Subj. W. Groups	36		89.786	2.494		
	Conventional	Conservative				Conservative
Within Subjects	240		599.047			
Days	6	1	195.251	32.542	23.56	.01
Surgery X Days	6	1	26.200	4.367	3.16	.10
Diet X Days	6	1	55.910	9.318	6.75	.05
Surgery X Diet X Days	6	1	23.317	3.886	2.81	
Days X Subj. W. Groups	216	36	298.369	1.381		
Total	279		1,339.284			

TABLE XXVI

AOV: SIMPLE EFFECTS OF THE SURGERY X DIET INTERACTION ON FOOD(g)/100g BODY WEIGHT DURING THE FIRST SEVEN DAYS OF TEST - 0.50M NaCl EXPERIMENT

Source	Degrees of Freedom	MS	F	p
Between Surgery W. Diet - Resin	1	56.452	22.63	.01
Between Surgery W. Diet - Cellulose	1	306.656	122.96	.01
Between Diet W. Surgery - Adrenalectomy	1	48.734	19.54	.01
Between Diet W. Surgery - Sham-Operation	1	228.292	115.59	.01

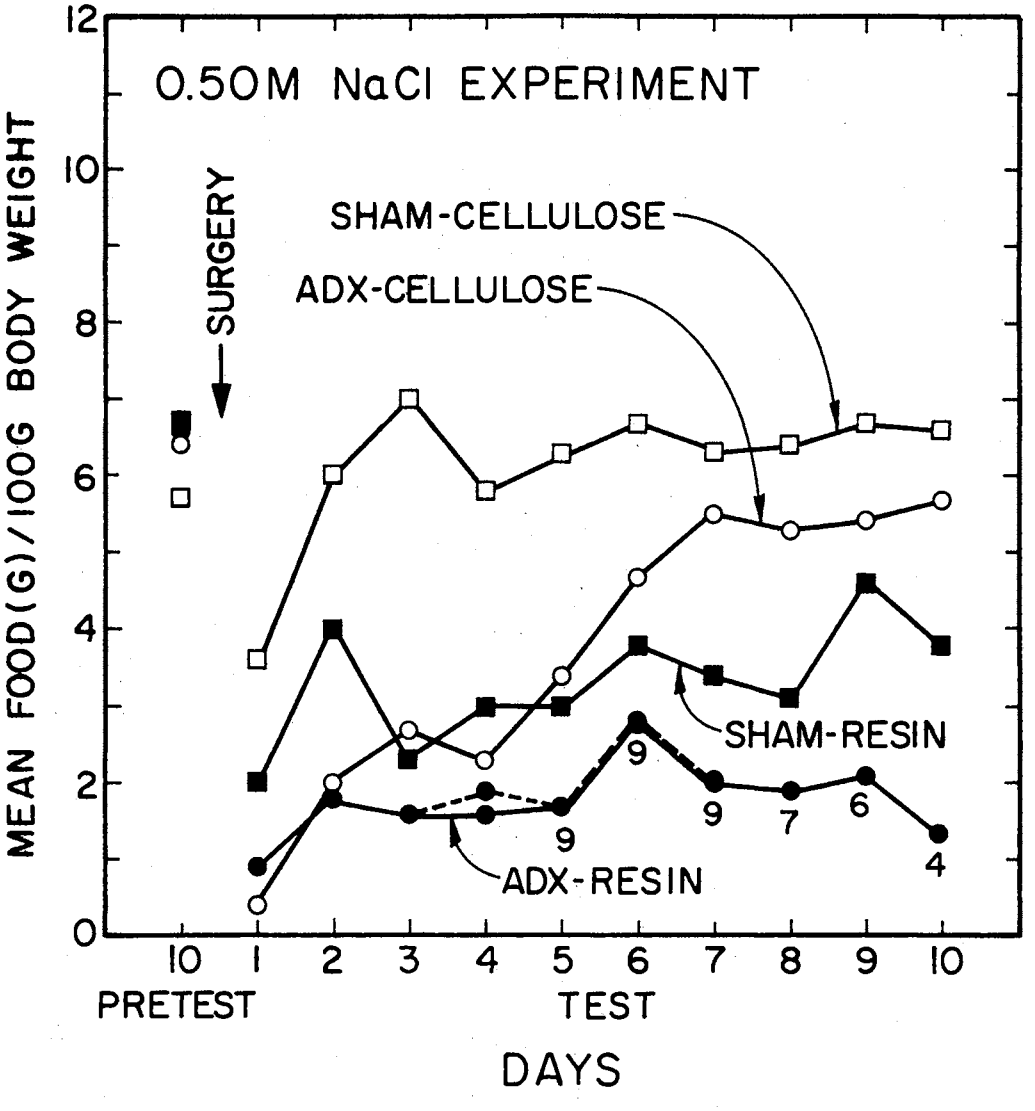

Figure 4. Mean Daily Food Intake on the Last Day of Pretest and on Each Test Day in the 0.50M NaCl Experiment. n = 10, unless otherwise indicated; ●--●, points containing estimated data for one Adx-Resin S.

TABLE XXVII

AOV: SIMPLE EFFECTS OF THE DIET X DAYS INTERACTION ON FOOD(g)/100g BODY WEIGHT DURING THE FIRST SEVEN DAYS OF TEST - 0.50M NaCl EXPERIMENT

Source	Degrees of Freedom	MS	F	p (conservative)
Between Diet W. Day 1	1	2.809	1.82	
Between Diet W. Day 2	1	11.200	7.27	.01
Between Diet W. Day 4	1	27.889	18.11	.01

Total Fluid(ml)/100g Body Weight

0.25M NaCl Experiment

Pretest. The average daily fluid intake in ml per 100g of body weight was 17.2ml (range, 3.2 - 48.4). All F tests in the ANOVA were nonsignificant (Table XLIX, Appendix F).

Test. As Figure 5 depicts, the Adx and Resin groups drank less fluid than did the Sham and Cellulose groups, respectively (both, $p < .01$). An overall increase in fluid intake is indicated by the significant Days factor in the ANOVA (Table XXVIII). Further, simple effects tests exploring the significant Diet X Days interaction show that while no difference in fluid intake occurred between the Diet groups during the first three days, afterwards the Cellulose groups drank significantly more fluid (Table XXIX). This is apparently due to the increasing intake levels of the Cellulose animals, while the Resin animals maintained approximately the same level. It should be noted that the increase in this measure was due to the increasing ingestion of both the NaCl solution and distilled water since the relative preference between these solutions did not change (see Figure 5).

0.50M NaCl Experiment

Pretest. The overall average daily fluid intake, corrected for body weight, during this period was 12.7ml (range, 4.2 - 37.3). None of the F tests were significant (Table L, Appendix F).

Test. As in the 0.25M NaCl experiment, the Sham groups drank more fluid than did the Adx groups ($p < .01$), and the Cellulose animals drank

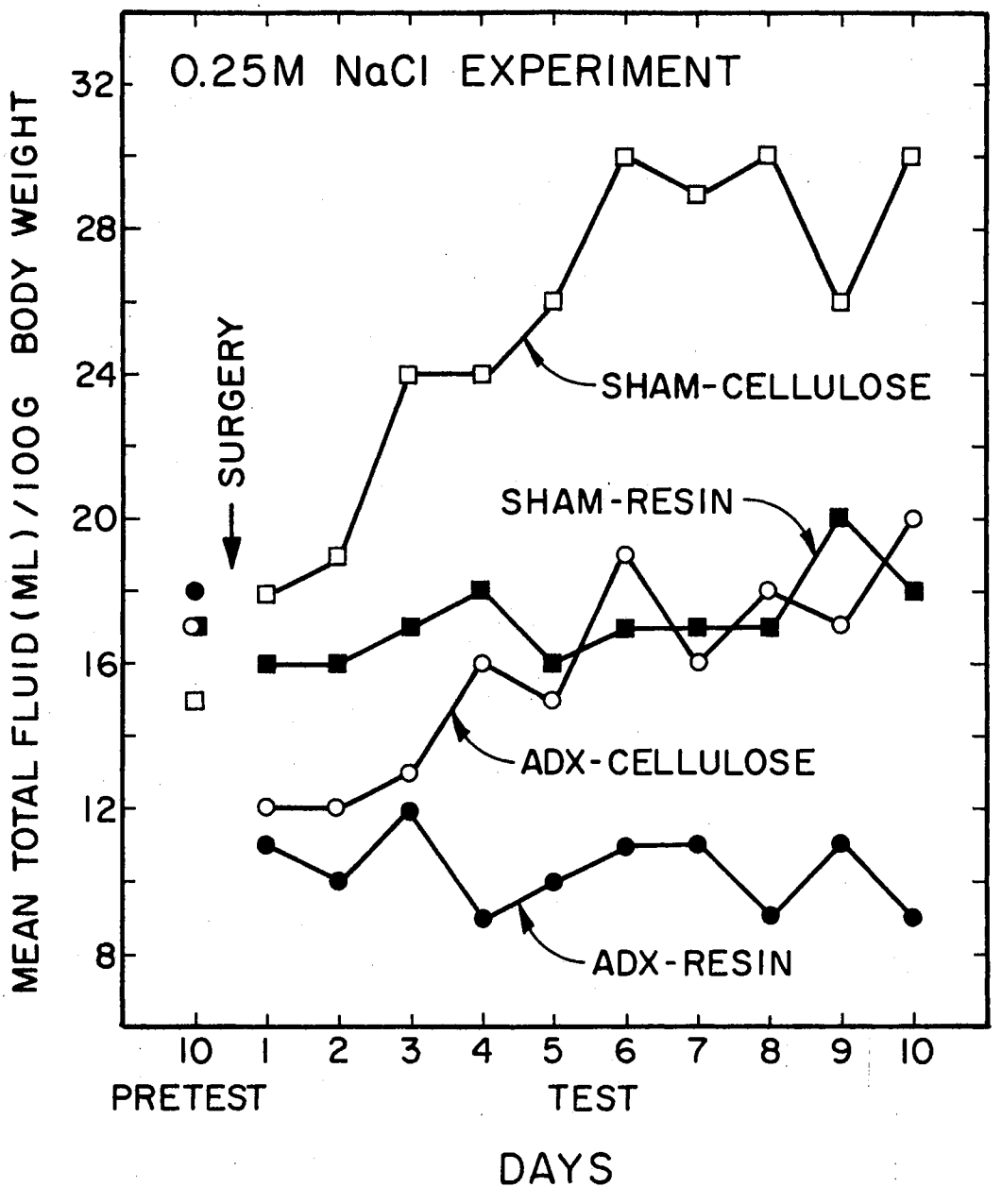

Figure 5. Mean Daily Total Fluid Intake (Distilled Water and 0.25M NaCl) on the Last Day of Pretest and on Each Test Day. $\underline{n}$ = 10.

TABLE XXVIII

SUMMARY OF THE ANALYSIS OF VARIANCE ON TOTAL FLUID(ml)/100g BODY WEIGHT DURING TEST - 0.25M NaCl EXPERIMENT

Source	Degrees of Freedom		SS	MS	F	p
Between Subjects	39		24,342.461			
Surgery	1		6,678.227	6,678.227	19.27	.01
Diet	1		4,939.681	4,939.681	14.21	.01
Surgery X Diet	1		213.132	213.132	0.61	
Subj. W. Groups	36		12,511.421	347.539		
	Conventional	Conservative				Conservative
Within Subjects	360		11,409.068			
Days	9	1	1,206.141	134.016	4.96	.05
Surgery X Days	9	1	172.698	19.189	0.71	
Diet X Days	9	1	1,101.556	122.395	4.53	.05
Surgery X Diet X Days	9	1	169.940	18.882	0.70	
Days X Subj. W. Groups	324	36	8,758.733	27.033		
Total	399		35,751.529			

TABLE XXIX

AOV: SIMPLE EFFECTS OF THE DIET X DAYS INTERACTION ON TOTAL FLUID(ml)/100g BODY WEIGHT DURING TEST - 0.25M NaCl EXPERIMENT

Source	Degrees of Freedom	MS	F	p (conservative)
Between Diet W. Day 1	1	17.689	0.30	
Between Diet W. Day 2	1	79.524	1.35	
Between Diet W. Day 3	1	161.604	2.74	
Between Diet W. Day 4	1	399.424	6.76	.05
Between Diet W. Day 5	1	667.489	11.30	.01
Between Diet W. Day 9	1	372.100	6.30	.05

more than the Resin ($p < .01$). In addition, the ANOVA showed a significant Surgery X Diet interaction (Table XXX). Simple effects indicated that Surgery produced no difference in fluid intake between groups fed the Resin diet, but a large difference obtained between groups receiving the Cellulose diet (Table XXXI). As Figure 6 shows, the levels of fluid intake by both Resin groups and the Adx-Cellulose group were about the same, while the Sham-Cellulose group drank considerably more.

NaCl(mg)/100g Body Weight

Since differences in body weight were expected, and did indeed occur, NaCl intake on each day was adjusted by the weight of the animal on that day. It was hoped that this procedure would lead to a more valid measure of NaCl intake by preventing the inflation of one group's scores due only to the greater weight of the rats therein. For the same reason, food intake and total fluid were adjusted in a similar manner.

0.25M NaCl Experiment

Pretest. The F tests for neither the main effects nor the interaction effects were significant (Table LI, Appendix F). The average daily amount of NaCl(mg)/100g body weight taken from the 0.25M NaCl solution was 161.5mg (range 0.0 - 661.1).

Test. The Surgery conditions did produce significant differences in this measure ($p < .01$; Table XXXII). Unexpectedly, it was the Sham animals which ingested more NaCl. The level of intake for these animals was similar to that during Pretest; however, that of the Adx animals appeared to be depressed (Figure 7). Although the F test for Days only approached significance ($p < .10$), there appeared to be a tendency for all Ss to

TABLE XXX

SUMMARY OF THE ANALYSIS OF VARIANCE ON TOTAL FLUID(ml)/100g BODY WEIGHT DURING THE FIRST SEVEN DAYS OF TEST - 0.50M NaCl EXPERIMENT

Source	Degrees of Freedom		SS	MS	F	p
Between Subjects	39		12,417.536			
Surgery	1		1,603.561	1,603.561	7.97	.01
Diet	1		2,423.141	2,423.141	12.05	.01
Surgery X Diet	1		1,150.305	1,150.305	5.72	.05
Subj. W. Groups	36		7,240.529	201.126		
	Conventional	Conservative				Conservative
Within Subjects	240		4,388.178			
Days	6	1	181.207	30.201	1.84	
Surgery X Days	6	1	211.824	35.304	2.15	
Diet X Days	6	1	255.399	42.566	2.60	
Surgery X Diet X Days	6	1	200.023	33.337	2.03	
Days X Subj. W. Groups	216	36	3,539.725	16.388		
Total	279		16,805.714			

TABLE XXXI

AOV: SIMPLE EFFECTS OF THE SURGERY X DIET INTERACTION ON TOTAL FLUID(ml)/100g BODY WEIGHT DURING THE FIRST SEVEN DAYS OF TEST - 0.50M NaCl EXPERIMENT

Source	Degrees of Freedom	MS	F	p
Between Surgery W. Diet - Resin	1	18.652	0.09	
Between Surgery W. Diet - Cellulose	1	2,735.096	13.60	.01
Between Diet W. Surgery - Adrenalectomy	1	117.212	0.58	
Between Diet W. Surgery - Sham-Operation	1	3,458.126	17.19	.01

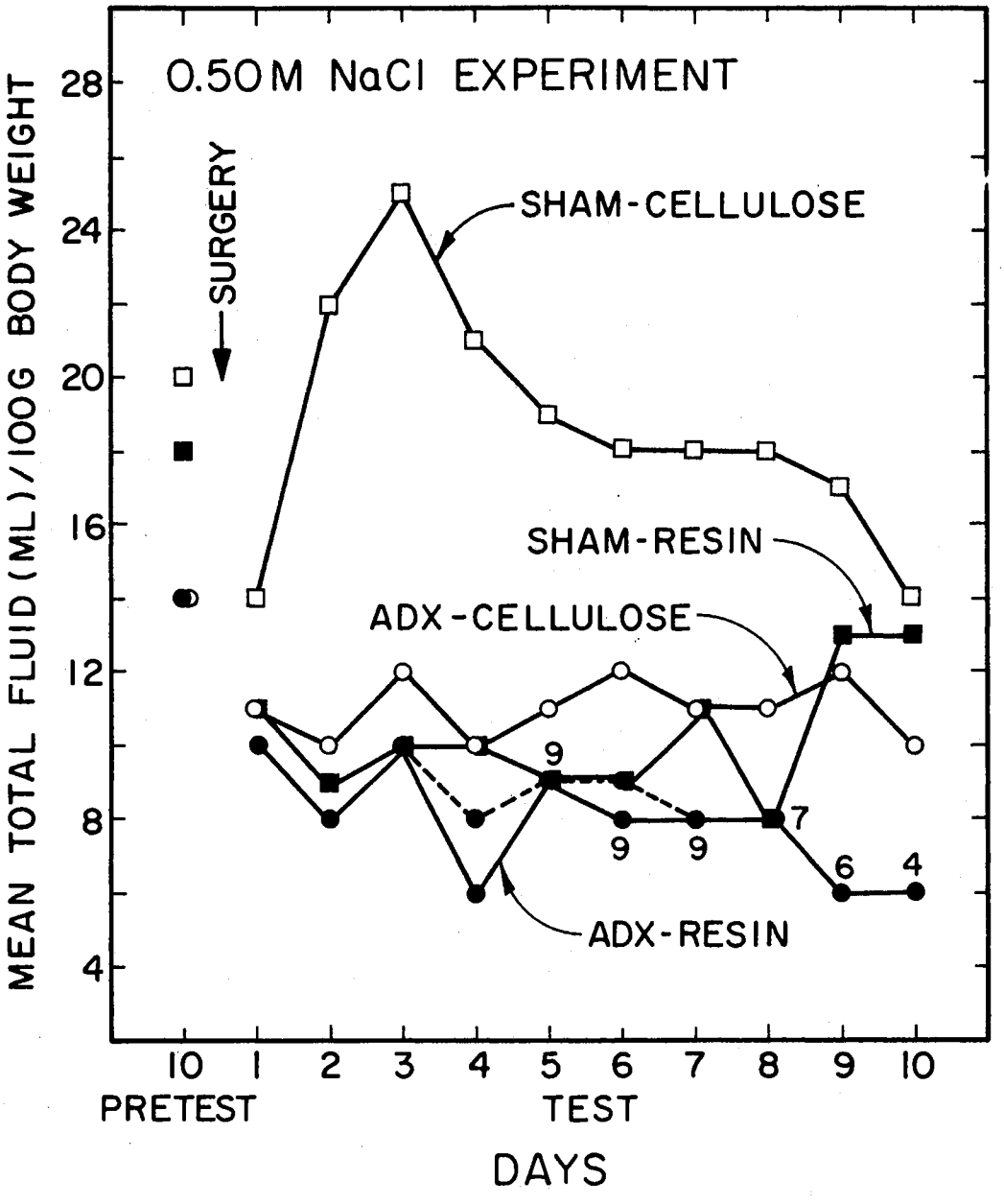

Figure 6. Mean Daily Total Fluid Intake (Distilled Water and 0.50M NaCl) on the Last Day of Pretest and on Each Test Day. n = 10, unless otherwise indicated; ●--●, points containing estimated data for one Adx-Resin S.

TABLE XXXII

SUMMARY OF THE ANALYSIS OF VARIANCE ON NaCl(mg)/100g BODY WEIGHT DURING TEST - 0.25M NaCl EXPERIMENT

Source	Degrees of Freedom		SS	MS	F	p
Between Subjects	39		2,276,714.999			
Surgery	1		381,197.360	381,197.360	7.51	.01
Diet	1		2,564.805	2,564.805	0.05	
Surgery X Diet	1		66,462.028	66,462.028	1.31	
Subj. W. Groups	36		1,826,490.806	50,735.856		
	Conventional	Conservative				Conservative
Within Subjects	360		1,418,057.112			
Days	9	1	114,872.603	12,763.621	3.44	.10
Surgery X Days	9	1	14,886.628	1,654.070	0.44	
Diet X Days	9	1	53,282.006	5,920.223	1.59	
Surgery X Diet X Days	9	1	32,062.505	3,562.500	0.96	
Days X Subj. W. Groups	324	36	1,202,953.370	3,712.819		
Total	399		3,694,772.111			

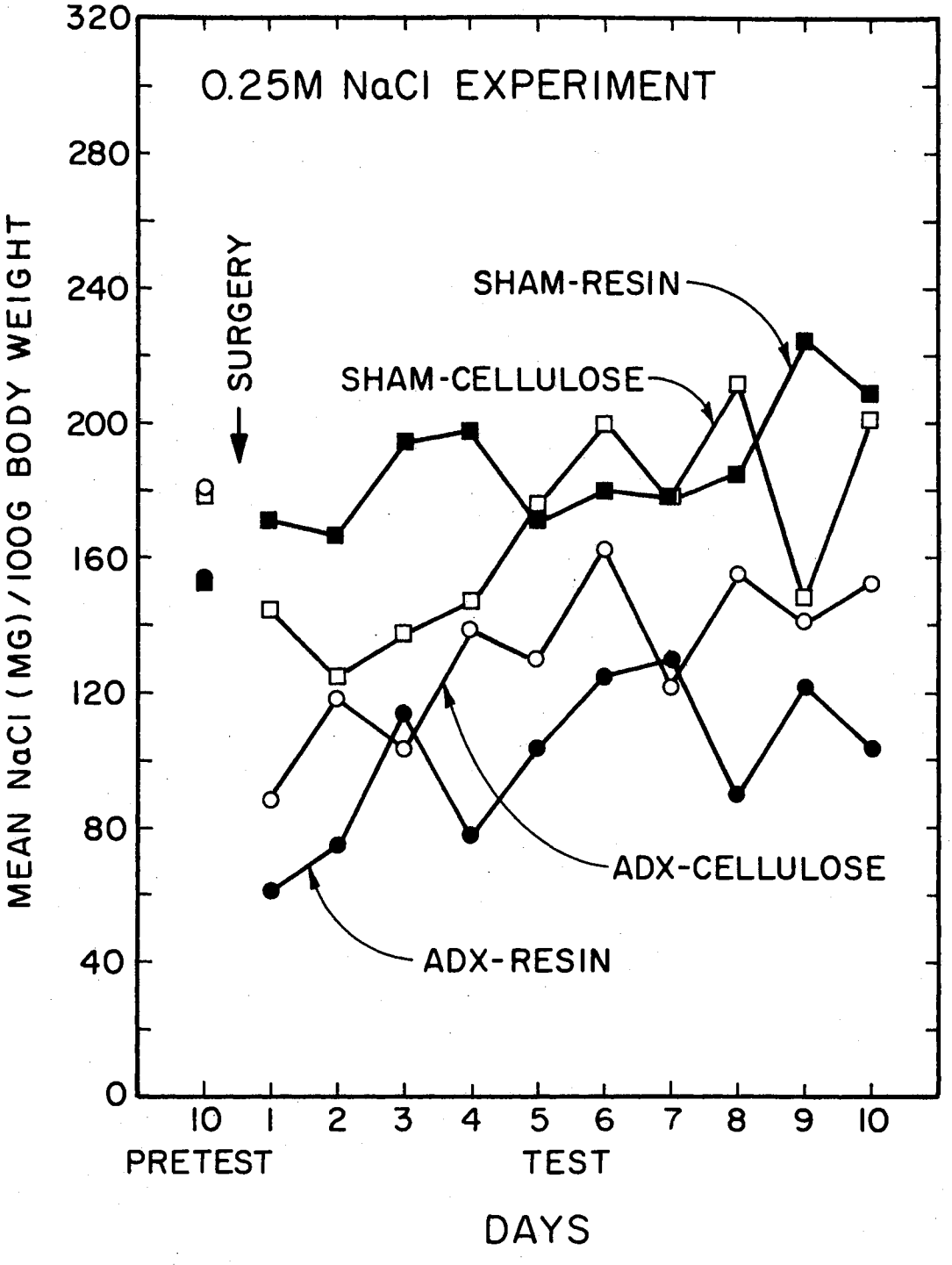

Figure 7. Mean Daily NaCl Intake From the 0.25M NaCl Solution on the Last Day of Pretest and on Each Test Day. $\underline{n}$ = 10.

increase daily NaCl intakes during the Test period.

0.50M NaCl Experiment

Pretest. ANOVA yielded no significant effects on this measure (Table LII, Appendix F). The average daily amount of NaCl(mg)/100g body weight ingested by means of the 0.50M NaCl solution was 62.1mg (range, 0.0 - 541.5).

Test. No differences due to the treatments or their interaction were found during the first seven days of this period (Table LIII, Appendix F). As in the 0.25M NaCl experiment, there was a slight tendency for all Ss to ingest more NaCl as the period progressed (Days, $p < .10$).

Comparison of NaCl(mg)/100g body weight intake on the average of Days 6 and 7 between the two experiments for each group yielded no significant differences. That is, when looking at the average intake for the sixth and seventh days following surgery and the presence of an adulterated diet, the performance of each Surgery-Diet combination was the same regardless of which concentration of NaCl was available, 0.25M or 0.50M.

% NaCl Solution Preference

This measure was determined by dividing the daily intake of the NaCl solution by the total daily fluid intake (NaCl solution and distilled water) and then multiplying by 100. While a value of 50% suggested indifference, values above and below that point were taken to represent preference and aversion, respectively (Kare, et al., 1957).

0.25M NaCl Experiment

Pretest. A moderate level of preference was exhibited daily by all groups throughout the entire period (mean, 58.5%; range, 0.0 - 100.0). The ANOVA yielded no significant effects (Table LIV, Appendix F).

Test. Significant differences between the Diet conditions were observed in this period (Table XXXIII). As can be seen from Figure 8, the Resin groups exhibited a greater preference overall (70.1%) than did the Cellulose groups (53.6%). It is interesting to note that there was no effect of adrenalectomy on preference for this NaCl concentration. The Surgery X Days interaction effect and the Days effect did approach significance (both, $p < .10$), reflecting, perhaps, the depressed preference of three of the groups, and especially the Adx-Resin animals, on the day following surgery. In Figure 8, it appears that a Surgery X Diet interaction was present over the last four days of Test. Results from an F test for the presence of the interaction indicated a nonsignificant effect.

0.50M NaCl Experiment

Pretest. Differences between the groups were not evident during this period (Table LV, Appendix F). The overall daily preference level (14.2%, range 0.0 - 87.3), indicated aversion to this concentration of NaCl.

Test. The ANOVA on the first seven days of this period revealed significant Surgery, Diet and Day effects (Table XXXIV). As Figure 9 shows, overall the Adx animals exhibited less of an aversion (26.9% preference) to 0.50M NaCl than the Sham (19.3% preference). Similarly, the Resin groups showed a 27.2% preference in comparison to 19.0% by the

TABLE XXXIII

SUMMARY OF THE ANALYSIS OF VARIANCE ON PERCENT NaCl PREFERENCE DURING TEST - 0.25M NaCl EXPERIMENT

Source	Degrees of Freedom		SS	MS	F	p
Between Subjects	39		170,104.443			
Surgery	1		257.838	257.838	0.07	
Diet	1		27,324.550	27,324.550	7.31	.05
Surgery X Diet	1		8,049.912	8,049.912	2.16	
Subj. W. Groups	36		134.472.143	3,735.337		
	Conventional	Conservative				Conservative
Within Subjects	360		84,407.812			
Days	9	1	5,826.364	647.374	3.28	.10
Surgery X Days	9	1	6,795.697	755.077	3.83	.10
Diet X Days	9	1	4,993.466	554.829	2.82	
Surgery X Diet X Days	9	1	2,960.863	328.985	1.67	
Days X Subj. W. Groups	324	36	63,831.422	197.010		
Total	399		254,512.255			

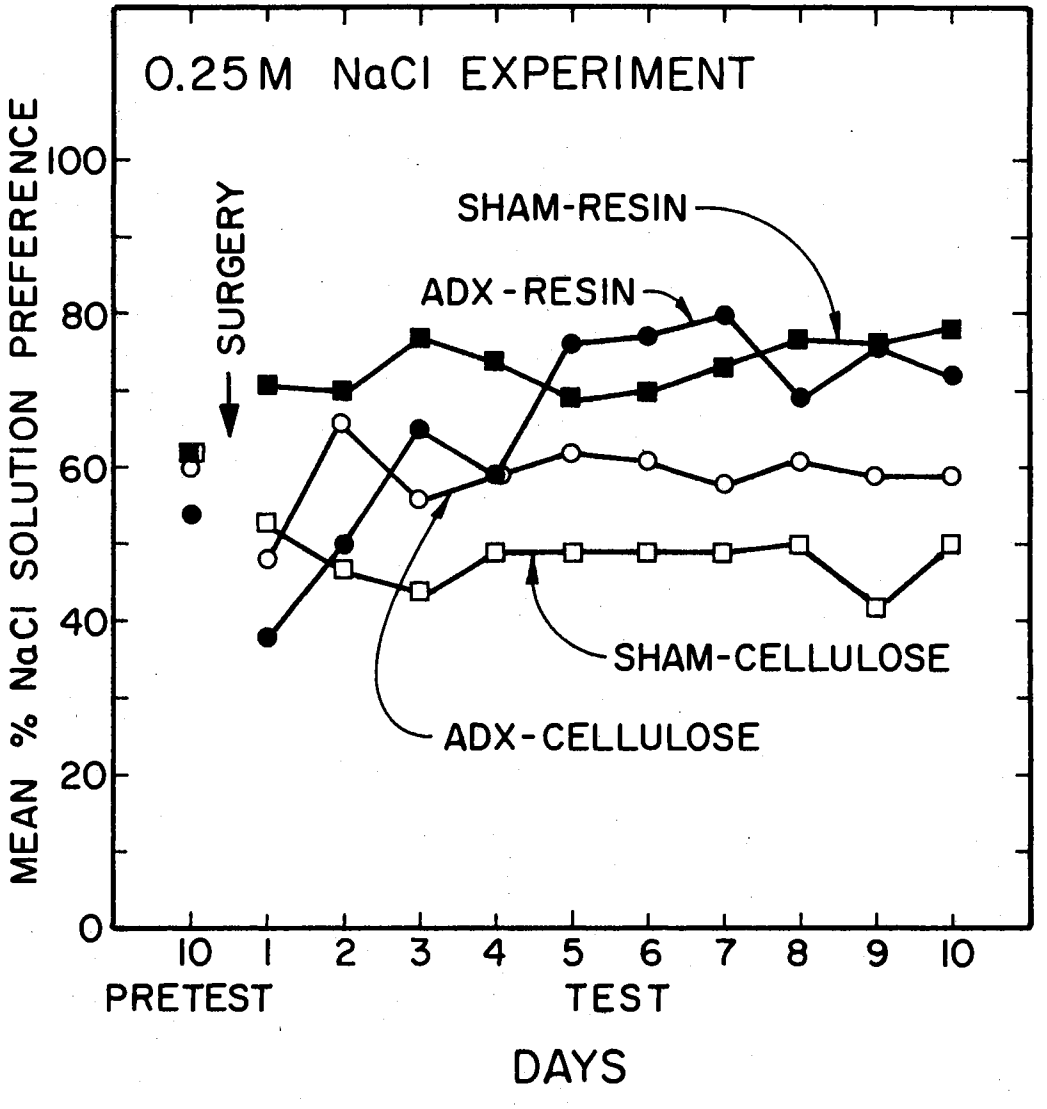

Figure 8. Mean Daily Percent of Preference for 0.25M NaCl Over Distilled Water on the Last Day of Pretest and on Each Test Day. n = 10.

TABLE XXXIV

SUMMARY OF THE ANALYSIS OF VARIANCE ON PERCENT NaCl PREFERENCE DURING THE FIRST SEVEN DAYS OF TEST - 0.50M NaCl EXPERIMENT

Source	Degrees of Freedom		SS	MS	F	p
Between Subjects	39		33,484.366			
Surgery	1		3,985.266	3,985.266	5.78	.05
Diet	1		4,652.707	4,652.707	6.74	.05
Surgery X Diet	1		11.802	11.802	0.02	
Subj. W. Groups	36		24,834.591	689.850		
	Conventional	Conservative				Conservative
Within Subjects	240		61,724.616			
Days	6	1	11,159.228	1,859.871	8.60	.01
Surgery X Days	6	1	2,140.728	356.788	1.65	
Diet X Days	6	1	312.402	52.067	0.24	
Surgery X Diet X Days	6	1	1,392.558	232.093	1.07	
Days X Subj. W. Groups	216	36	46,719.640	216.295		
Total	279		95,208.982			

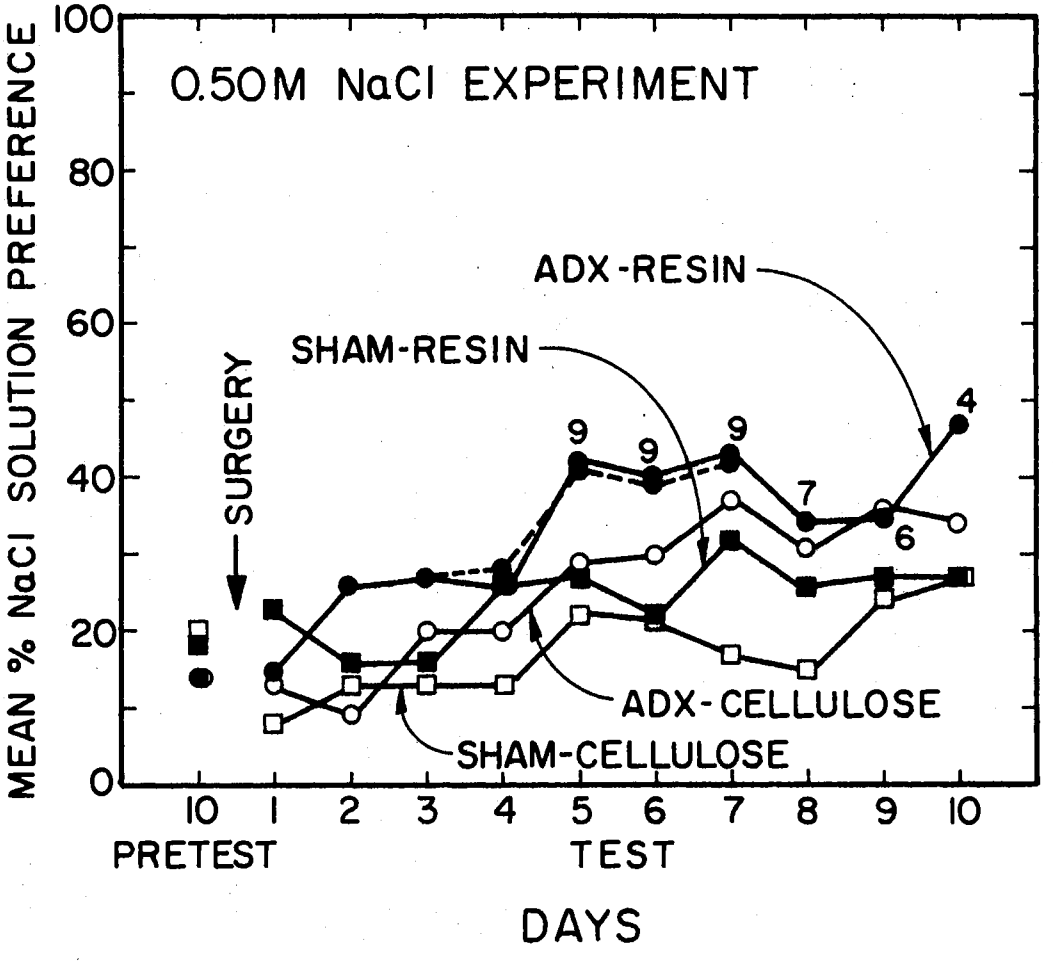

Figure 9. Mean Daily Percent of Preference for 0.50M NaCl Over Distilled Water on the Last Day of Pretest and on Each Test Day. n = 10, unless otherwise indicated; ●--●, points containing estimated data for one Adx-Resin S.

Cellulose groups. The significant F test for Days reflects a decreasing aversion over time by all groups.

Days to Death

In Table XXXV are the mean and standard deviation of the Days to Death values for each group in both experiments. The score for each S was determined as the number of days S was alive at the daily recording time following surgery. Subjects which died within 48 hours of surgery were discarded, making two the minimum score possible. A Two X two ANOVA was used to analyse the Days to Death data in each experiment.

Significant Surgery, Diet and Interaction effects were found in both experiments (Tables XXXVI-XXXVII). Simple effects tests of the interaction indicate that Adx-Resin animals died sooner than did the Sham-Resin animals while there was no difference on this measure for the Cellulose groups. This result was found in both experiments (Tables XXXVIII-XXXIX). It should be noted that all of the Sham animals in both experiments survived the post-surgical period and, thus, each received the maximum score of 17.

TABLE XXXV

DAYS TO DEATH*

Experiment	Adx-Resin		Adx-Cellulose		Sham-Resin		Sham-Cellulose	
	M	SD	M	SD	M	SD	M	SD
0.25M NaCl	14.9	2.0	16.7	0.9	17.0	0.0	17.0	0.0
0.50M NaCl	10.8	4.8	16.2	1.2	17.0	0.0	17.0	0.0

*The number of days preceding that day on which S was found dead at the daily recording time. The maximum score possible was 17, the duration in days of the experiment following surgery.

TABLE XXXVI

SUMMARY OF THE ANALYSIS OF VARIANCE ON DAYS TO DEATH - 0.25M NaCl EXPERIMENT

Source	Degrees of Freedom	SS	MS	F	p
Surgery	1	14.400	14.400	12.06	.01
Diet	1	8.100	8.100	6.78	.05
Surgery X Diet	1	8.100	8.100	6.78	.05
Within Cell	36	43.000	1.194		
Total	39	73.600			

TABLE XXXVII

SUMMARY OF THE ANALYSIS OF VARIANCE ON DAYS TO DEATH - 0.50M NaCl EXPERIMENT

Source	Degrees of Freedom	SS	MS	F	p
Surgery	1	122.500	122.500	19.76	.01
Diet	1	72.900	72.900	11.76	.01
Surgery X Diet	1	72.900	72.900	11.76	.01
Within Cell	36	223.200	6.20		
Total	39	491.500			

TABLE XXXVIII

AOV: SIMPLE EFFECTS OF THE SURGERY X DIET INTERACTION ON DAYS TO DEATH - 0.25M NaCl EXPERIMENT

Source	Degrees of Freedom	MS	F	p
Between Surgery W. Diet - Resin	1	22.050	18.47	.01
Between Surgery W. Diet - Cellulose	1	0.450	0.38	
Between Diet W. Surgery - Adrenalectomy	1	16.200	13.57	.01
Between Diet W. Surgery - Sham-Operation	1	0.000	0.00	

TABLE XXXIX

AOV: SIMPLE EFFECTS OF THE SURGERY X DIET INTERACTION ON DAYS TO DEATH - 0.50M NaCl EXPERIMENT

Source	Degrees of Freedom	MS	F	p
Between Surgery W. Diet - Resin	1	192.200	31.00	.01
Between Surgery W. Diet - Cellulose	1	3.200	0.52	
Between Diet W. Surgery - Adrenalectomy	1	145.800	23.52	.01
Between Diet W. Surgery - Sham-Operation	1	0.000	0.00	

CHAPTER IV

DISCUSSION

Effectiveness of the Ion Exchange Resin

It is apparent from the results of the fecal element determinations that the ion exchange resin, in combination with 1% EDTA, used in the present investigations was effective in significantly raising the fecal concentrations of Na, K, Ca, and Mg. The most important finding in this regard was the strong differential increase in Na concentration of the feces of the Resin diet animals. It is concluded, therefore, that the ion exchange resin served the purpose for which it was intended: to reduce the need-alleviating properties of a given amount of ingested NaCl by preventing at least part of the Na from being absorbed from the gastrointestinal system.

In addition to these Diet effects, significant Surgery effects were found for K in both experiments. Increased concentrations in the feces of the Adx rats might reflect the increased plasma K levels associated with adrenalectomy. While this is consistent with the findings in the 0.25M NaCl experiment, it was the Sham groups that exhibited the higher fecal K concentrations in the 0.50M NaCl experiment (Table II). The explanation for these results is unclear at this time. Also unclear are the reasons behind the significant Surgery and Surgery X Diet effects in fecal Mg levels.

Body Weight and Food Intake

A similar pattern emerged from the Test period body weight data in both experiments. In each case the groups with access to the Resin diet gradually lost weight while the Cellulose groups either maintained or gained weight (Figures 1 and 2). The weight loss by the Resin animals appears to be due, at least in part, to the fact that these rats ate less food on a g/100g body weight basis than did those receiving the Cellulose diet (see Figures 3 and 4). The Resin diet may have been relatively unpalatable, and this accounted for the lower intake levels. If so, differences in diet palatability were not reflected in differences in amount of food spillage, which would be predicted on the basis of Rozin's (1967) work.

Another cause for the decreasing weight and concomitantly lowered food intake may have been some toxic consequences of the Resin diet. Nevertheless, McChesney (1952a) reported that toxic effects of a sulfonic resin-containing diet were not seen below the 15% dietary level. In contrast, all Resin Ss in the present study experienced diarrhea from about the second day of Test. It is therefore likely that ingestion of 14% Resin plus 1% EDTA had some aversive and debilitating effects. Levels of these agents which minimize the toxic effects while assuring the binding of significant amounts of Na would be desirable for future investigations.

The Adx rats in both experiments ate less food than did the Sham animals. This is consistent with the findings of Moyer & Been (1964). Leshner (1972) suggests that the decrease in food intake may be due to an attempt by the Adx rat specifically to reduce the intake of protein, the utilization of which is impaired following adrenalectomy. His data support this position.

In the 0.25M NaCl experiment, neither an effect of Surgery on body weight nor a Surgery X Diet interaction were found. This leads to the conclusion that although the Adx Ss were eating less on a g/100g body weight basis within each Diet condition, the Adx animals were compensating for their deficiency. On the contrary, over the first seven Test days of the 0.50M NaCl experiment, the Adx animals weighed less than the Shams, indicating a smaller degree of compensation.

Fluid Intake, NaCl Intake and Preference

Throughout the Test period, the Adx animals in both experiments drank significantly less fluid than did the Shams. It is known that following adrenalectomy rats are susceptible to toxic overhydration due to a decrease in the diuretic response to water (Gaunt, 1944). Toxic overhydration, or water intoxication, in Adx rats is characterized by tremors, mild convulsions, a general state of "flaccid collapse", a decrease in body temperature and eventual death. Thus, on the one hand, fluid intakes by the Adx rats in this study were probably limited by this lack of tolerance for water. On the other hand, the difference in the fluid intake between the two Diet groups was probably due to either the dryness of the Cellulose diet, physiological consequences of ion exchange resin ingestion (e.g., acidosis) or a combination of these factors.

In terms of NaCl intake in mg per 100g body weight, the Sham groups in the 0.25M NaCl experiment ingested more NaCl than did the Adx animals during Test. As noted earlier with respect to body weight change during Test, the Adx rats compensated for deficiency of sodium. The lower level of NaCl intake may therefore reflect the fact that these animals did not need to take in a greater amount of Na and adjusted their drinking

accordingly. Richter (1936) concluded that appetite may be used as a measure of deficiency. The inflated intake of the Shams was probably a result of the high palatability value of the 0.25M NaCl solution.

The Surgery effect was not seen in the 0.50M NaCl experiment, and the lowered body weights of the Adx groups indicated that they did not compensate to as great a degree as did the 0.25M NaCl Adx rats. In light of this, it is curious that the average level of Na intake on Test Days 6 and 7 for each group was not significantly different from its counterpart in the other experiment.

Differential preference for the NaCl solution by the Adx rats was not seen in the 0.25M NaCl experiment. Again, the high palatability value of this solution may have contributed to this effect (Figure 8). In the case where a relatively unpalatable solution was available, the Adx animals did show the greater NaCl acceptance (Figure 9).

In both experiments, the Resin groups preferred the NaCl solution more than did the Shams. It could be that the Resin animals were responding to a decrease in reinforcement value of the ingested Na caused by the Na binding of the resin as suggested by Epstein & Stellar (1955). Since the absolute amount of Na ingested did not change, only the preference for it, and the effect was seen in the supposedly non-depleted Shams as well, it is likely that some effect of the Resin diet was operating to increase preference independently of any lessening in reinforcing properties of the NaCl solutions.

Survival

It is obvious from the above that the NaCl intake measure and the NaCl preference measure are actually reflecting different processes. In

neither experiment are the same effects seen in both measures. And, it would be difficult, if not impossible, to say which of these measures more accurately indicates the adaptive value of the animal's behavior. The most direct measures of how well the animal is adapting to the situation are the extent to which it can maintain its health (e.g., body weight) and, of course, whether it survives.

As earlier noted concerning the 0.25M NaCl experiment, no effect of adrenalectomy on body weight was present. That is, within the restrictions placed on body weight change by the Diet conditions, the Adx rats were able to maintain the same body weight as were the Shams. When the unadulterated, mineral-containing diet was returned, and the NaCl solution removed, the Shams immediately started gaining weight while the Adx rats started to lose. In Figure 1, an upward trend in body weight is seen for the Adx-Resin group, beginning at about Posttest Day 3. After Day 2, animals in this group began to die, and, since they were the lightest in weight, the mean body weight of those remaining was raised. This rise occurred almost everytime an Adx rat in either experiment died during Posttest (see also Figure 2).

Even though both Adx groups drinking 0.25M NaCl were apparently compensating well during Test, a difference between them appeared during Posttest. In spite of the fact that both groups were fed the same, presumably complete, ration, the mean survival time of the Adx-Resin rats in Posttest was only 4.9 days while that of the Adx-Cellulose rats was 6.7 days (see Table XXXV). It appears that some consequence of the Resin diet experience made the Adx-Resin animals less able to survive the lack of NaCl.

Because a significant effect of Surgery on body weight during Test

was found in the 0.50M NaCl experiment, the Adx animals may not have compensated as well as had those given 0.25M NaCl (even though no direct test between the experiments was made). The Days to Death data make this conclusion even more attractive. Despite the lowered body weight during Test, the Adx-Cellulose animals survived the removal of NaCl about as long as their counterparts in the 0.25M NaCl experiment (mean, 6.2 days). On the other hand, the Adx-Resin animals not only evidenced the body weight effect but also began dying much sooner than did any of the other Adx groups during Test, when NaCl was available for consumption. At the end of the Test period, only 4 members (40%) of this group were still alive. In contrast, the first member of the Adx-Resin group in the 0.25M NaCl experiment to die did so only after two days of Posttest.

The NaCl intake of the Adx-Resin animals drinking 0.50M NaCl was obviously not adequate to overcome the adrenalectomy-induced deficiency plus the Resin-associated lowered postingestional benefit of drinking a given amount of NaCl. Since the 0.25M NaCl Adx-Resin animals did ingest sufficient amounts, the conclusion that palatability is important in this situation seems warranted. A way in which it might operate is as follows: When the available NaCl solution is palatable (50+% preference), a lack of experience with the beneficial consequences of its ingestion prior to a diminution in those consequences is not a critical factor. On the other hand, when only an unpalatable solution is available, lack of experience in this situation interferes with adequate intake.

A better and more direct test of the above hypothesis could be made in the Mook (1969) esophagostomy-gastric cannula situation where taste and postingestional events can be separated. Here, the animal's

experience with both taste, benefit and their combination, along with degree of benefit associated with a given taste can be precisely controlled.

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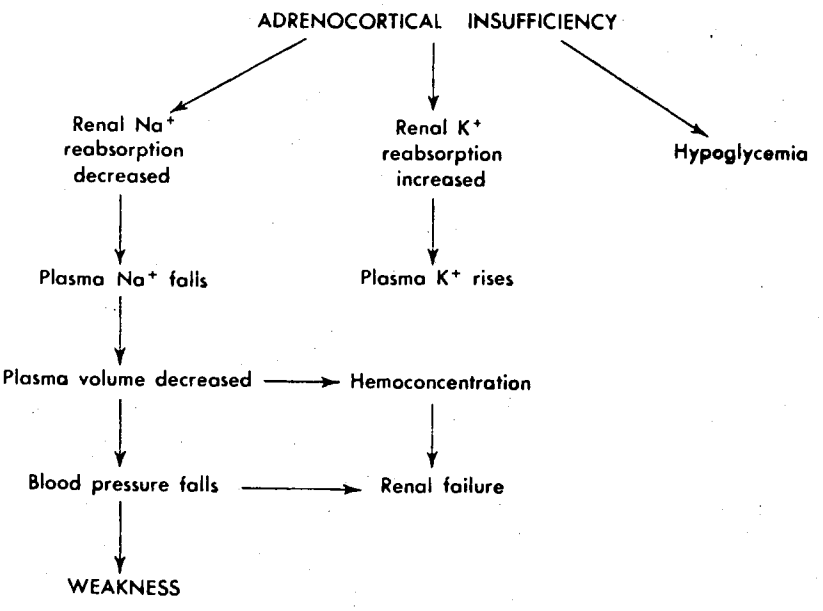
APPENDIXES

APPENDIX A

SEQUENCE OF EVENTS RESULTING FROM ADRENOCORTICAL INSUFFICIENCY



Source: Langley, L. L., & Cheraskin, E. Physiology of man. (3rd ed.) New York: Reinhold, 1965, p. 618.

Figure 10. Sequence of Events Resulting From Adrenocortical Insufficiency

APPENDIX B

PROPERTIES OF DOWEX-X8 ION EXCHANGE RESIN

TABLE XL

PROPERTIES OF DOWEX-X8 ION EXCHANGE RESIN*

Category	Specification
Type	Strong-acid cation exchanger
Active Group	Nuclear sulfonic acid
Standard Crosslinkage - % Divinylbenzene	8
Ionic Form	H^+
Physical Form	Spheres
Mesh Size	100-200, 200-400
Shipping Density (lb/ft^3)	50
Moisture Content (%)	53.3
Volume Change (%)	$Na^+ - H^+ = +8\%$
Effective pH Range	0 - 14
Selectivity	Na^+/H^+ = approx. 1.2
Order of Selectivity for Ions	Monovalent: Ag > Cs > Rb > K > NH_4 > Na > H > Li; divalent: Ba > Sr > Ca > Mg > Be
Total Exchange Capacity	
Kgr as $CaCO_3/ft^3$	37.00
Meq/g Dry Resin	5.00
Meq/ml Wet Resin	1.95
Sphericity (%)	> 95
Bed Expansion	15 - 28% maximum at 4 gpm/ft^2 at 25°C
Pressure Drop	Approx. 0.45 $lb/in^2/ft$ at 5 gpm/ft^2
Stability	
Thermal	Good up to 150°C
Solvent	Very good
Oxidation	Slow solution in hot 15% HNO_3
Reduction	Very good
Attrition	Excellent

*Modified from: Dow Chemical Company. Dowex: Ion exchange. Midland, Mich.: Dow Chemical, 1964, P. 70.

APPENDIX C

IONIC COMPOSITION OF CONTENT OF SMALL INTESTINE

TABLE XLI

IONIC COMPOSITION OF CONTENT OF SMALL INTESTINE*

Ion	Meq./L.
Potassium	4 - 5
Sodium	140
Calcium	2.5 - 6.4
Magnesium	1 - 2
Chloride	74 - 103
Sulfate	Trace
Phosphate	2.61 - 7.66
Bicarbonate	2 - 32
Titratable Acidity or Alkalinity	158.2

*Source: Martin, G. J. Ion exchange and adsorption agents in medicine. Boston: Little, Brown, 1955, P. 38.

APPENDIX D

FECAL SAMPLE PREPARATION PROCEDURE

Fecal Sample Preparation Procedure

(Modified from Black, 1965)

The samples were stored in cork-stoppered test tubes and refrigerated until preparation began. Later the samples were placed in individual aluminum trays, weighed, and then dried in an oven at 180°F for 22 1/2 to 26 1/2 hours. After drying, the samples were again weighed. Immediately after removal from the oven, they were placed in a desiccator until being weighed.

Ten ml of a mixture (3:1) of nitric and perchloric acid were added to each sample and allowed to digest for approximately 17 - 22 hours. The solutions were then boiled dry. Ten of the 79 samples were not completely digested at the end of the procedure. An additional 10 ml of the acid mixture were added to each of these which were then reboiled.

APPENDIX E

WINER'S CASE II - THREE FACTOR EXPERIMENT WITH REPEATED MEASURES ON ONE FACTOR

WINER'S CASE II - THREE FACTOR EXPERIMENT WITH REPEATED MEASURES ON ONE FACTOR

Model: $X_{ijkm} = \mu + \alpha_i + \beta_j + \alpha\beta_{ij} + \pi_{m(ij)} + \gamma_k + \alpha\gamma_{ik} + \beta\gamma_{jk} + \alpha\beta\gamma_{ijk} + \gamma_{km(ij)} + \varepsilon_{o(ijkm)}$

Summary of Analysis of Variance

Source of variation	df	E(MS)†
Between subjects	$npq - 1$	
A	$p - 1$	$\sigma_\varepsilon^2 + r\sigma_\pi^2 + nqr\sigma_\alpha^2$
B	$q - 1$	$\sigma_\varepsilon^2 + r\sigma_\pi^2 + npr\sigma_\beta^2$
AB	$(p - 1)(q - 1)$	$\sigma_\varepsilon^2 + r\sigma_\pi^2 + nr\sigma_{\alpha\beta}^2$
Subj w. groups [error (between)]	$pq(n - 1)$	$\sigma_\varepsilon^2 + r\sigma_\pi^2$
Within subjects	$npq(r - 1)$	
C	$r - 1$	$\sigma_\varepsilon^2 + \sigma_{\gamma\pi}^2 + npq\sigma_\gamma^2$
AC	$(p - 1)(r - 1)$	$\sigma_\varepsilon^2 + \sigma_{\gamma\pi}^2 + nq\sigma_{\alpha\gamma}^2$
BC	$(q - 1)(r - 1)$	$\sigma_\varepsilon^2 + \sigma_{\gamma\pi}^2 + np\sigma_{\beta\gamma}^2$
ABC	$(p - 1)(q - 1)(r - 1)$	$\sigma_\varepsilon^2 + \sigma_{\gamma\pi}^2 + n\sigma_{\alpha\beta\gamma}^2$
C × subj w. groups [error (within)]	$pq(n - 1)(r - 1)$	$\sigma_\varepsilon^2 + \sigma_{\gamma\pi}^2$

† Assumes *A*, *B*, and *C* fixed factors.

Note - "In this design, when the pattern assumptions on the variance-covariance matrices are questionable, critical values of the conservative tests involving factor C have the form

$F_{1-\alpha}[1,pq(n-1)]$ instead of $F_{1-\alpha}[(r-1),pq(n-1)(r-1)]$,

$F_{1-\alpha}[(p-1),pq(n-1)]$ instead of $F_{1-\alpha}[(p-1)(r-1),pq(n-1)(r-1)]$."

Source: Winer, B. J. Statistical principles in experimental design. (2nd ed.) New York: McGraw-Hill, 1971. Pp. 560-563.

APPENDIX F

STATISTICAL TABLES

TABLE XLII

SUMMARY OF THE ANALYSIS OF VARIANCE ON BODY WEIGHT (g)
DURING PRETEST - 0.25M NaCl EXPERIMENT

Source	Degrees of Freedom		SS	MS	F	p
Between Subjects	39		290,928.372			
Surgery	1		6.875	6.875	0.00	
Diet	1		468.437	468.437	0.05	
Surgery X Diet	1		4.404	4.404	0.00	
Subj. W. Groups	36		290,448.656	8,068.018		
	Conventional	Conservative				Conservative
Within Subjects	400		224,371.705			
Days	10	1	217,160.262	2,716.023	1158.68	.01
Surgery X Days	10	1	238.762	23.876	1.27	
Diet X Days	10	1	110.084	11.008	0.59	
Surgery X Diet X Days	10	1	115.597	11.560	0.62	
Days X Subj. W. Groups	360	36	6,747.000	18.742		
Total	439		515,300.077			

TABLE XLIII

SUMMARY OF THE ANALYSIS OF VARIANCE ON FOOD(g)/100g BODY WEIGHT DURING PRETEST - 0.25M NaCl EXPERIMENT

Source	Degrees of Freedom		SS	MS	F	p
Between Subjects	39		144.315			
Surgery	1		5.663	5.663	1.50	
Diet	1		0.137	0.137	0.04	
Surgery X Diet	1		2.256	2.256	0.60	
Subj. W. Groups	36		136.259	3.785		
	Conventional	Conservative				Conservative
Within Subjects	360		666.245			
Days	9	1	352.359	39.151	44.19	.01
Surgery X Days	9	1	7.952	0.884	1.00	
Diet X Days	9	1	6.625	0.736	0.83	
Surgery X Diet X Days	9	1	12.360	1.373	1.55	
Days X Subj. W. Groups	324	36	286.949	0.886		
Total	399		810.560			

TABLE XLIV

SUMMARY OF THE ANALYSIS OF VARIANCE ON FOOD(g)/100g BODY WEIGHT DURING PRETEST - 0.50M NaCl EXPERIMENT

Source	Degrees of Freedom		SS	MS	F	p
Between Subjects	39		170.069			
Surgery	1		0.066	0.066	0.02	
Diet	1		14.629	14.629	3.39	.10
Surgery X Diet	1		0.003	0.003	0.00	
Subj. W. Groups	36		155.371	4.316		
	Conventional	Conservative				Conservative
Within Subjects	360		957.576			
Days	9	1	358.196	39.800	23.63	.01
Surgery X Days	9	1	10.034	1.115	0.66	
Diet X Days	9	1	15.439	1.715	1.02	
Surgery X Diet X Days	9	1	28.265	3.141	1.86	
Days X Subj. W. Groups	324	36	545.642	1.684		
Total	399		1,127.645			

TABLE XLV

SUMMARY OF THE ANALYSIS OF VARIANCE ON FOOD SPILLAGE (g)
DURING PRETEST - 0.25M NaCl EXPERIMENT

Source	Degrees of Freedom	SS	MS	F	p
Between Subjects	39	498.221			
Surgery	1	6.100	6.100	0.49	
Diet	1	39.815	39.815	3.19	.10
Surgery X Diet	1	3.460	3.460	0.28	
Subj. W. Groups	36	448.846	12.468		
	Conventional Conservative				Conservative
Within Subjects	360	2,601.941			
Days	9	89.457	9.940	1.36	
Surgery X Days	9	57.798	6.422	0.88	
Diet X Days	9	41.564	4.618	0.63	
Surgery X Diet X Days	9	52.273	5.808	0.80	
Days X Subj. W. Groups	324	2,360.849	7.286		
Total	399	3,100.162			

TABLE XLVI

SUMMARY OF THE ANALYSIS OF VARIANCE ON FOOD SPILLAGE (g)
DURING TEST - 0.25M NaCl EXPERIMENT

Source	Degrees of Freedom		SS	MS	F	p
Between Subjects	39		1,397.311			
Surgery	1		54.242	54.242	1.46	
Diet	1		9.828	9.828	0.26	
Surgery X Diet	1		1.200	1.200	0.03	
Subj. W. Groups	36		1,332.041	37.001		
	Conventional	Conservative				Conservative
Within Subjects	360		3,752.483			
Days	9	1	212.660	23.629	2.50	
Surgery X Days	9	1	73.103	8.122	0.86	
Diet X Days	9	1	258.368	28.708	3.04	.10
Surgery X Diet X Days	9	1	146.884	16.320	1.73	
Days X Subj. W. Groups	324	36	3,061.468	9.449		
Total	399		5,149.794			

TABLE XLVII

SUMMARY OF THE ANALYSIS OF VARIANCE ON FOOD SPILLAGE (g)
DURING PRETEST - 0.50M NaCl EXPERIMENT

Source	Degrees of Freedom		SS	MS	F	p
Between Subjects	39		653.698			
Surgery	1		0.336	0.336	0.02	
Diet	1		18.662	18.662	1.06	
Surgery X Diet	1		0.017	0.017	0.00	
Subj. W. Groups	36		634.683	17.630		
	Conventional	Conservative				Conservative
Within Subjects	360		2,628.308			
Days	9	1	64.237	7.137	0.99	
Surgery X Days	9	1	64.834	7.204	1.00	
Diet X Days	9	1	50.477	5.608	0.78	
Surgery X Diet X Days	9	1	115.253	12.806	1.78	
Days X Subj. W. Groups	324	36	2,333.507	7.202		
Total	399		3,282.006			

TABLE XLVIII

SUMMARY OF THE ANALYSIS OF VARIANCE ON FOOD SPILLAGE (g) DURING THE FIRST SEVEN DAYS OF TEST - 0.50M NaCl EXPERIMENT

Source	Degrees of Freedom		SS	MS	F	p
Between Subjects	39		1,296.226			
Surgery	1		29.900	29.900	0.86	
Diet	1		0.296	0.296	0.01	
Surgery X Diet	1		14.766	14.766	0.42	
Subj. W. Groups	36		1,251.264	34.757		
	Conventional	Conservative				Conservative
Within Subjects	240		1,166.684			
Days	6	1	33.675	5.612	1.19	
Surgery X Days	6	1	41.762	6.960	1.48	
Diet X Days	6	1	56.425	9.404	2.00	
Surgery X Diet X Days	6	1	18.115	3.019	0.64	
Days X Subj. W. Groups	216	36	1,016.707	4.707		
Total	279		2,462.910			

TABLE XLIX

SUMMARY OF THE ANALYSIS OF VARIANCE ON TOTAL FLUID(ml)/100g BODY WEIGHT DURING PRETEST - 0.25M NaCl EXPERIMENT

Source	Degrees of Freedom		SS	MS	F	p
Between Subjects	39		12,463.737			
Surgery	1		10.386	10.386	0.03	
Diet	1		380.598	380.598	1.14	
Surgery X Diet	1		52.728	52.728	0.16	
Subj. W. Groups	36		12,020.025	333.890		
	Conventional	Conservative				Conservative
Within Subjects	360		9,682.230			
Days	9	1	479.012	53.224	2.01	
Surgery X Days	9	1	279.831	31.092	1.17	
Diet X Days	9	1	144.871	16.097	0.61	
Surgery X Diet X Days	9	1	185.601	20.622	0.78	
Days X Subj. W. Groups	324	36	8,592.915	26.521		
Total	399		22,145.967			

TABLE L

SUMMARY OF THE ANALYSIS OF VARIANCE ON TOTAL FLUID(ml)/100g BODY WEIGHT DURING PRETEST - 0.50M NaCl EXPERIMENT

Source	Degrees of Freedom		SS	MS	F	p
Between Subjects	39		4,830.846			
Surgery	1		190.296	190.296	1.53	
Diet	1		0.007	0.007	0.00	
Surgery X Diet	1		174.063	174.063	1.40	
Subj. W. Groups	36		4,466.480	124.069		
	Conventional	Conservative				Conservative
Within Subjects	360		3,948.009			
Days	9	1	256.111	28.457	2.70	
Surgery X Days	9	1	137.825	15.314	1.45	
Diet X Days	9	1	44.058	4.895	0.46	
Surgery X Diet X Days	9	1	98.009	10.890	1.03	
Days X Subj. W. Groups	324	36	3,412.066	10.531		
Total	399		8,778.855			

TABLE LI

SUMMARY OF THE ANALYSIS OF VARIANCE ON NaCl (mg)/100g BODY WEIGHT DURING PRETEST - 0.25M NaCl EXPERIMENT

Source	Degrees of Freedom		SS	MS	F	p
Between Subjects	39		2,785,994.313			
Surgery	1		17,348.370	17,348.370	0.23	
Diet	1		33,075.930	33,075.930	0.44	
Surgery X Diet	1		63.888	63.888	0.00	
Subj. W. Groups	36		2,735,506.125	75,986.281		
	Conventional	Conservative				Conservative
Within Subjects	360		2,410,750.094			
Days	9	1	101,169.805	11,241.086	1.69	
Surgery X Days	9	1	67,100.624	7,455.621	1.12	
Diet X Days	9	1	40,236.162	4,470.684	0.67	
Surgery X Diet X Days	9	1	44,820.090	4,980.008	0.75	
Days X Subj. W. Groups	324	36	2,157,423.413	6,658.714		
Total	399		5,196,744.407			

TABLE LII

SUMMARY OF THE ANALYSIS OF VARIANCE ON NaCl(mg)/100g BODY WEIGHT DURING PRETEST - 0.50M NaCl EXPERIMENT

Source	Degrees of Freedom		SS	MS	F	p
Between Subjects	39		1,222,696.131			
Surgery	1		43,654.515	43,654.515	1.39	
Diet	1		6,298.826	6,298.826	0.20	
Surgery X Diet	1		42,010.626	42,010.626	1.33	
Subj. W. Groups	36		1,130,732.164	31,409.227		
	Conventional	Conservative				Conservative
Within Subjects	360		1,346,558.792			
Days	9	1	83,673.555	9,297.058	2.44	
Surgery X Days	9	1	11,639.353	1,293.261	0.34	
Diet X Days	9	1	6,348.431	705.381	0.18	
Surgery X Diet X Days	9	1	10,795.554	1,199.506	0.31	
Days X Subj. W. Groups	324	36	1,234,101.899	3,808.956		
Total	399		2,569,254.923			

TABLE LIII

SUMMARY OF THE ANALYSIS OF VARIANCE ON NaCl(mg)/100g BODY WEIGHT DURING THE FIRST SEVEN DAYS OF TEST - 0.50M NaCl EXPERIMENT

Source	Degrees of Freedom		SS	MS	F	p
Between Subjects	39		499,452.611			
Surgery	1		25.355	25.355	0.00	
Diet	1		2,685.665	2,685.665	0.20	
Surgery X Diet	1		6,498.207	6,498.207	0.48	
Subj. W. Groups	36		490,243.384	13,617.872		
	Conventional	Conservative				Conservative
Within Subjects	240		1,176,656.672			
Days	6	1	113,465.300	18,910.883	4.10	.10
Surgery X Days	6	1	17,233.138	2,872.190	0.62	
Diet X Days	6	1	10,361.789	1,726.965	0.37	
Surgery X Diet X Days	6	1	38,911.286	6,485.211	1.40	
Days X Subj. W. Groups	216	36	996,685.159	4,614.283		
Total	279		1,676,109.283			

TABLE LIV

SUMMARY OF THE ANALYSIS OF VARIANCE ON PERCENT NaCl PREFERENCE DURING PRETEST - 0.25M NaCl EXPERIMENT

Source	Degrees of Freedom	SS	MS	F	p
Between Subjects	39	105,959.676			
Surgery	1	1,401.094	1,401.094	0.49	
Diet	1	630.284	630.284	0.22	
Surgery X Diet	1	385.440	385.440	0.13	
Subj. W. Groups	36	103,542.858	2,876.190		
	Conventional Conservative				Conservative
Within Subjects	360	94,616.856			
Days	9	5,801.790	644.643	2.53	
Surgery X Days	9	1,498.917	166.546	0.65	
Diet X Days	9	2,444.188	271.576	1.06	
Surgery X Diet X Days	9	2,242.140	249.127	0.98	
Days X Subj. W. Groups	324	82,629.821	255.030		
Total	399	200,576.532			

TABLE LV

SUMMARY OF THE ANALYSIS OF VARIANCE ON PERCENT NaCl PREFERENCE DURING PRETEST - 0.50M NaCl EXPERIMENT

Source	Degrees of Freedom		SS	MS	F	p
Between Subjects	39		39,711.031			
Surgery	1		1,129.202	1,129.202	1.10	
Diet	1		268.595	268.595	0.26	
Surgery X Diet	1		1,212.574	1,212.574	1.18	
Subj. W. Groups	36		37,100.660	1,030.574		
	Conventional	Conservative				Conservative
Within Subjects	360		41,763.913			
Days	9	1	3,272.392	363.599	3.14	.10
Surgery X Days	9	1	240.853	26.761	0.23	
Diet X Days	9	1	372.538	41.393	0.36	
Surgery X Diet X Days	9	1	309.131	34.349	0.30	
Days X Subj. W. Groups	324	36	37,568.999	115.954		
Total	399		81,474.944			

VITA

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Master of Science

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