8-1976

Inhibition of Gastric Secretion and Ulcer Formation by Lithium Chloride in the Rat

Thomas H. Adair

INHIBITION OF GASTRIC SECRETION AND ULCER FORMATION BY LITHIUM CHLORIDE IN THE RAT

by

Thomas H. Adair

A Thesis
Submitted to the
Faculty of The Graduate College
in partial fulfillment
of the
Degree of Master of Arts

Western Michigan University
Kalamazoo, Michigan
August 1976

ACKNOWLEDGEMENTS

In researching and writing this thesis, I have benefited from the aid and encouragement of Professors Leonard J. Beuving, Arthur Diani, and André Robert. I thank André Robert for allowing me to work in his laboratory, for his many hours of discussion, and for providing me with continuous intellectual challenge. The financial assistance, as well as research opportunities, provided by the Upjohn Company are greatly appreciated. Special thanks go to James E. Nezamis, Cleo Lancaster, Alexander J. Hanchar, Steve Nichols, and Julie Gips for their technical advice and assistance.

Thomas H. Adair

MASTERS THESIS M-8864

ADAIR, Thomas Harvey
INHIBITION OF GASTRIC SECRETION AND ULCER FORMATION BY LITHIUM CHLORIDE IN THE RAT.

Western Michigan University, M.A., 1976
Physiology

TABLE OF CONTENTS

INTRODUCTION

The administration of lithium has been advocated for the treatment of a variety of diseases during the last one hundred years. Most of these applications are now considered useless; however, the discovery that lithium salts are prophylactic in the treatment of affective disorders of the central nervous system has stimulated a considerable amount of research on their biologic effects. Several excellent reviews[1-3] have summarized the effects of lithium on various biologic systems.

The ability of lithium chloride to inhibit gastric secretion as well as ulceration in the rat was discovered in this laboratory. The possible mechanisms through which lithium mediates these effects forms the basis of this paper.

MATERIALS AND METHODS

Gastric Secretion Studies

Female Upjohn rats (derived from the Sprague-Dawley strain), weighing 195-210 gm, were used in all experiments. Food, but not water, was withheld from the animals (starting at 3:30 a.m.) 24 hours prior to study. On the night prior to experimentation the rats were placed in cylindrical stainless steel tubes to prevent them from bending. They were thus unable to consume hair and feces which may contaminate the gastric juice. This type of restraining device has not proved stressful and has been described elsewhere.[4]

On the morning of study, lost body fluids from fasting were replaced with the administration of 10 ml saline subcutaneously. It was observed that rats drank very little when deprived of food and lost approximately 10 gm during food deprivation. Two hours after the saline administration, the pylorus was ligated under ether anesthesia. Four hours after pylorus ligation, the animals were killed with CO_2, their stomachs were removed, and the accumulated gastric juice was collected.

The volume of gastric juice was measured in a graduated centrifuge tube to the nearest 0.1 ml; acid was titrated with 0.1 N NaOH to pH 7 with the use of a glass electrode (Copenhagen radiometer) and expressed in mEq/L (concentration) and mEq/4 hr (output). Pepsin content was determined by the hemoglobin method,[5] as modified

by Vatier and colleagues,[6] for an autoanalyzer. Pepsin was expressed as μEq tyrosine/ml (concentration) and μEq tyrosine/4 hr (output).

Lithium Chloride (LiCl) or sodium chloride was administered either orally using a gastric tube (in 1 ml water) or subcutaneously (in 2 ml water) at the following doses: 0.1, 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 1.75 and 2.0 mMoles. Each agent was administered at various times prior to pylorus ligation: 0, 2, 6, 12, and 18 hours. In all experiments water controls were used for oral treatment, whereas saline controls were used for subcutaneous treatment. At the 0-hour administration time, the salts were injected immediately following pylorus ligation while the animals were still under ether anesthesia. For convenience, the administration times shall be referred to as 0 hour, -2 hour, -6 hour, etc.

Determination of Ions in Serum and Gastric Juice

Under ether anesthesia, aortic blood was withdrawn and Li^+ concentration determined. The blood was permitted to clot overnight at 4°C, after which it was centrifuged at 3000X g for 15 minutes. Serum and gastric juice samples were analyzed utilizing an atomic absorption spectrophotometer (Jarrell-Ash, model 82526). Values of Li^+, K^+, and Na^+ were expressed in mEq/L (concentration) and mEq/4 hr (output).

Shay Ulcer Studies

The Shay rat was prepared according to the method of Shay and associates,[7] as modified by Robert and associates.[8] Lithium

chloride was administered either orally or subcutaneously in various doses, i.e., 0.75, 1.0, and 1.5 mMoles, two hours prior to pylorus ligation; rats were autopsied 22 hours after pylorus ligation. Stomachs were removed, opened along the greater curvature, and examined with the aid of 2X binoculars for the presence of fore-stomach ulcerations. The presence of gastric perforations was also recorded. Percent incidence of animals with ulcers and with perforations was recorded.

Statistical Tests

Results were expressed as percent of control (figures), or percent from control (tables) so that different experiments could be statistically compared. Significance for ulcer studies was determined using the Chi Square test. The Student 't' test (with pooled variance) was applied to observations within an experiment, whereas whole sets of observations were compared using the Sign test.[9] Statistical differences with p values less than 0.05 were considered significant.

RESULTS

Gastric Secretion Studies

Lithium chloride reduced acid concentration and acid output in a dose-related manner after both oral and subcutaneous administration, regardless of the time of treatment, i.e., 0 hr or -2 hr, (Table 1). As shown in Figure 1 (p. 6), the antisecretory effects of LiCl were long-lasting; one mMole LiCl administered subcutaneously at -18 hour significantly reduced acid concentration and acid output.

Table 1. Acid concentration and output for oral and subcutaneous administration of graded doses of LiCl at 0 hour and -2 hour. Results are expressed as percent change from control. Each number represents the mean value from ten rats. (* = significant $\geq$0.05 level)

Route and administration time		mMoles LiCl				
		.1	.5	1.0	1.5	2.0
Oral						
0 hr	concentration	+ 3	-27*	-46*	-	-93*
	S.E.	±3.4	±3.9	±1.1	-	±2.6
	output	+25*	-10	-14	-	-93*
	S.E.	±9.6	±9.6	±5.4	-	±2.9
-2 hr	concentration	+14	-25*	-54*	-	-93*
	S.E.	±2.8	±9.8	±3.2	-	±2.4
	output	+17	-34*	-51*	-	-92*
	S.E.	±9.0	±18.5	±7.3	-	±2.7
Subcutaneous						
0 hr	concentration	-16*	-93*	-99*	-95*	-95*
	S.E.	±4.7	±1.5	±0.9	±3.0	±1.4
	output	-72*	-98*	-99*	-99*	-99*
	S.E.	±7.4	±0.6	±0.4	±0.8	±0.4
-2 hr	concentration	+ 1	-28*	-74*	-93*	-97*
	S.E.	±3.4	±6.3	±3.2	±1.2	±0.9
	output	- 1	-55*	-84*	-95*	-98*
	S.E.	±15.0	±6.0	±2.7	±0.7	±0.5

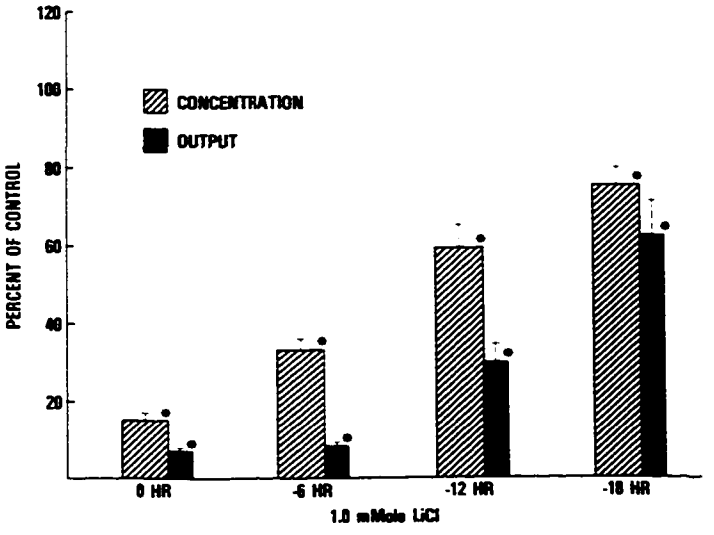

Figure 1. Duration of action of LiCl antisecretory effect. Mean decrease in acid concentration and output expressed as percent of control is shown as LiCl is given at various times prior to pylorus ligation. Each column represents the mean value from 12 rats. (For all figures, verticle bars indicate standard error and the asterisk [*] indicates significance above the 0.05 level.)

Pepsin concentration and output were reduced in a dose-related manner after oral administration at -2 hour and 0 hour (Fig. 2a, p. 7). Subcutaneous administration, on the other hand, reduced the pepsin concentration and output in a dose-related manner at the -2 hour, but not the 0-hour administration time (Fig. 2b, p. 7). The reduction in pepsin output at 0 hour was due to a decrease in the volume of gastric juice as indicated by the relatively small change in pepsin concentration at 0 hour. Subcutaneous administration at the 0, -6, -12, and -18 hour administration times significantly decreased pepsin output but did not affect pepsin concentration, although both concentration and output were significantly reduced at -2 hour (Fig. 3, p. 8).

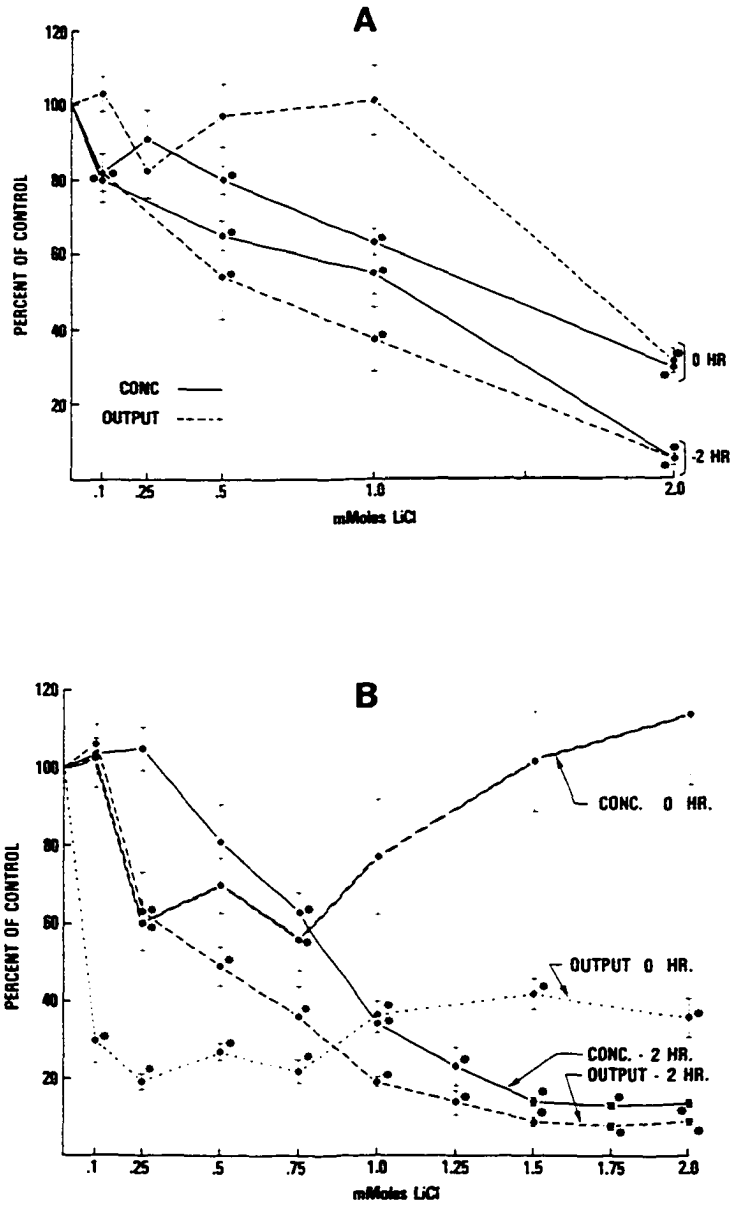

Figure 2a & b. Pepsin content after oral (a) and subcutaneous (b) administration of LiCl. Mean decrease in pepsin concentration and output expressed as percent of control is shown as a function of various doses of LiCl given at 0 hour and -2 hour. Each point represents the mean value from 10 rats.

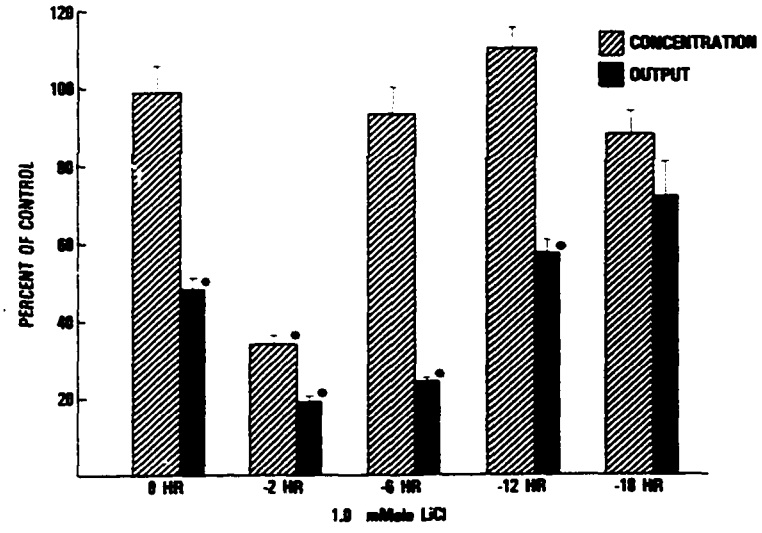

Figure 3. Effect of subcutaneous administration of LiCl on pepsin concentration and output are expressed as percent of control. Each column represents the mean value from 12 rats.

The volume of gastric juice was significantly reduced after subcutaneous administration (Fig. 4a, p. 9), but was unchanged or even slightly increased after oral administration (Fig. 4b, p. 9).

Whenever LiCl was administered at -2 hour, either orally or subcutaneously, the gastric juice was yellow, suggesting bile reflux. To explore this possibility, gastric juice secreted from rats receiving LiCl subcutaneously at either -2 hour or 0 hour was compared. When LiCl was administered subcutaneously at 0 hour, that is, immediately after pylorus ligation, 1) the gastric juice did not exhibit bile staining, 2) the volume of the gastric juice was significantly reduced (according to the Sign test [Fig. 4a, p. 9]), and 3) the pepsin concentration was not reduced (Fig. 2b, p. 7), whereas it was

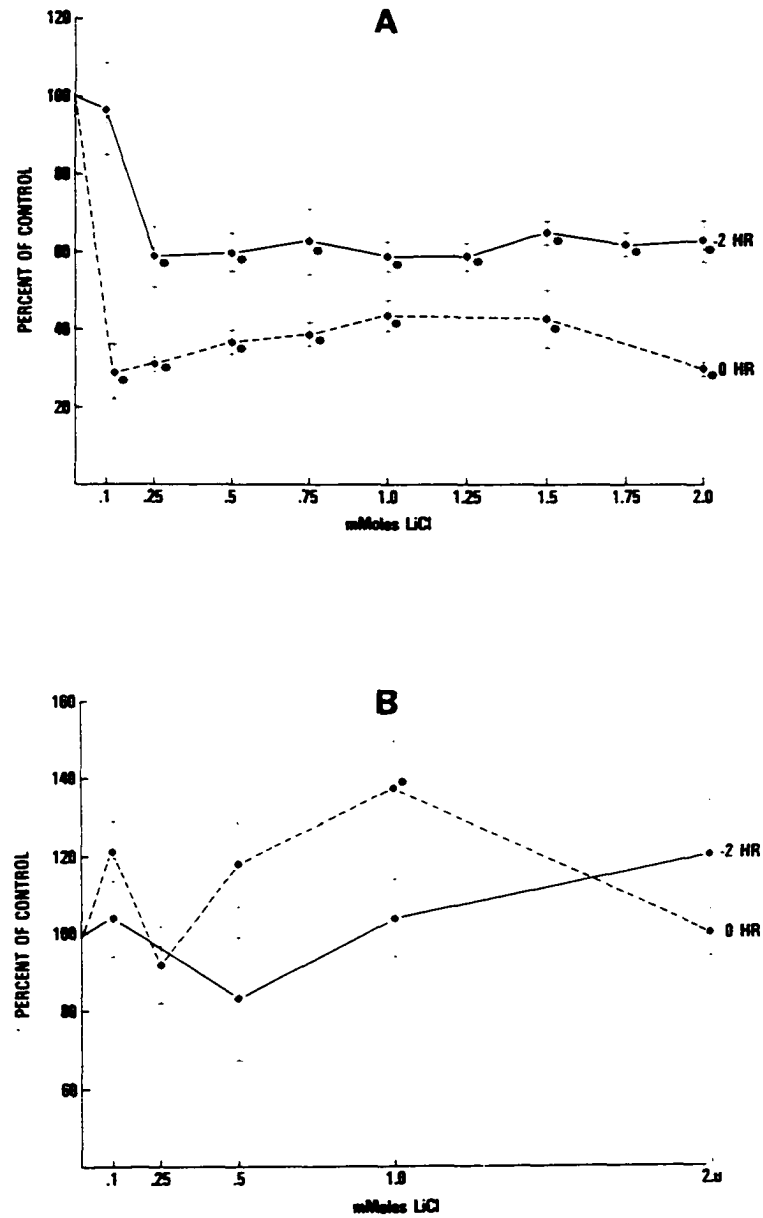

Figure 4a & b. Volume of gastric juice after subcutaneous (a) and oral (b) administration of LiCl. Volume, expressed as percent of control, is shown as a function of various doses of LiCl given at 0 hour and -2 hour. Each point represents the mean value from 10 rats.

reduced at 0 hour after oral administration (Fig. 2a, p. 7). A bile reflux was not observed after NaCl administration.

Both LiCl and NaCl (0.5-2.0 mMole) reduced acid and pepsin (concentration and output) after oral administration, whereas only LiCl was antisecretory after subcutaneous administration. After oral administration at 0 hour, both salts demonstrated equal potency in reducing acid concentration and output (Fig. 5a, p. 11) and pepsin concentration and output (Fig. 5b, p. 11). When the salts were administered at -2 hour, however, LiCl was more antisecretory than NaCl; LiCl reduced both acid (Fig. 6a, p. 12) and pepsin (Fig. 6b, p. 12) more significantly (according to the Sign test) than did NaCl.

Determination of Ions in Serum and Gastric Juice

Oral administration of LiCl at 0 hour produced a dose-related increase in sodium (Na^+) concentration and output and Li^+ concentration and output and a decrease in potassium (K^+) concentration and output in gastric juice (Table 2, p. 13). When LiCl was administered orally at -2 hour, Li^+ serum concentration was significantly higher than when administered orally at 0 hour (according to the Sign test [Fig. 7, p. 14]). Furthermore, when 1.0 mMole LiCl was administered subcutaneously, Li^+ concentrations in gastric juice were more than twice as high as serum concentrations regardless of the time of LiCl administration (Fig. 8, p. 14). Subcutaneous administration of LiCl (1.0 mMole) at various times prior to pylorus ligation, i.e., 0 hour, -2 hour, -6 hour, -12 hour, and -18 hour, increased Na^+ concentration and output in gastric juice (Table 3, p. 15).

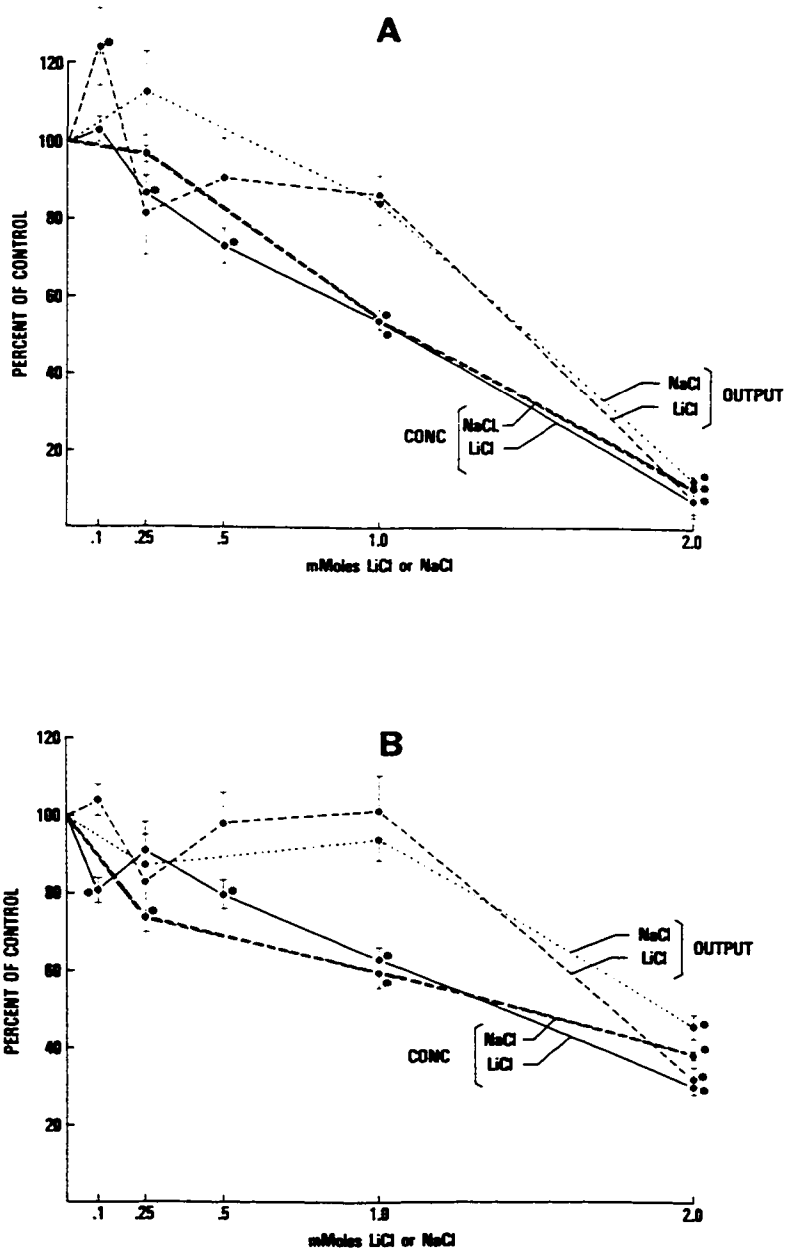

Figure 5a & b. Comparison of oral administration of LiCl and NaCl on acid (a) and pepsin (b) content at 0 hour. Mean decrease in acid and pepsin (concentration and output) expressed as percent of control are shown as a function of various doses of the salts. Each point represents the mean value from eight rats.

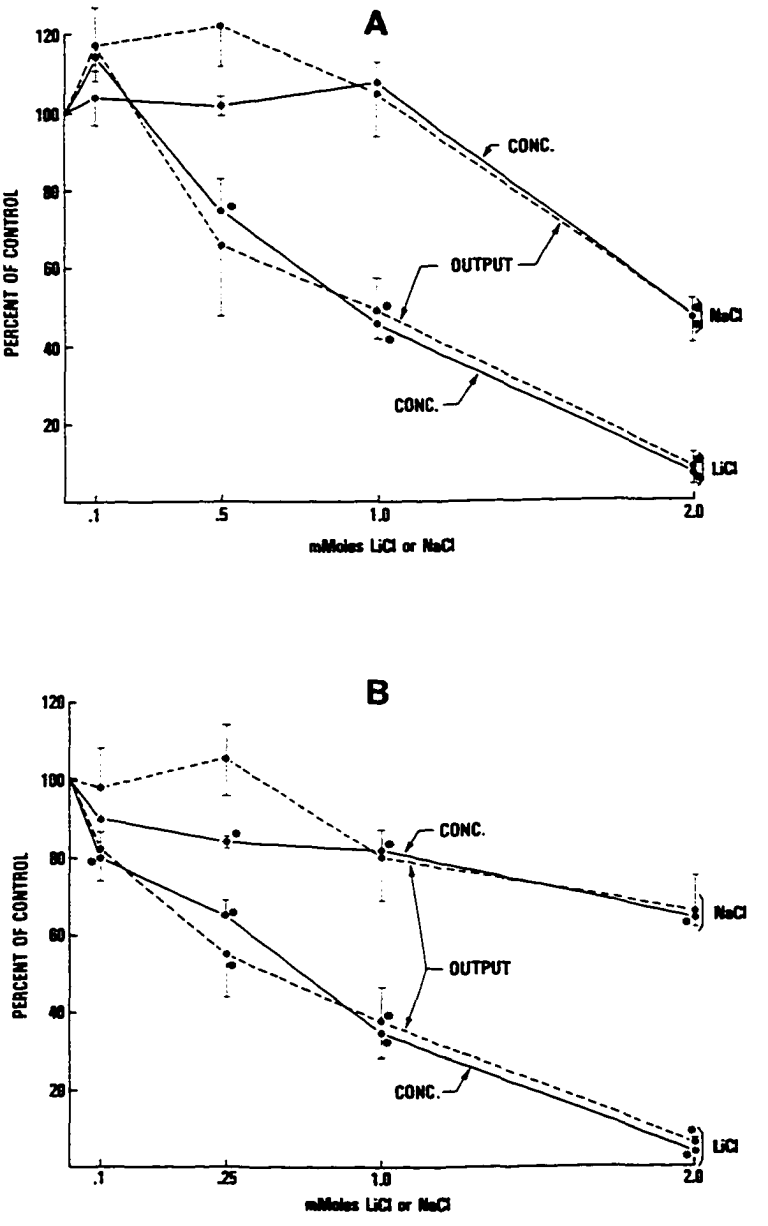

Figure 6a & b. Comparison of oral administration of LiCl and NaCl on acid (a) and pepsin (b) content at -2 hour. Mean decrease in acid and pepsin (concentration and output) expressed as percent of control are shown as a function of various doses of the salts. Each point represents the mean value from eight rats.

Table 2. Concentration and output of various ions in gastric juice after oral administration of graded doses of lithium chloride at 0 hr. Concentration and output of ions are expressed as mEq/L and mEq/4 hr respectively. Each numeral represents the mean value from eight rats. Numerals to the right indicate standard error. (* = significant $\geq$0.05 level)

Concentration and output of ions		mMoles LiCl					
		Water	.1	.25	.5	1.0	2.0
Gastric juice							
H^+	mEq/L	112.1±3.9	115.5±3.9	96.9*±5.4	81.3*±4.4	60.7*±1.3	7.4*±2.9
	mEq/4 hr	.839±0.1	1.116*±0.1	.679±0.0	.754±0.1	.724±0.1	.060*±0.0
Na^+	mEq/L	28.5±1.9	24.2±1.6	28.0±1.9	34.2±3.5	47.9*±1.4	68.9*±1.3
	mEq/4 hr	.217±0.0	.237±0.0	.192±0.0	.325±0.1	.576*±0.1	.520*±0.0
K^+	mEq/L	8.85±0.6	7.87±0.6	9.20±0.5	6.39*±0.6	4.10*±0.6	4.33*±0.4
	mEq/4 hr	.064±0.0	.078±0.0	.062±0.0	.058±0.0	.048±0.0	.033*±0.0
Li^+	mEq/L	0	7.9±0.4	30.5*±4.3	43.1*±4.2	63.3*±3.3	178.9*±8.3
	mEq/4 hr	0	0.75*±0.0	.215*±0.0	.379*±0.0	.746*±0.0	1.337*±0.1

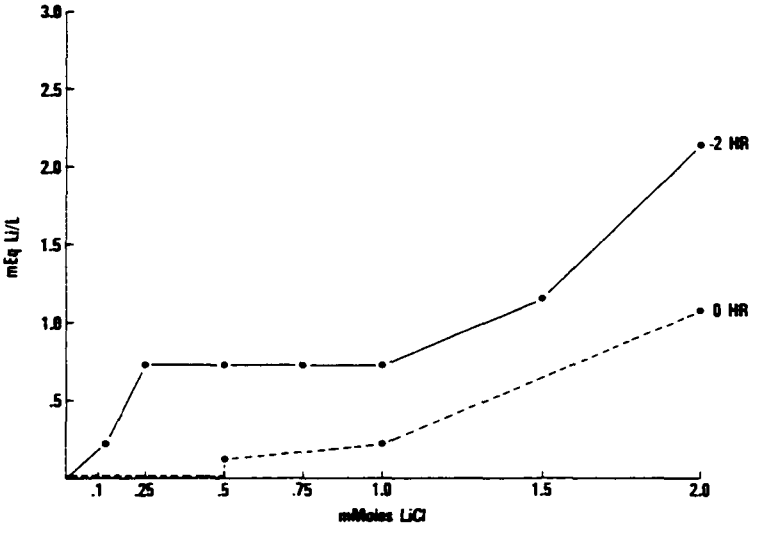

Figure 7. Lithium concentration in serum after oral administration of LiCl. Mean increase in serum Li^+ concentration (mEq Li^+/L) is shown as a function of various doses of LiCl given orally at 0 hour and -2 hour. Atomic absorption did not detect Li^+ in control animals treated with saline. Each point represents the mean value from eight rats.

Figure 8. Lithium concentration in serum and gastric juice. Mean increase in Li^+ concentration (mEq Li^+/L) is shown as a function of LiCl given subcutaneously at various times before pylorus ligation. Atomic absorption did not detect Li^+ in control animals treated with saline. Each column represents the mean value from eight rats.

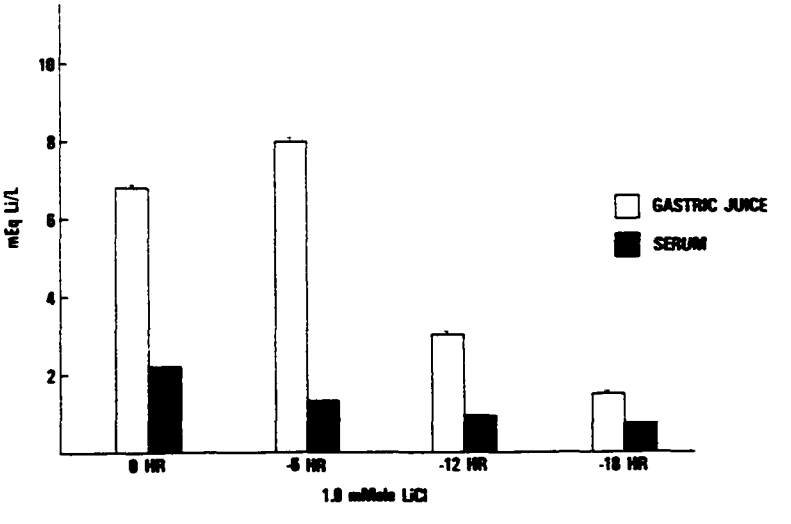

Table 3. Concentration and output of ions in gastric juice after subcutaneous administration of lithium chloride at various times before pylorus ligation. Concentration and output of ions are expressed as mEq/L and mEq/4 hr respectively. Each numeral represents the mean value from eight rats. Numerals to the right indicate standard error. (* significant $\geq$0.05 level)

Concentration and output of ions		Saline Control	LiCl 1.0 mMole				
			0 hr	-2 hr	-6 hr	-12 hr	- 18 hr
H^+	mEq/L	117.3±6.2	17.5*±2.0	31.1*±3.1	36.2*±3.3	70.6*±6.8	91.7*±5.4
	mEq/4 hr	0.816±0.1	0.057*±0.0	0.117*±0.0	0.069*±0.0	0.227*±0.0	0.509*±0.1
Na^+	mEq/L	24.4±1.7	81.2*±1.6	94.2*±5.2	103.7*±7.9	62.6*±7.4	38.1*±3.7
	mEq/4 hr	0.172±0.0	0.275*±0.0	0.348*±0.1	0.203±0.0	0.179±0.0	0.245±0.1

Shay Ulcer Studies

Lithium chloride reduced the incidence of Shay ulcers and of forestomach perforations. The acid concentration, however, did not correlate with ulcer inhibition. For example, oral treatment with LiCl (0.75 mMole) reduced the acid concentration by 41% (Table 4) and did not significantly reduce the incidence of Shay ulcers (Fig. 9, p. 17); oral treatment with LiCl (1.0 mMole) reduced acid concentration by only 27% (Table 4), but significantly reduced Shay ulcers (Fig. 9, p. 17).

Table 4. Shay ulcer study: volume and acid concentration after oral or subcutaneous administration at -2 hr. Results are expressed as percent change from control. Each numeral represents the mean value from eight rats. (* = significant $\geq$0.05 level)

Volume and acid concentration of gastric juice	mMoles LiCl					
	Oral			Subcutaneous		
	.75	1.0	1.5	.75	1.0	1.5
Volume	+10	- 4	+10	-27*	-37*	-37*
S.E.	±8.2	±7.2	±7.9	±6.2	±5.8	±6.0
Acid	-41*	-27*	-62*	-13*	-36*	-85*
S.E.	±6.0	±6.2	±4.3	±3.8	±5.4	±1.3

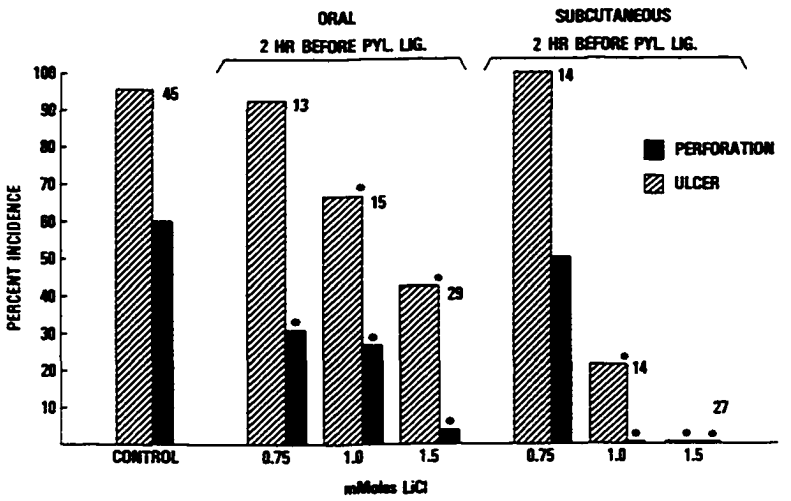

Figure 9. Antiulcer effect of LiCl. Animals were sacrificed 22 hours after pylorus ligation. Percent incidence of animals with ulceration and perforation is indicated by verticle columns. Numerals next to columns indicate the number of rats.

DISCUSSION

Oral administration of LiCl at hypertonic doses appears to increase gastric mucosal permeability to ions. These studies indicate that Na^+ concentration increases while K^+ and H^+ concentrations decrease in gastric juice after oral administration of LiCl (Table 2, p. 13). Apparently, Na^+ moves across the gastric wall from serosa to mucosa while H^+ and K^+ travel in the opposite direction (from mucosa to serosa). Under normal conditions H^+ and K^+ are found in blood at lower concentrations than in gastric juice, whereas Na^+ is more concentrated in blood.[10] The observations noted in this study suggest that oral administration of LiCl at hypertonic doses increases the permeability of the gastric mucosa to H^+, K^+, and Na^+, allowing them to move more freely across the gastric mucosa in response to their concentration gradients. The slight increase in volume observed with oral administration of NaCl and LiCl at hypertonic doses may have been due to osmotic pull.[11-13]

Other investigators have observed a reduction in acid content of the gastric juice in dogs after topical application of hypertonic salt solutions ranging from 1.2 to 2.0 mM.[13,14] Frenning and colleagues[15] attributed their observations to increased mucosal permeability. Altamirano[11] observed increased mucosal permeability to Na^+, K^+, and Cl^- after topical application of hypertonic solutions of non-electrolytes (e.g., sucrose, glucose, and urea). Interestingly, the increase in mucosal permeability to ions is selective; most of

the Li^+ remained in the stomach even though other ions (e.g., H^+, K^+ and Na^+) appear to freely move across the gastric wall.

Subcutaneous administration of LiCl caused an increase in Na^+ concentration and output in gastric juice regardless of the time of administration. The increase in Na^+ content of gastric juice, after LiCl administration, correlates with the inhibition of acid secretion. Interestingly, this correlation does not appear to result from permeability changes induced by lithium's hypertonicity in gastric juice. The Li^+ content in gastric juice was approximately ten times higher after oral administration (Table 2, p. 13) as compared to subcutaneous administration (Fig. 8, p. 14). Many investigators have suggested that H^+ and Na^+ are exchanged across the gastric mucosa mole for mole.[16-18]

The observation that the lithium ion appears to remain in the stomach after oral administration (Table 3, p. 15) may be contradictory to the work of Chung.[19] His work on the canine stomach indicates that Li^+ and H^+ move out of the gastric lumen by the same pathway. His studies, however, were performed under resting conditions, whereas the present study was performed under active secretory conditions. Altamirano[20] suggests that the permeability of the resting mucosa is greater than that of the actively secreting mucosa. In this study the efflux of Li^+ was not calculated. Only Li^+ concentration in gastric juice and serum were measured. Therefore, the possibility that Li^+ leaves the stomach at approximately the same rate as it is absorbed by other tissues and/or excreted by the kidney cannot be excluded. Chung's work[19] has stimulated a number of investigators

to explore the possibility of using Li^+ as a marker for H^+ ion back-diffusion across the gastric mucosa.

Some investigators have found that Li^+ is indeed a reliable marker for back-diffusion of H^+ ions,[21-23] although Ivey[24] provided convincing evidence against this. The data presented in this report that LiCl is antisecretory, and the fact that Li^+ has profound effects on Na^+ transport systems[1,2] further devaluates the possibility of using Li^+ as a marker for back-diffusion of H^+ ions.

As described in the Results section, 1) gastric juice was yellow after both oral and subcutaneous administration of LiCl at -2 hours, but not at 0 hour, 2) volume was significantly greater (according to the Sign test) after subcutaneous administration at -2 hours as compared to subcutaneous administration at 0 hour, and 3) pepsin concentration was not reduced after subcutaneous administration at 0 hour, whereas it was after subcutaneous administration at -2 hours. From these results the following are postulated: 1) a duodenal reflux occurs within the first 2 hours after LiCl administration; 2) the reflux might contain trypsin (from pancreatic secretion) and bile; 3) since the optimal pH for trypsin is around 7.0, the dose-related reduction of acid concentration produced by LiCl at the -2 hour administration time (Fig. 10, p. 21) may have caused the concomitant digestion of pepsin by trypsin. Moreover, the duodenal reflux may have been alkaline (above pH 7) causing the irreversible degradation of pepsin.[25] This would denature the pepsin present at the time of reflux but could not damage the pepsin released after the gastric pH dropped below 7.0. The above mechanisms

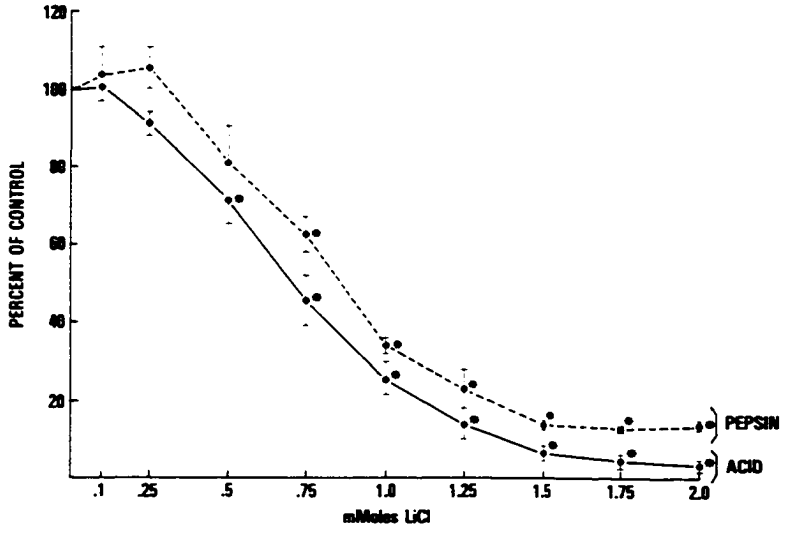

Figure 10. Acid and pepsin concentration after subcutaneous administration of LiCl. Mean decrease of acid and pepsin concentration, expressed as percent of control, is shown as a function of various doses of LiCl given subcutaneously at -2 hour. Each point represents the mean value from 10 rats. Verticle bars indicate standard error. (* = significant $\geq$0.05 level).

would explain the reduction in pepsin concentration by LiCl when given either orally or subcutaneously two hours before pylorus ligation, but not when given orally after pylorus ligation.

Although hypertonic solutions of NaCl and LiCl are equipotent in their ability to reduce acid and pepsin after oral administration at 0 hour, LiCl is more antisecretory than NaCl at -2 hours. This difference may be due to parenteral effects of LiCl not shared by NaCl. The evidence for this is as follows: 1) the serum concentration of Li^+ after oral treatment at -2 hours is significantly greater than at 0 hour, and 2) hypertonic solutions of LiCl are

antisecretory after subcutaneous administration whereas equitonic solutions of NaCl are not. Apparently, very little Li^+ is absorbed from the stomach and when administered orally at -2 hours, Li^+ enters the intestine through the pylorus and is absorbed by the small intestine. Thus, the reduction of acid by oral administration of LiCl at -2 hours may result from both increased mucosal permeability and a parenteral effect.

The duodenal reflux produced by LiCl after administration at -2 hours may have contributed to the reduction of acid and pepsin. The buffering effects of bile and pancreatic bicarbonate may have reduced the acid and pepsin content, whereas trypsin (from pancreatic secretion) could be responsible for the increased depression of pepsin content. Even though the alkaline bile may have buffered the acid at the time of reflux, the fact that bile is a potent stimulator of gastric secretion[26] could provide additional evidence that LiCl is a potent inhibitor of gastric secretion. Furthermore, since LiCl was antisecretory after subcutaneous administration at 0 hour, that is, after pylorus ligation, the contribution of duodenal reflux to parenteral inhibition of gastric acid secretion is small. Such reflux could not have occurred when LiCl was administered after pylorus ligation.

The observation that the concentration of Li^+ was higher in gastric juice than in serum after subcutaneous administration provided a clue to the mechanism of LiCl in reducing acid secretion. We proposed that Li^+ could substitute for H^+ on the H^+-pump and that this might explain the decrease in acid concentration and the high

Li^+ concentration in gastric juice. To explore this possibility, an anticholinergic agent, methscopolamine bromide, was administered (10 mg/kg) at -2 hours subcutaneously, and LiCl was administered at 0 hour at doses of 1.0 and 2.0 mMole subcutaneously. At that dose, methscopolamine bromide completely inhibited H^+ secretion; however, methscopolamine bromide had no effect on Li^+ concentration in gastric juice (Table 5).

Table 5. Effect of saline or methscopolamine bromide administration on concentration of ions in gastric juice after subcutaneous administration of lithium chloride at 0 hr. Concentration of ions was expressed as mEq/L. (* = significant $\geq$0.05 level)

Concentration of ions in gastric juice	Saline			Methscopolamine Bromide		
	Saline Control	LiCl (mMole) 1.0	2.0	Saline Control	LiCl (mMole) 1.0	2.0
# Animals	15	17	17	8	8	7
H^+ (mEq/L)	142.2	9.65*	4.30*	1.20	2.20	3.57
S.E.	±4.5	±2.6	±1.0	±0.5	±0.6	±0.7
Li^+ (mEq/L)	0	5.76*	11.02*	0	5.94*	12.25*
S.E.		±0.3	±0.9		±0.3	±1.0

Since methscopolamine bromide inhibited H^+ secretion by impairing vagal stimulation of parietal cells, but had no effect on Li^+ accumulation in gastric juice, the following was postulated: 1) methscopolamine bromide indirectly blocks active transport of H^+ by inhibiting vagal stimulation of parietal cells, and 2) since methscopolamine bromide did not influence the ability of Li^+ to accumulate in gastric juice, Li^+ was not actively transported by the H^+-pump.

Although the accumulation of Li^+ in gastric juice cannot be attributed to substitution of Li^+ for H^+ on the H^+-pump, this accumulation may be accounted for by other means. Some investigators have shown that Li^+ accumulates in cardiac cells of the heart[27] and other tissues.[1] The fact that Li^+ can compete with Na^+ in passive transport,[1,2,28] but not active transport,[1,2,28-30] might explain this phenomenon. Indeed, Li^+ might enter the stomach via the Na^+ passive transport system, acting as though it were Na^+, in response to the Na^+ concentration gradient. Once in the stomach, Li^+ might be trapped there because of its inability to substitute for Na^+ on the Na^+-pump. Moreover, the possibility that renal excretion of Li^+ occurs at a faster rate than Li^+ movement out of the stomach cannot be excluded. Schou[1] has suggested this possibility for Li^+ accumulation in other tissues.

Lithium chloride may have reduced gastric secretion by inhibiting vagal nerve function. The rat is a spontaneous secretor, secreting copiously without exogenous stimulation even when fasted. This continuous secretion is mediated by vagal stimulation. The effect of lithium on the vagus has been described in detail by Ploeger.[31-33] His studies indicate that Li^+ is an irreversible competitive inhibitor of the Na^+/K^+-pump. Furthermore, Li^+ ions have been shown to inhibit synthesis and release of acetylcholine.[34,35] These observations indicate that LiCl could inhibit gastric secretion by causing vagal dysfunction.

Lithium might interfer with the cyclic nucleotides thereby inhibiting gastric secretion. Lithium chloride inhibits cAMP synthesis

in a number of tissues: thyroid, kidney, fat cells, ovary, toad bladder, and central nervous system.[3] Most investigators concur that Li^+ inhibits cAMP by inhibiting hormone-induced adenylate cyclase.[2,36,37] Whether or not cAMP is necessary for acid secretion seems to depend upon the species under investigation. Sewing and associates[38,39] have provided evidence suggesting cAMP mediated acid secretion in the rat. Assuming that cAMP is necessary for gastric secretion, LiCl could inhibit gastric secretion at this biochemical level.

Even though LiCl inhibited Shay ulcers, ulcer inhibition did not correlate with acid inhibition. This may be due to the presence of blood in the gastric juice of animals with severe ulcerations; the buffering effect of blood may have neutralized the acid formed. Lithium chloride offered better protection when administered subcutaneously than orally (Fig. 9, p. 17). Indeed, at 1.5 mMole, there was complete protection (Fig. 9, p. 17). As shown in Table 5, page 16, the volume of gastric juice was significantly greater with oral administration. We hypothesize that, 1) the greater volume observed with oral treatment distended the stomach and this distension may have aggravated the ulcers, and 2) the higher concentration of LiCl in gastric juice observed with oral administration may have damaged the gastric mucosa.

The ability of LiCl to prevent the formation of Shay ulcers and histamine-induced ulcers (unpublished observations) suggests that lithium may be a potential antiulcer agent. Additional studies need to be performed, however, to validate this possibility.

CONCLUSIONS

1. Lithium chloride reduces gastric secretion regardless of the route of administration.
2. The reduction of gastric secretion after oral administration is due to lithium hypertonicity and appears to work by increasing gastric mucosal permeability to ions.
3. The reduction of gastric acid secretion after subcutaneous administration is not due to lithium hypertonicity in blood or gastric juice and appears to result from a parenteral effect of lithium chloride.
4. Lithium chloride reduces Shay ulcers and forestomach perforations regardless of the route of administration.

REFERENCES

1. Schou M: Biology and pharmacology of the lithium ion. Pharmacol Rev 9:17-58, 1957.

2. Schou M: Possible mechanisms of action of lithium salts: Approaches and perspectives. Biochem Soc Trans 1:81-87, 1973.

3. Singer I, Rotenberg D: Mechanisms of lithium action. N Engl J Med 289:254-260, 1973.

4. Robert A, Bayer RB, Nezamis JE: Gastric mucus content during development of ulcers in fasting rats. Gastroenterology 45:740-751, 1963.

5. Anson ML: The estimation of pepsin, trypsin, papain, and cathepsin with hemoglobin. J Gen Physiol 22:79-89, 1938.

6. Vatier MM, Cheret AM, Bonfils S: Le dosage automatique de 1' activit proteolytique du sue gastrique. Biologie Gastroenterol 1:15-29, 1968.

7. Shay H, Komarov SA, Fels SS, Meranze D, Gruenstein M, Siplet H: A simple method for the uniform production of gastric ulceration in the rat. Gastroenterology 5:43-61, 1945.

8. Robert A, Nezamis JE, Phillips JP: Effect of prostaglandin E_1 on gastric secretion and ulcer formation in the rat. Gastroenterology 55:481, 1968.

9. Conover WJ: Practical nonparametric statistics. John Wiley and Sons Inc, New York, 1971.

10. Konturek SJ: Gastric Secretion. In: Gastrointestinal Physiology. Physiology Series One. E Jacobsen (ed), University Park Press, Baltimore, 4:227-264, 1974.

11. Altamirano M: Action of concentrated solutions of nonelectrolytes on the dog gastric mucosa. Am J Physiol 216:33-40, 1969.

12. Kitahara S: Active transport of Na^+ and Cl^- by in vitro non-secreting cat gastric mucosa. Am J Physiol 213:819-823, 1967.

13. Rehm WS, Schlesinger H, Dennis WH: Effect of osmotic gradients on water transport, hydrogen ion and chloride ion production in the resting and secreting stomach. Am J Physiol 175:473-486, 1953.

14. Kowalewski K, Schier JF, Koheil A: Response of canine gastric mucosa to histamine following experimental impairment of the gastric mucus barrier. Canad J Surg 13:295-302, 1970.

15. Frenning B: The effects of large osmolality variations on the gastric mucosal ion permeability. Acta Physiol Scand 90:1-13, 1974.

16. Berkowitz JM, Janowitz HD: Alteration in composition of hydrochloric acid solutions by gastric mucosa. Am J Physiol 210:216-220, 1966.

17. Bugajski J, Code CF, Schlegel JF: Sodium-hydrogen ion exchange across canine resting gastric mucosa. Am J Physiol 222:858-863, 1972.

18. Ventura VL, Schlegel JF, La Force RC, Code CF: Acceleration of exchange of Na^+ for H^+ across gastric mucosa by short chain fatty acids. Am J Physiol 225:33-37, 1973.

19. Chung RSK, Field M, Silen W: Permeability of gastric mucosa to hydrogen and lithium. Gastroenterology 64:593-598, 1973.

20. Altamirano M: Back diffusion of H^+ during gastric secretion. Am J Physiol 218:1-6, 1970.

21. Chung RSK, Field M, Silen W: Gastric permeability to hydrogen and lithium: A new method for quantitation of the gastric mucosal barrier. Surg Forum 21:297-299, 1970.

22. Gordon MJ, Skillman JJ, Silen W: Assessment of human gastric mucosal permeability by an acid-free technique. Gastroenterology 62:846, 1972.

23. Smith BM, Skillman JJ, Edwards BG, Silen W: Permeability of the human gastric mucosa; alteration by acetylsalicylic acid and ethanol. N Engl J Med 285:716-721, 1971.

24. Ivey KJ, Parsons C, Gray C: Failure of lithium to provide a marker for gastric hydrogen ion back-diffusion in man. Gastroenterology 66:69-72, 1974.

25. Piper DW, Fenton BH: pH stability and activity curves of pepsin with special reference to their clinical importance. Gut 6:506-508, 1965.

26. Nahrwold DL: Bile as a gastric secretory stimulant. Surgery 71:157-160, 1972.

27. Carmeliet EE: Influence of lithium ions on the transmembrane potential and cation content of cardiac cells. J Gen Physiol 47:501-530, 1964.

28. Gardner DR, Kerkut GA: A comparison of the effects of sodium and lithium ions on action potentials from Helix aspersa neurones. Comp Biochem Physiol 25:33-48, 1968.

29. Baker PF: Phosphorus metabolism of intact crab nerve and its relation to the active transport of ions. J Physiol 180:383-423, 1965.

30. Connelly CM: Recovery processes and metabolism of nerve. Rev mod Physics 31:475-484, 1959.

31. Ploeger EJ: The effects of lithium on excitable cell membranes. On the mechanism of inhibition of the sodium pump of non-myelinated nerve fibers of the rat. Europ J Pharmacol 25:316-321, 1974.

32. Ploeger EJ: The effects of lithium on excitable cell membranes. The influence of the ATPase of homogenates of the non-myelinated nerve fibers of the rat. Arch int Pharmacodyn 210:374-382, 1974.

33. Ploeger EJ, den Hertog A: The effects of lithium on excitable cell membranes. II. The effect on the electrogenic sodium pump of non-myelinated nerve fibers of the rat. Europ J Pharmacol 21:24-29, 1973.

34. Bjegovic M, Randic M: Effects of lithium ions on the release of acetylcholine from cerebral cortex. Nature 230:587-588, 1971.

35. Vizi ES, Illes P, Ronai A, Knoll J: The effect of lithium on acetylcholine release and synthesis. Neuropharmacol 11:521-530, 1972.

36. Donsa T, Hechter O: The effect of NaCl and LiCl on vasopressin-sensitive adenyl cyclase. Life Sciences 9:765-770, 1970.

37. Wolf J, Berens SC, Jones AB: Inhibition of thyrotropin-stimulated adenyl cyclase activity of beef thyroid membranes by low concentration of lithium ion. Biochem Biophys Res Commun 39:77-82, 1970.

38. Ruoff HJ, Sewing KF: Cyclic 3',5'-adenosine monophosphate in the rat gastric mucosa after starvation, feeding, and pentagastrin. Scand J Gastroent 8:241-243, 1973.

39. Ruoff HJ, Sewing KF: Rat gastric mucosal cAMP following cholinergic and histamine stimulation. Europ J Pharmacol 28:338-343, 1974.