THE EFFECT OF DIETARY MANIPULATION IN CHRONIC URTICARIA AND ANGIOEDEMA

by

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ABSTRACT

Urticaria and angioedema symptoms result primarily from the physiological actions of histamine. Some individuals with urticaria have a decreased ability to degrade dietary histamine before it enters the circulation. Foods high in histamine, such as fermented foods, may exacerbate urticaria and angioedema in these individuals. Artificial food colour, benzoates, butylated hydroxytoluene and butylated hydroxyanisole may exacerbate urticaria and angioedema by increasing endogenous release of histamine. The objectives of the study were to assess the effect of a histamine-reducing diet on urticaria and angioedema symptoms and nutrient intake. Nineteen subjects with chronic urticaria or angioedema were randomized to a treatment group (n=9) or a control group (n=10). The treatment group followed a histamine-reducing diet, and the control group eliminated artificial sweeteners from their diets. The subjects recorded antihistamine medication intake, number of wheals, severity of pruritus and angioedema for two weeks prior to starting the diet and for six weeks during the dietary intervention. Three day food records were completed every two weeks. There were no significant group differences throughout the study with respect to the symptom variables. The mean antihistamine intake of the treatment group was 17±12 tablets during the two weeks prior to the diet and
12±13 tablets during the first two weeks of the dietary intervention. This difference was significant (p<0.05). There were significant group by time interactions (p<0.05) for fat, calcium, vitamin C and vitamin B12. Observation of the results indicate that total fat, calcium and vitamin B12 intake decreased and vitamin C intake increased in subjects consuming the treatment diet compared to subjects consuming the control diet.

The histamine-reducing diet did not result in an improvement in urticaria and angioedema symptoms. However, dietary intervention may have decreased the need for antihistamine medication. Adherence to the histamine-reducing diet may result in a reduced intake of some nutrients. Therefore, dietary counselling and follow-up are essential components of dietary intervention.
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>ABSTRACT</th>
<th>ii</th>
</tr>
</thead>
<tbody>
<tr>
<td>TABLE OF CONTENTS</td>
<td>iv</td>
</tr>
<tr>
<td>LIST OF TABLES</td>
<td>viii</td>
</tr>
<tr>
<td>LIST OF FIGURES</td>
<td>x</td>
</tr>
<tr>
<td>ACKNOWLEDGEMENT</td>
<td>xi</td>
</tr>
<tr>
<td>CHAPTER 1: INTRODUCTION</td>
<td>1</td>
</tr>
<tr>
<td>STUDY OBJECTIVES</td>
<td>3</td>
</tr>
<tr>
<td>NULL HYPOTHESES TESTED</td>
<td>3</td>
</tr>
<tr>
<td>CHAPTER 2: LITERATURE REVIEW</td>
<td>4</td>
</tr>
<tr>
<td>INTRODUCTION TO LITERATURE REVIEW</td>
<td>4</td>
</tr>
<tr>
<td>PATHOLOGY OF URTICARIA AND ANGIOEDEMA</td>
<td>5</td>
</tr>
<tr>
<td>EFFECT OF DIET ON BODY HISTAMINE</td>
<td>9</td>
</tr>
<tr>
<td>Histamine Poisoning</td>
<td>9</td>
</tr>
<tr>
<td>Altered Histamine Metabolism in Urticaria Subjects</td>
<td>11</td>
</tr>
<tr>
<td>Factors Affecting Histamine Metabolism</td>
<td>15</td>
</tr>
<tr>
<td>Histamine Releasing Food and Food Additives</td>
<td>18</td>
</tr>
<tr>
<td>Micronutrient Intake</td>
<td>21</td>
</tr>
<tr>
<td>Summary</td>
<td>22</td>
</tr>
<tr>
<td>PREVIOUS DIETARY MANIPULATION STUDIES IN CHRONIC URTICARIA AND ANGIOEDEMA</td>
<td>23</td>
</tr>
<tr>
<td>Uncontrolled Food-Additive Free Diets</td>
<td>23</td>
</tr>
<tr>
<td>Controlled Food-Additive Free Diets</td>
<td>25</td>
</tr>
<tr>
<td>Low Histamine Diets</td>
<td>27</td>
</tr>
</tbody>
</table>

iv
APPENDIX A: RECRUITMENT POSTER .......................................................... 106
APPENDIX B: HISTAMINE-REDUCING DIET .............................................. 107
APPENDIX C: CONTROL DIET ................................................................. 108
APPENDIX D: URTICARIA/ANGIOEDEMA DAILY ASSESSMENT .................. 109
APPENDIX E: THREE-DAY FOOD RECORD .............................................. 110
APPENDIX F: FOOD SOURCES OF SELECTED NUTRIENTS ....................... 111
APPENDIX G: CONSENT FORM ............................................................... 112
APPENDIX H: ETHICS APPROVAL FORM ................................................ 114
APPENDIX I: REASONS GIVEN BY POTENTIAL SUBJECTS FOR NOT
PARTICIPATING IN THE STUDY ............................................................. 115
APPENDIX J: URTICARIA AND ANGIOEDEMA SYMPTOM ASSESSMENT
SCALES WHICH WERE NOT COMPLETED ............................................. 116
APPENDIX K: STARTING AND ENDING DATES FOR EACH SUBJECT .......... 117
APPENDIX L: DIETARY NONCOMPLIANCE AND CONFOUNDING VARIABLE
CHANGES .................................................................................................. 118
APPENDIX M: WEIGHT CHANGE OVER THE STUDY PERIOD ...................... 121
LIST OF TABLES

Table 1: POSSIBLE CAUSES OF URTICARIA ........................................ 9
Table 2: SYMPTOMS OF HISTAMINE POISONING ................................. 10
Table 3: HISTAMINE RELEASING FOODS ........................................... 19
Table 4: HISTAMINE RELEASE FROM THE WASHED LEUCOCYTES OF 30
SUBJECTS ON EXPOSURE TO FOOD ADDITIVES OR ASPIRIN .............. 21
Table 5: DIETARY MANIPULATION STUDIES IN CHRONIC URTICARIA .... 24
Table 6: RESULTS OF FOOD ADDITIVE CHALLENGES IN CHILDREN WITH
ANGIOEDEMA AND URTICARIA .................................................. 26
Table 7: AMINES AND THE AMINO ACID PRECURSOR .......................... 31
Table 8: NUMBER OF SUBJECTS INQUIRING ABOUT AND ENTERING THE
STUDY .................................................................................. 58
Table 9: SUBJECT CHARACTERISTICS .............................................. 60
Table 10: TOTAL NUMBER OF ANTIHISTAMINE TABLETS TAKEN .......... 62
Table 11: NUMBER OF DAYS ANTIHISTAMINE TABLETS WERE TAKEN .... 62
Table 12: TOTAL NUMBER OF ANTIHISTAMINE TABLETS TAKEN BEFORE THE
CONTROL OR TREATMENT DIET (TIME 1) AND AFTER THE INITIATION
OF THE DIET (TIME 2) ............................................................. 63
Table 13: TOTAL NUMBER OF WHEALS REPORTED ............................. 63
Table 14: NUMBER OF DAYS WHEALS WERE REPORTED ..................... 64
Table 15: TOTAL SEVERITY OF ITCHINESS SCORES ............................. 64
Table 16: SEVERITY OF ITCHINESS OF INDIVIDUALS WITH URTICARIA AND
ANGIOEDEMA ................................................................. 65
Table 17: NUMBER OF DAYS THAT ITCHINESS WAS REPORTED ........... 65
Table 18: TOTAL SEVERITY OF ANGIOEDEMA SCORES ....................... 66
Table 19: NUMBER OF DAYS THAT ANGIOEDEMA WAS REPORTED ....... 66
Table 20: ADJUSTED CRITICAL F AND CALCULATED F FOR EIGHT
URTICARIA AND ANGIOEDEMA VARIABLES ................................ 67
Table 21: MACRONUTRIENT INTAKE OF INDIVIDUALS WITH URTICARIA AND
ANGIOEDEMA COMPARED TO THE RECOMMENDED NUTRIENT INTAKES 70
Table 22: MINERAL INTAKE OF INDIVIDUALS WITH URTICARIA AND ANGIOEDEMA COMPARED TO THE RECOMMENDED NUTRIENT INTAKES 71
Table 23: VITAMIN INTAKE OF INDIVIDUALS WITH URTICARIA AND ANGIOEDEMA COMPARED TO THE RECOMMENDED NUTRIENT INTAKES 72
Table 24: CALCIUM AND VITAMIN C INTAKE OF INDIVIDUALS WITH URTICARIA AND ANGIOEDEMA 73
Table 25: P AND F VALUES FOR NUTRIENTS THAT SATISFY THE ASSUMPTION OF SPHERICITY 73
Table 26: ADJUSTED CRITICAL F AND CALCULATED F FOR EIGHT NUTRIENTS THAT DID NOT SATISFY THE ASSUMPTION OF SPHERICITY 74
Table 27: THE EFFECT OF THE TREATMENT DIET ON URTICARIA AND ANGIOEDEMA SYMPTOMS (SUBJECT 11) 79
Table 28: THE EFFECT OF THE TREATMENT DIET ON URTICARIA AND ANGIOEDEMA SYMPTOMS (SUBJECT 12) 79
Table 29: THE EFFECT OF THE TREATMENT DIET ON URTICARIA AND ANGIOEDEMA SYMPTOMS (SUBJECT 13) 80
Table 30: THE EFFECT OF THE TREATMENT DIET ON URTICARIA AND ANGIOEDEMA SYMPTOMS (SUBJECT 17) 80
LIST OF FIGURES

Figure 1: HISTAMINE METABOLISM .......................... 11

Figure 2: FOOD-INDUCED HISTAMINOSIS ...................... 13

Figure 3: SAMPLE SIZE CALCULATION .......................... 42

Figure 4: GROUP X TIME INTERACTION: Fat ...................... 75

Figure 5: GROUP X TIME INTERACTION: Calcium .................. 75

Figure 6: GROUP X TIME INTERACTION: Vitamin B12 .............. 76

Figure 7: GROUP X TIME INTERACTION: Vitamin C .............. 76
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I thank my friends and family for their support during the last two and a half years. The term "boomerang children" has a new meaning to my parents.

Finally, I would like to thank all of my subjects for their commitment to the study.
Urticaria affects 15 - 20 percent of the population at least once in their lifetime (Lessof, 1991). The cosmetic burden and associated pruritus of chronic urticaria and angioedema limit the quality of life for those affected with the condition. The management of this condition is a frustrating and confusing area in medical practice, both for the clinician and the patient.

Antihistamine medication is the current treatment for chronic urticaria and angioedema. Many patients take the medication every day for the duration of the disease. Drowsiness is a significant side-effect of first-generation antihistamines, and this may interfere with patient safety and productivity. Second-generation, non-sedating, antihistamines are very expensive. Recent research suggests that certain antihistamines may promote tumour growth. The research was conducted because the structure of antihistamines is similar to a tamoxifen analogue which promotes tumour growth at low doses. Loratadine (Claritin®), astemizole (Hismanal®) and hydroxyzine (Atarax®) were shown to promote tumour growth when injected into mice (Brandes et al., 1994). Further experimental research and
Introduction

epidemiological studies are required to determine the significance of these findings in the human. Currently antihistamine medications are considered safe, and the benefits of their use appear to be greater than the potential risks (Simons, 1994). However, some individuals do not want to use antihistamine medication on a continuous basis.

If dietary components cause or contribute to urticaria and angioedema symptoms, dietary intervention must be considered as a possible treatment. However, an inadequate nutrient intake is a concern associated with a histamine-reducing diet. Thus, the purpose of the present study was to investigate the effects of a histamine-reducing diet on urticaria and angioedema and nutrient intake.
STUDY OBJECTIVES
The specific objectives of the present study were:

1. To evaluate the effect of a histamine-reducing diet\(^1\) in chronic urticaria and angioedema by monitoring:
   
   a) the absolute number of antihistamine tablets taken, the number of wheals and the severity of urticaria and angioedema
   
   b) the number of days that antihistamine tablets were taken, and the number of days that wheals, pruritus and angioedema were reported

2. To evaluate the effect of a histamine-reducing diet on nutrient intake.

NULL HYPOTHESES TESTED

1. There will be no difference between the treatment and control groups with respect to:
   
   a) the absolute number of antihistamine tablets taken, the number of wheals, the severity of urticaria and angioedema
   
   b) the number of days that antihistamine tablets were taken and wheals, pruritus and angioedema were reported

2. There will be no difference between the treatment and control groups with respect to intake of:
   
   a) kilocalories, protein, carbohydrate and total fat
   
   b) calcium, iron, magnesium, phosphorus and zinc
   
   c) vitamins A, B\(1\), B\(2\), B\(3\), B\(6\), B\(12\), C and folacin

\(^1\) The histamine-reducing diet eliminates food additives, foods that may stimulate endogenous histamine release and foods which have elevated levels of histamine.
INTRODUCTION TO LITERATURE REVIEW

Histamine is an important mediator of urticaria and angioedema, and the present study was designed to assess whether decreasing dietary histamine and food additives which may increase endogenous release of histamine would affect the symptoms of chronic urticaria and angioedema. In this section the literature relevant to the hypothesis is reviewed. The first section addresses the key role of body histamine in the pathology of urticaria and angioedema. Next, the scientific evidence supporting the influence of diet on body histamine and urticaria and angioedema is reviewed. Finally, the formation of food histamine is discussed to provide a rationale for the histamine-reducing diet.

PATHOLOGY OF URTICARIA AND ANGIOEDEMA

Urticaria is characterized by local pruritic hives and erythema in the dermis. Individual wheals\(^2\) vary from one millimetre to several centimetres in diameter and may be found on

\(^2\) A temporary red or pale raised area of the skin, often accompanied by severe itching.
any part of the body. The wheals usually last less than four hours. Angioedema is similar to urticaria, but with larger edematous areas that involve deeper swelling of the dermis and mucous membranes. Angioedema usually affects the eyelids, lips and tongue. The face, ears, chin, genitalia, hands, feet, trunk and arms may also be affected (Holgate & Church, 1993).

Urticaria and angioedema result from mast cell degranulation in the dermis of the skin. Under an electron microscope, degranulated mast cells are seen at the affected site (Burrall et al., 1990). An investigation of the affected sites of 43 patients with chronic urticaria, revealed ten times the normal number of mast cells (Natbony et al., 1983). Mast cells are an integral component of the immune system. These cells are found throughout the body, but are most abundant around connective tissues, blood vessels, lymphatic vessels and nerves (White, 1990). The purpose of mast cells is to degranulate and release powerful inflammatory chemicals into surrounding tissues during an immune system defence. These inflammatory chemicals are responsible for the symptoms of urticaria and angioedema.

Histamine, a biogenic amine, is stored preformed within mast cells and is released immediately upon mast cell degranulation. Subjects with chronic urticaria have a significantly increased amount of histamine in the skin (Smith et
This may result from an increased number of mast cells or an increased amount of histamine in each mast cell or both. The biological effects of histamine are very important in urticaria and angioedema (Armenaka et al., 1992; White, 1990). The effects of histamine are mediated through histamine receptors in the tissues. The result of histamine 1 (H1) receptor stimulation includes increased vascular permeability, pruritus, smooth muscle contraction, prostaglandin generation, decreased atrioventricular node conduction time with resultant tachycardia, activation of vagal reflexes and increased levels of cyclic guanosine monophosphate. The result of histamine 2 (H2) receptor stimulation includes gastric acid secretion, increased lower airway mucus secretion, increased levels of cyclic adenosine monophosphate and esophageal contraction. The result of combined H1/H2 receptor stimulation includes vasodilation (hypotension, flushing and headache) and tachycardia (White, 1990). Vasodilation, pruritus and increased vascular permeability are the central features of urticaria and angioedema. As a result of these vascular changes, fluid seeps from the blood vessels into the surrounding tissues causing tissue swelling.

Prasad et al. (1967) found the blood histamine levels of urticaria subjects in active disease to be significantly higher than normal controls. Other studies, however, have not found a
difference in plasma histamine between urticaria and control subjects (Murdoch et al., 1987; Pollock et al., 1991). There is little research investigating the circulating plasma level of histamine, even though this is crucial information (Taylor, 1986). Concomitant symptoms may occur with urticaria, such as headaches, arthralgia, the sensation of a lump in the throat, hoarseness, shortness of breath, wheezing, nausea, vomiting, abdominal pain and diarrhea (Soter, 1991). These symptoms may be systemic manifestations of excess plasma histamine.

Inflammatory mediators other than histamine also contribute to urticaria and angioedema symptoms. Antihistamine medication does not completely relieve hives, and hives last longer than the time that could be attributed to the effect of histamine alone (Holgate & Church, 1993). Prostaglandins, kinins, platelet-activating factor and major basic protein\(^3\) function with histamine to produce urticaria and angioedema. The relative importance of each of the inflammatory mediators varies among individuals.

Mast cells are degranulated by a variety of immunological and non-immunological factors. As a result, many factors have been identified in the pathogenesis of urticaria (Table 1). In

\(^3\) Major basic protein, a toxic product of eosinophil degranulation, is elevated in the lesional skin of subjects with chronic urticaria (Armenaka & Rosenstrech, 1992).
Literature Review

75% of chronic urticaria cases, the inciting agent remains unknown (Burrall et al., 1990). Diet may contribute to chronic urticaria and angioedema symptoms in some individuals.

<table>
<thead>
<tr>
<th>Cause</th>
<th>Examples</th>
</tr>
</thead>
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<tr>
<td>Physical Stimuli</td>
<td>Pressure, change of temperature, sweating, exercise, sunlight</td>
</tr>
<tr>
<td>Immune Changes</td>
<td>Bacterial, viral and parasitic infections, allergic diseases, lupus erythematosus, mastocytosis, and urticarial vasculitis</td>
</tr>
<tr>
<td>Hormonal Changes</td>
<td>Hormone replacement therapy, menarche, menopause, menstrual cycle</td>
</tr>
<tr>
<td>Drug ingestion</td>
<td>Morphine, codeine</td>
</tr>
<tr>
<td>Dietary</td>
<td>Benzoates, tartrazine, strawberries</td>
</tr>
<tr>
<td>Psychological</td>
<td>Stress</td>
</tr>
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References: Burrall, 1990; Lessof, 1991; Soter, 1991; Armenaka & Rosenstreich, 1992

EFFECT OF DIET ON BODY HISTAMINE

Histamine Poisoning

Histamine poisoning results from the ingestion of food with very high levels of histamine. Spoiled fish and cheese are the primary foods associated with histamine poisoning (Taylor, 1986). A variety of symptoms develop several minutes to a few hours after the implicated food is eaten (Table 2). The symptoms usually resolve after a few hours. A total of 110 histamine
Literature Review

Poisoning outbreaks were reported in the United States between 1968 and 1981 (Taylor, 1986). Under a medically supervised research study, healthy volunteers deliberately consumed spoiled mackerel samples to determine the level of food histamine necessary to produce histamine poisoning. The amount of histamine in each food sample did not correlate with the clinical reactions to the samples (Ijomah et al., 1991). As food samples spoil, histamine as well as other amines increase in the food. These amines, such as cadaverine, inhibit the enzymes which degrade histamine, allowing plasma histamine levels to rise (Bjeldanes et al., 1977). The lack of correlation between the histamine in food samples and the clinical reactions may reflect varying levels of other amines in the food samples. Additionally, the

Table 2: Symptoms of Histamine Poisoning

<table>
<thead>
<tr>
<th>Body System</th>
<th>Symptom</th>
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<tbody>
<tr>
<td>Cutaneous</td>
<td>Rash, urticaria, edema, localized inflammation</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Nausea, vomiting, diarrhea, cramping</td>
</tr>
<tr>
<td>Hemodynamic</td>
<td>Hypotension</td>
</tr>
<tr>
<td>Neurological</td>
<td>Headaches, palpitations, flushing, tingling, burning, itching</td>
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Reference: Taylor, 1986
effectiveness of the enzymes which degrade histamine may differ among individuals resulting in varying sensitivity to dietary histamine (Lessof, 1991).

Altered Histamine Metabolism in Urticaria Subjects

Histamine is degraded by two enzymes, N-methyltransferase and diamine oxidase (Figure 1).

Figure 1: HISTAMINE METABOLISM

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**Figure 1:** Synthesis and catabolism of histamine. Percentage recovery of histamine and its metabolites in the urine in the 12 hours after intradermal [14C]histamine in human males. (Modified from Douglas WW. Histamine and 5-hydroxytryptamine (serotonin) and their autacoids. In: Gilman AG, Goodman LS, Gilman A, eds. Goodman and Gilman’s The pharmacologic basis of therapeutics. 6th ed. New York: Macmillan Publishing, 1980:618.)

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**Figure 1:** White M. The role of histamine in allergic disease. J Allergy Clin Immunol 1990; 86,4(2):599-605.
Diamine oxidase (DAO) on the villus tip of the intestinal mucosa degrades intestinal histamine, preventing the entry of large amounts of histamine into the portal circulation. Some urticaria subjects have significantly reduced DAO activity. Lessof et al. (1990) measured small bowel DAO activity using a post-heparin plasma DAO curve and direct jejunal biopsy. The urticaria subjects had a significantly decreased DAO activity compared to the control subjects (p<0.02). In four of the five urticaria subjects studied, jejunal DAO activity was less than the lowest control group response (n=10).

N-methyl transferase and circulating diamine oxidase degrade plasma histamine. These enzymes may be deficient in some subjects with urticaria and angioedema. Control and urticaria subjects received intravenous histamine infusions at increasing rates until a clinical endpoint, such as vasodilation, flushing or headaches was reached. The half life of plasma histamine was significantly greater in urticaria subjects than control subjects (6.2 ± 1.3 minutes compared to 4.0 ± 0.7; p=0.02), and significantly less histamine was required to reach a clinical endpoint in the urticaria subjects (Pollock et al., 1991). The wheal and flare response to intradermal injection of histamine

---

4 Intravenous administration of heparin results in the release of DAO from the villus tip into the circulation. DAO activity in the plasma is measured over time.
Literature Review

was shown to be significantly longer in urticaria subjects than in control subjects (Maxwell et al., 1990). These studies suggest that urticaria subjects have a compromised ability to remove histamine from the circulation.

Sattler & Lorenz (1990) proposed Food-Induced Histaminosis as a distinct disease concept (Figure 2).

Fig. 2. Scheme for the disease concept of enteral-induced histaminosis: histamine in the gastrointestinal tract (from food or upper GI bleeding) can only enter the circulation in case of DAO blockade (risk factor). Elevated plasma histamine leads to the well-known disease presentation (Lorenz et al., 1982) which is denominated here as histaminosis. This model is originally based on epidemiological terms (Fletcher et al., 1982) and was modified by Sattler and Lorenz (1987) for enteral-induced histaminosis.


Figure 2: FOOD-INDUCED HISTAMINOSIS
Increased histamine and DAO blocking agents in the intestinal lumen lead to histamine absorption, increased plasma histamine and disease presentation. To demonstrate the food-induced histaminosis concept, Sattler et al. (1988) randomized pigs to receive a DAO blocker or saline. The pigs were given a 60 mg oral histamine dose. Blood histamine and clinical symptoms increased significantly in the pigs which received the DAO blockers, but did not increase in the control pigs (p<0.001). Similar results have been demonstrated in sheep (Sjaastad, 1967).

Kanny et al. (1993) applied these concepts to human subjects with urticaria. Control and urticaria subjects were given 120 mg of histamine through duodenal instillation. The plasma histamine levels remained stable in the control subjects, and they did not exhibit symptoms other than transient facial flushing. Thirty-two percent of the urticaria subjects developed urticaria within one hour of the histamine instillation, and overall, 64% of the urticaria subjects developed urticaria within 12 hours of the histamine instillation. The urticaria subjects exhibited other symptoms, such as accelerated heart rate, drop in blood pressure, facial flushing, pruritus, headache, gastrointestinal disturbance (bloating, cramps, nausea or epigastric burning), rhinitis and coughing. These symptoms may have resulted from increased plasma histamine. Plasma histamine was similar between the groups at
time 0, but was significantly higher in the urticaria subjects 5, 15 and 45 minutes after histamine instillation. It was concluded that urticaria subjects have a deficiency of histamine degrading enzymes, and this resulted in increased plasma histamine and clinical symptoms. However, the urticaria attacks may have been due to the natural occurrence of the symptoms in these subjects and not the histamine instillation. A separate urticaria control group which received a placebo treatment would allow stronger conclusions to be drawn from this study.

Factors Affecting Histamine Metabolism

The activity of diamine oxidase and N-methyltransferase may be inhibited by concomitant oral consumption of food or drugs. Histamine poisoning results from consumption of histamine-rich food, such as spoiled fish; however, consumption of histamine alone does not produce histamine poisoning (Taylor, 1986). Cadaverine and putrescine are amines that increase in spoiled food with histamine. Cadaverine has been shown to inhibit the activity of diamine oxidase in vitro (Taylor & Lieber, 1978). Bjeldanes et al. (1977) studied the ability of these amines to potentiate histamine toxicity. Oral administration of 150 mg/kg of histamine did not cause mortality in five guinea-pigs. Administration of the same histamine dose with 50 mg/kg of
cadaverine resulted in the death of 3 out of 9 guinea-pigs. A 75 mg/kg cadaverine dose resulted in the death of 5 out of 6 guinea-pigs. Simultaneous administration of cadaverine and histamine resulted in the greatest mortality. Administration of putrescine did not result in death. Sattler & Lorenz (1990) investigated the in vitro potential of 486 drugs to inhibit purified intestinal DAO activity. Ninety-four drugs inhibited diamine oxidase. Several cases of histamine poisoning have been associated with isoniazid® which is used in the treatment of tuberculosis (Uragoda & Kottegoda, 1977). However, in Sattler & Lorenz's study, isoniazid® was only a weak inhibitor of diamine oxidase. Further in vivo studies are necessary to clarify the relevance of drugs and food amines in human histamine poisoning.

Diamine oxidase is located on the villus tip of the enterocytes. Conditions which damage the villus tip may decrease the activity of diamine oxidase. Rat intestinal mucosa was damaged by a perfusion with hyperosmolar sodium sulphate solution which resulted in a significant decrease in mucosal and plasma DAO (p<0.005) (Luk et al., 1980). Coeliac patients in active disease exhibit below normal postheparin plasma DAO curves. The diamine oxidase curves improved after 3 and 6 months on a gluten-free diet (p<0.001) (D'Agostino et al., 1987). Conditions or diseases which damage the intestinal mucosa may decrease DAO
activity and allow intestinal histamine to be absorbed more readily into the circulation. Therefore, the integrity of the mucosa may be a relevant factor in the presentation of urticaria and angioedema.

Many factors contribute to intestinal histamine. The intestinal flora may have the ability to decarboxylate histidine and therefore produce histamine. Irvine et al. (1959) demonstrated an increase in urinary histamine, 2 to 4 hours after meat consumption. A similar increase was observed when oral histidine, which approximated the histidine in the meat meal, was administered. Urinary histamine did not increase after a bread and milk meal. This suggests that the histidine in the meat meal was responsible for the increase in urinary histamine. After an antibiotic was administered to the subjects, neither the meat meal nor the histidine increased urinary histamine. These results suggest that intestinal flora are necessary for histamine production. The study was conducted on four men and three dogs, and a statistical analysis was not performed. There have been no well-controlled studies to support these findings.

Mast cells, which are numerous in the intestinal wall, may contribute to intestinal histamine. Blood particles remaining in the gut after gastrointestinal bleeding may also contribute to intestinal histamine (Sattler & Lorenz, 1990). Conditions which
increase intestinal histamine may be relevant to the presentation of urticaria and angioedema if the intestinal histamine is absorbed into the circulation.

In summary, diamine oxidase and N-methyltransferase enzymes are deficient in some subjects with urticaria, allowing intestinal histamine to be absorbed into the circulation and slowing degradation of plasma histamine. These individuals may experience urticaria after consumption of histamine containing food. Factors, such as amine and drug consumption, may further inhibit these enzymes and worsen urticaria. Chronic urticaria and angioedema may also be exacerbated by increased endogenous release of histamine after consumption of food and food additives.

Histamine Releasing Food and Food Additives

Certain foods have been termed "histamine releasing foods", because they exacerbate food allergy symptoms (Finn, 1987). However, research studies to evaluate these claims have not been conducted (Ortolani, 1992). The "histamine releasing foods" have constituents which may account for the exacerbation of allergic reactions (Table 3).
Literature Review

Table 3: HISTAMINE RELEASING FOODS

<table>
<thead>
<tr>
<th>FOOD</th>
<th>CONSTITUENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pineapple</td>
<td>Salicylate</td>
</tr>
<tr>
<td>Strawberry</td>
<td>Benzoate</td>
</tr>
<tr>
<td>Tomato</td>
<td>Salicylate</td>
</tr>
<tr>
<td>Fish</td>
<td>Histamine</td>
</tr>
<tr>
<td>Chocolate</td>
<td>Amines</td>
</tr>
<tr>
<td>Alcohol</td>
<td>Amines</td>
</tr>
<tr>
<td>Egg white</td>
<td>Allergen</td>
</tr>
</tbody>
</table>

References: Jacobsen, 1987 and Swain et al., 1985

Twenty to forty percent of chronic urticaria cases are aggravated by acetylsalicylic acid (Burrall et al., 1990) through an unknown mechanism. Acetylsalicylic acid inhibits the cyclo-oxygenase enzyme and alters prostaglandin and leukotrienes production from arachidonic acid. This may be responsible for the exacerbation of urticaria. Salicylates in food may have a similar, but weaker, cyclo-oxygenase effect (Stevenson, 1986). The structure of benzoates is similar to acetylsalicylic acid; therefore, benzoates may also inhibit the cyclo-oxygenase enzyme (Holgate & Chruch, 1993).

The role of food additives in histamine release have been studied in vitro and in vivo. Murdoch et al. (1987) incubated washed mast cells and other leucocytes obtained from urticaria and control subjects in a Tris ACM buffer. Histamine release was
measured after addition of various food additives to the buffer. The concentrations of the food additives in the buffers were determined by an estimate of the plasma concentration after maximum daily ingestion of the food additives. A histamine release greater than the spontaneous release of histamine in the Tris ACM buffer alone plus two standard deviations was considered a positive response. There was no significant difference between the urticaria and control subjects (Table 4). Significant histamine release occurred in a minority of subjects.

In a separate study, Murdoch, Pollock & Naeem (1987) challenged ten healthy subjects with tartrazine or a placebo. There was a significant rise in plasma histamine after a 150 mg tartrazine challenge (p<0.005). There was no significant rise in plasma histamine after a challenge of either 5 or 50 mg of tartrazine or a placebo. These studies suggest that ingestion of tartrazine and other food additives may result in endogenous histamine release in some individuals.
Table 4: HISTAMINE RELEASE FROM THE WASHED LEUCOCYTES OF 30 SUBJECTS EXPOSED TO FOOD ADDITIVES OR ASPIRIN

<table>
<thead>
<tr>
<th>Class</th>
<th>Compound</th>
<th>Number of Subjects with Significant Histamine Release</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Healthy Subjects (Total 18)</td>
</tr>
<tr>
<td>Azo Colour</td>
<td>Amaranth</td>
<td>2</td>
</tr>
<tr>
<td>Azo Colour</td>
<td>Sunset Yellow</td>
<td>1</td>
</tr>
<tr>
<td>Azo Colour</td>
<td>Carmoisine</td>
<td>3</td>
</tr>
<tr>
<td>Azo Colour</td>
<td>Tartrazine</td>
<td>3</td>
</tr>
<tr>
<td>Non-azo Colour</td>
<td>Green S</td>
<td>0</td>
</tr>
<tr>
<td>Non-azo Colour</td>
<td>Quinoline Yellow</td>
<td>1</td>
</tr>
<tr>
<td>Non-azo Colour</td>
<td>Indigo Carmine</td>
<td>2</td>
</tr>
<tr>
<td>Natural Colour</td>
<td>Annatto</td>
<td>1</td>
</tr>
<tr>
<td>Antioxidant</td>
<td>BHA</td>
<td>1</td>
</tr>
<tr>
<td>Antioxidant</td>
<td>BHT</td>
<td>4</td>
</tr>
<tr>
<td>Other</td>
<td>Sodium Benzoate</td>
<td>3</td>
</tr>
<tr>
<td>Other</td>
<td>Acetylsalicylic acid</td>
<td>2</td>
</tr>
</tbody>
</table>

Reference: Murdoch et al, 1987
BHA= butylated hydroxyanisole; BHT= butylated hydroxytoluene

Micronutrient Intake

Johnston et al. (1992) evaluated the effect of ascorbic acid supplementation on blood histamine levels. Blood histamine was significantly lower during 2 weeks of daily supplementation with 2000 mg of ascorbic acid than during two weeks with a placebo.
A significant difference was not found during two weeks of supplementation with 500 mg of ascorbic acid.

Histamine metabolism in the rat may be influenced by dietary magnesium levels. In response to an eight day magnesium restricted diet, urinary histamine, histamine content of some tissues and histidine decarboxylase activity of some tissues increased (p<0.05). Duodenal DAO activity decreased. These changes indicate an increase in body histamine during magnesium deficiency. The changes were reversed after a two day magnesium refeeding period (Nishio et al., 1987).

Summary

Histamine is a significant factor in urticaria and angioedema. Dietary intake may alter plasma histamine through exogenous or endogenous means. The histamine in food may be absorbed into the circulation if the integrity of the histamine catabolizing enzymes are compromised. Certain food and food additives may induce endogenous release of histamine. Several studies have evaluated the effect of dietary manipulation in chronic urticaria and angioedema.
PREVIOUS DIETARY MANIPULATION STUDIES IN CHRONIC URTICARIA AND ANGIOEDEMA

Uncontrolled Food-Additive Free Diets

Clinical evaluation of several food additive-free diets have reported approximately 30 to 90% complete or partial remission of urticaria symptoms (Table 5). The positive responses may have been partially due to placebo effect or spontaneous remission of symptoms. However, with such a high percentage of subjects improving it is likely that the diets were partially responsible for the symptom improvement. Challenge studies\(^5\) have implicated tartrazine, sunset yellow, benzoates, butylated hydroxytoluene (BHT) and butylated hydroxyanisole (BHA) as the most likely additives to exacerbate urticaria.

\(^5\) In a challenge study, subjects consume food additives and the clinical response to each additive is monitored.
<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Foods eliminated</th>
<th>Number of Patients</th>
<th>Complete Remission</th>
<th>Partial Remission</th>
<th>No Remission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thune &amp; Granholt</td>
<td>1975</td>
<td>subjects followed an elimination diet&lt;sup&gt;1&lt;/sup&gt;</td>
<td>100</td>
<td>12</td>
<td>50</td>
<td>38</td>
</tr>
<tr>
<td>Ros et al. &lt;sup&gt;2&lt;/sup&gt;</td>
<td>1976</td>
<td>food colours, benzoates</td>
<td>75</td>
<td>24</td>
<td>57</td>
<td>19</td>
</tr>
<tr>
<td>Warin &amp; Smith</td>
<td>1976</td>
<td>salicylates, azo dyes, benzoates, yeast</td>
<td>38</td>
<td></td>
<td>75&lt;sup&gt;4&lt;/sup&gt;</td>
<td>25</td>
</tr>
<tr>
<td>Doeglas</td>
<td>1977</td>
<td>salicylates, tartrazine, benzoates</td>
<td>18</td>
<td></td>
<td>67&lt;sup&gt;4&lt;/sup&gt;</td>
<td>33</td>
</tr>
<tr>
<td>Gibosn &amp; Clancy</td>
<td>1980</td>
<td>subjects followed an elimination diet</td>
<td>65</td>
<td>75</td>
<td>15</td>
<td>10</td>
</tr>
<tr>
<td>Rudzki et al. &lt;sup&gt;3&lt;/sup&gt;</td>
<td>1980</td>
<td>subjects followed an elimination diet</td>
<td>158</td>
<td></td>
<td>32&lt;sup&gt;4&lt;/sup&gt;</td>
<td>68</td>
</tr>
<tr>
<td>Valverde et al.</td>
<td>1980</td>
<td>tartrazine, benzoates, and specific foods based on individual potential food allergies</td>
<td>258</td>
<td>62</td>
<td>22</td>
<td>16</td>
</tr>
</tbody>
</table>

<sup>1</sup> An exclusion diet allows consumption of only a few foods. The diet is additive free, and it would be lower in histamine than the histamine-reducing diet because almost all foods are eliminated.

<sup>2</sup> The symptom changes were evaluated by the subjects' opinions of their own symptoms 6 to 24 months after the initiation of the diet and not objective measures.

<sup>3</sup> The criteria for a positive response to diet was remission of symptoms on a 5-day elimination diet, followed by relapse of symptoms on a 3-5 day normal diet, and finally remission of symptoms on a second 5-day elimination diet.

<sup>4</sup> The percentage of subjects improving was not differentiated into complete or partial remission.
Controlled Food-Additive Free Diets

Controlled food-additive challenge studies have also yielded inconclusive results. Forty-three children with angioedema and/or urticaria who showed improvement on an additive-free diet, were challenged with various additives or a placebo in a double-blind design (Supramaniam, 1986). The challenge quantities used were less than average daily intakes. The primary criterion for a positive reaction was appearance of urticaria or angioedema within four hours of the challenge. Of the nine food colours and additives challenged, the most common compounds leading to exacerbation of urticaria and angioedema were tartrazine and sunset yellow (Table 6). The results were reproduced in six out of six repeat challenges; however, statistical analysis was not completed.

Sixty-five subjects who had complete remission of urticaria symptoms on an additive and dairy-free diet were challenged with various food additives (Gibson and Clancy, 1980). Appearance of urticaria or angioedema within 24 hours of the challenge was considered a positive response. Fifty-four percent of the subjects responded to salicylate, 34% responded to benzoate and 26% responded to tartrazine. There was no response to the placebo. The challenge quantities used were two to three times greater.
Table 6: RESULTS OF FOOD ADDITIVE CHALLENGES IN CHILDREN WITH ANGIOEDEMA AND URTICARIA

<table>
<thead>
<tr>
<th>Food Additive</th>
<th>Number Challenged</th>
<th>Number Who Reacted (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (lactose)</td>
<td>43</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Tartrazine</td>
<td>43</td>
<td>11 (26%)</td>
</tr>
<tr>
<td>Sunset Yellow</td>
<td>36</td>
<td>10 (28%)</td>
</tr>
<tr>
<td>Amaranth</td>
<td>37</td>
<td>4 (11%)</td>
</tr>
<tr>
<td>Indigo Carmine</td>
<td>19</td>
<td>3 (16%)</td>
</tr>
<tr>
<td>Carmoisine</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Sodium Benzoate</td>
<td>27</td>
<td>4 (15%)</td>
</tr>
<tr>
<td>Monosodium Glutamate</td>
<td>36</td>
<td>3 (8%)</td>
</tr>
<tr>
<td>Sodium Metabisulphite</td>
<td>12</td>
<td>1 (8%)</td>
</tr>
</tbody>
</table>

Reference: Supramaniam and Warner, 1986

than the quantities used in Supramaniam and Warner's study. This may account for the increased frequency of reactions. Double-blind challenges with 44 chronic urticaria subjects did not result in greater reactions to tartrazine, sodium benzoate, benzoic acid, BHT or BHA than to the placebo (Hannuksela and Lahti, 1986). Two individuals with idiopathic urticaria who showed improvement on an additive-free diet were challenged with food additives and a placebo in a double-blind trial (Goodman et al., 1990). Both patients responded on three separate occasions to BHA/BHT challenges but not to the placebo. Neither of the patients responded to tartrazine or benzoates. One patient
responded to sodium salicylate. From these studies it is clear that food additives lead to an exacerbation of urticaria and angioedema in some individuals; however, the prevalence of these reactions is uncertain.

Low Histamine Diets

Wantke et al. (1993) evaluated the effect of a low histamine diet. Forty-five patients with chronic headaches and food and wine intolerance (flushing, pruritus, rhinitis, diarrhoea and shortness of breath, after consuming food or wine) were followed over a four week period while consuming a low histamine diet. Thirty-three (73%) patients had more than a 50% decrease in frequency of symptoms and/or drug use (p<0.01).

Sixty-seven subjects with chronic urticaria followed a low tyramine and low food-additive diet. This diet also eliminated many, but not all, foods high in histamine. Thirty-seven (55%) subjects had complete or partial remission of urticaria symptoms. The subjects who responded positively to the diet presented to the study with increased frequency of urticaria attacks, shorter duration of disease, younger age, family history of atopy, family history of urticaria and angioedema and presence of gastrointestinal disturbances (Verschave et al., 1983). The duration of the diet and the time periods that symptoms were
evaluated were not reported. Remission of symptoms is common in chronic urticaria. If the period of time between the initial and the final evaluation of symptoms was lengthy, the remission of symptoms may have been due to the natural progression of the disease and not the treatment diet. Low histamine diets appear to benefit urticaria, angioedema and other conditions which are mediated by histamine.

OTHER CONDITIONS WHICH MAY BENEFIT FROM A HISTAMINE-REDUCING DIET

Atopic Disease

Atopic disease is a disorder caused by Immunoglobulin E mediated release of inflammatory mediators from mast cells and basophils. The common manifestations of atopy are rhinitis, asthma, eczema and urticaria. The prevalence of atopic diseases is not greater in chronic urticaria subjects (Soter, 1991; Supramaniam & Warner, 1986).

Antihistamine medication often controls the symptoms of allergic rhinitis indicating that histamine is the primary mediator. A histamine-reducing diet may be effective in controlling allergic rhinitis.
Migraine Headaches

Wantke et al. (1993) reported a significant reduction in headaches after four weeks on a low histamine diet. Tyramine may be an important mediator of food-induced headaches (Vaughan & Mansfield, 1987). Many foods high in histamine are also high in tyramine (Stratton et al., 1991). The histamine-reducing diet may improve migraine headaches.

Gastrointestinal Disturbances

Defects in intestinal function, such as abdominal pain and diarrhea are seen in 40% of patients with chronic urticaria (Moneret-Vautrin D, 1987; Juhlin, 1981). Histamine may mediate the process by which excess bile acids in the colon cause diarrhea. Excess bile acids may result in diarrhea by increasing chloride secretion from the enterocytes. In vivo, this action is inhibited by H1 antagonists (antihistamine medication) (Gelbmann et al., 1995). A histamine-reducing diet may be effective for some cases of diarrhea caused by excess colonic bile acids.

BACKGROUND LITERATURE RELATED TO THE TREATMENT AND CONTROL DIETS

The treatment diet will eliminate potential histamine releasing food, food additives and food which is high in histamine.
Formation of Histamine in Food

Conditions Necessary for the Formation of Amines

Histamine is produced from the decarboxylation of histidine (Figure 1). Several microorganism genera have histidine decarboxylase activity (Taylor, 1986). Free histidine, decarboxylase-producing microorganisms and adequate conditions for microbiological growth are necessary for histamine formation (Halász et al., 1994). The amount of histamine formed in foods varies considerably. Proteinaceous foods that are aged and fermented are likely to have increased histamine.

Important genera with decarboxylase activity are *Escherichia, Salmonella, Clostridium, Bacillus* and *Lactobacillus* (Halász et al., 1994; Taylor, 1986). Decarboxylase activity varies between and within strains of microorganisms. Factors such as growth conditions and growth phase of the microorganism affect activity (Halász et al., 1994). Microorganisms may be present in a food through natural occurrence, contamination or as a starter culture for fermentation (Halász et al., 1994). Temperature, pH and salt concentration of a food influence microorganism growth and therefore amine formation.

Free amino acids may occur naturally in food or result from proteolytic activity (Halász et al., 1994). Scombroid or mackerel family fish tissues have increased levels of free histidine, and
are therefore susceptible to histamine formation (ten Brink et al., 1990).

Other amines are produced by decarboxylation of the corresponding amino acids (Table 7). The microorganisms which decarboxylate histidine, may, but do not necessarily,

<table>
<thead>
<tr>
<th>Amine</th>
<th>Precursor amino acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histamine</td>
<td>Histidine</td>
</tr>
<tr>
<td>Tryptamine</td>
<td>Tryptophan</td>
</tr>
<tr>
<td>Tyramine</td>
<td>Tyrosine</td>
</tr>
<tr>
<td>Phenylethylamine</td>
<td>Phenylalanine</td>
</tr>
<tr>
<td>Putrescine</td>
<td>Ornithine</td>
</tr>
<tr>
<td>Cadaverine</td>
<td>Lysine</td>
</tr>
</tbody>
</table>

Reference: ten Brink et al, 1990

decarboxylate other amino acids. A large variety of microorganisms may be present during food processing; therefore, the amine content will also be quite variable (ten Brink, 1990).

Amine Content of Susceptible Food

Cheese: Histamine levels vary extensively between and within cheese varieties. *Lactobacillus buchneri* was isolated from a batch of Swiss cheese that was implicated in an outbreak of
Literature Review

histamine poisoning, and it is likely the most important histamine forming microorganism in cheese (Stratton et al., 1991). However, histidine decarboxylase activity is limited to only a few strains of L. buchneri. The activity of histidine decarboxylase strains of L. buchneri varies with growth conditions. A storage temperature of 21°C resulted in histamine levels of 6.8 mmol/kg of Gouda cheese. A storage temperature of 9°C resulted in histamine levels of 2.2 mmol/kg of cheese. A storage pH of 5.39 resulted in twice as much histamine formation as a storage pH of 5.19. Storage at 21°C and pH 5.39 resulted in histamine levels of 9.4 mmol/kg of cheese after 1 year of ripening (Joosten, 1988). The histidine decarboxylase activity of L. buchneri is not affected by heat treatment (Joosten, 1988). If the milk used to produce the cheese contains L. buchneri, pasteurization will not decrease the risk of histamine formation.

Most commercially available starter cultures do not possess histidine decarboxylase activity (ten Brink et al., 1990). Therefore, histamine formation usually results from contamination of the milk with a histidine decarboxylase-producing microorganism.

Putrescine, tyramine, cadaverine and other amines have also been reported in cheese. Cheese samples with elevated histamine
often, but not always, have elevated levels of other amines (Stratton et al., 1991).

**Fish:** Histamine poisoning from fish usually involves scombroid fish due to the large amount of free histidine in the muscle tissues. Scombroid fish includes tuna, bonito, skipjack, albacore and mackerel. Non-scombroid fish have occasionally been associated with histamine poisoning (Rohani et al., 1985). Fish is considered toxic if it contains more than 100 mg of histamine per 100 g of fish. Fish products will not be imported by Canada or the United States if they contain more than 10 mg of histamine per 100 g of fish. Random samples of four types of scombroid fish were obtained from a retail fish outlet in Serdang, Selangor (Rohani et al., 1985). Three of 56 samples contained 4.5 mg/100g, 10.9 mg/100g, and 18.6 mg/100g of histamine. Ten duplicate samples of canned tuna and fourteen duplicate samples of canned mackerel processed in Serdang, Selangor for export were analyzed for histamine content. Three canned tuna samples were found to contain 2.3 mg/100g, 9.4 mg/100g and 15.9 mg/100g of histamine. Histamine formation occurred due to inadequate cold storage prior to canning. No mackerel samples contained histamine. Histamine levels as high as 180 to 500 mg/g of fish have been reported (Malone & Metcalfe, 1986). Kim & Bjeldanes (1979) evaluated 15 samples of canned tuna implicated in an outbreak of scombroid
fish poisoning and found the histamine, cadaverine and putrescine content to be higher than 34 cans of supermarket tuna. The mean histamine content in the 15 tuna samples was 116±6 mg/100g.

Fermented fish products and fish paste often have increased histamine content. Ten samples of salted tenggiri fish contained between 3.5 mg/100g and 12.0 mg/100g of histamine (Rohani et al., 1985). Sugar-salted herring stored in barrels were found to have between 31 mg/100g and 101 mg/100g of histamine. Canned herring were found to have histamine levels of 0 - 18 mg/100g (Stratton et al., 1991).

Fermented beverages: A survey of American and English wine reported a histamine range from non-detectable to 30 mg/L, with red wines and sherries generally having higher histamine contents (Stratton et al., 1991). Elevated levels of cadaverine and tyramine have also been reported in wine (Baucom et al., 1986). Beer was reported to have a histamine range of 2.6 to 20.0 mg/L (Stratton et al., 1991). Histamine was not detected in brandy, scotch whiskey or cognac (Granerus et al., 1969).

Meat and Meat Products: Zee et al. (1983) found low levels of histamine, cadaverine, putrescine and tyramine in fresh pork and processed meat. Processing decreased the amine content of fresh beef. Amine formation can occur during storage at inappropriate time and temperature. Sayem-El-Daher et al. (1984)
analyzed 62 randomly chosen samples of fresh ground beef. The histamine content ranged between 0.0 to 21.7 mg/100g with a mean level of 0.57 mg/100g. There was a positive correlation between the levels of putrescine, cadaverine and tyramine and time and temperature of storage.

Fermented meats have increased histamine levels. The histamine content of 27 dry-sausage samples ranged between non-detectable and 19.74 mg/100g of dry matter (Vanerkerckhove, 1990).

**Fermented Vegetables:** Raw cabbage contains a variety of microorganisms. The contamination of sauerkraut production depends on harvest time, hygienic practice and processing treatment. In a survey of 50 samples of retail sauerkraut, the range of histamine was 0.91 to 13.0 mg/100g and the average histamine content was 5.06 mg/100g (Taylor et al., 1978).

**Fermented Soy Products:** In a survey of oriental foods, the histamine level of tamari was 2392 µg/g and one brand of soy sauce was 220 µg/g (Chin et al., 1989). Soy sauce made from black bean is generally higher in histamine than regular soy sauce (Stratton, 1991).

Food production and storage methods which limit amine formation are essential. Low temperature storage inhibits the growth of microorganisms. Starter cultures used in food
production must be rejected if the microorganism has
decarboxylase activity. Raw foods are often contaminated with
microorganisms; therefore, hygienic practice is essential. Low
temperature storage and hygienic handling of food must be
observed in the food industry and in the home.

The formation of amines in food depends on the particular
microorganisms in the food, presence of free amino acids and
growth conditions. Literature values of amines in selected foods
are quiet variable (Zee et al., 1983). The physiological effect
of food borne amines will depend on the level of each amine in
the particular food and the sensitivity of the individual
consuming the food.

Natural and Artificial Food Constituents

**Benozoates:** Benzoic acid and sodium benzoate are widely used
as antimycotic and antibacterial preservatives in foods and
beverages. Benzoic acid is commonly added to tomato products,
processed fruit, margarine and meat products. Benzoyl peroxide is
used as a bleaching, maturing and dough conditioning agent for
flour. The presence of benzoates must be declared on the
ingredient label. Additionally, benzoates occur naturally in
food. Levels of natural benzoates are highest in prunes,
cinnamon, nutmeg, cloves, teas, anise and many berries especially
strawberries, raspberries and cranberries (Jacobsen, 1987; Heimuber & Herrmann, 1990). Levels of benzoates vary considerably with growing conditions (Heimuber & Herrmann, 1990). Food products labelled with benzoic acid, sodium benzoate, benzoyl peroxide and foods with high levels of naturally occurring benzoates should be eliminated from a histamine-reducing diet.

**Salicylates:** Salicylates occur naturally in a wide variety of food. Salicylate levels vary with growing conditions, food variety, stage of ripeness and processing. The most comprehensive investigation of salicylate levels in food was completed by Swain et al. (1985). The quantity of salicylate necessary to provoke clinical symptoms is not known. Foods with greater than 5 mg per common portion size (arbitrary limit) should be eliminated from a histamine-reducing diet. These foods include curry powder, hot paprika, prunes and raisins (Swain et al., 1985).

**BHA and BHT:** BHA and BHT are used as antioxidant preservatives in food such as fats and oils, breakfast cereals and baked food products. The presence of BHA and BHT must be declared on the ingredient label. All food products containing BHA and BHT should be eliminated from a histamine-reducing diet. Food products with BHA and BHT in the package material may be permitted.
Artificial food colours: Artificial colours are used to improve the appearance of prepared food. Tartrazine is the food colour which is most likely to exacerbate urticaria. Artificial food colour must be declared on the ingredient label; however, specific colours are not necessarily labelled. Therefore, food products labelled as containing artificial food colour should be eliminated from a histamine-reducing diet.

Control Diet

For the purpose of the present study a control diet was designed as one in which artificial sweeteners were eliminated, because they are commonly believed to exacerbate urticaria but have been shown to not do so.

Kulczycki (1986) reported a single case study of urticaria following a blinded challenge with the artificial sweetener aspartame® (aspartic acid, phenylalanine and methanol). In 1984, the American Centers for Disease Control evaluated 76 reports of allergic or dermatologic symptoms resulting from aspartame® consumption. It was concluded that a controlled research study was necessary to determine the relevance of aspartame® consumption in allergic and dermatologic disease presentation.

Geha et al. (1993) conducted a randomized, double-blind, placebo-controlled, crossover clinical study to determine if
aspartame® consumption resulted in urticaria. The study was conducted at six hospitals in Canada and the United States. Individuals who experienced urticaria and/or angioedema within 12 hours of aspartame® consumption or had resolution of symptoms when aspartame® was removed from the diet were invited to participate in the study. Recruitment letters were mailed to 4700 allergists in Canada and the United States and 11 local allergy and dermatology societies. One hundred and two individuals who had reported urticaria and/or angioedema symptoms after consumption of aspartame® to the Nutrasweet Company, the producers of aspartame, were invited to participate in the study. One hundred and eleven potential candidates called a toll-free number that had been established for subject recruitment. Twenty-one subjects entered the study. Forty-four subjects did not meet the study criteria, 32 did not wish to participate, 9 were lost to follow-up, 3 were able to consume aspartame® without problem, 1 was pregnant and 1 had physical urticaria. The subjects stayed at the study centres for the five days and were challenged with placebo, aspartame® and the conversion products of aspartame®, aspartylphenylalanine diketopiperazine and β-aspartame. Subjects with a body weight greater than 40 kg received 950 mg of aspartame®. Subject who weighed less than 40 kg received 475 mg of aspartame®. The aspartame® dose was 5 to 6 times the average
amount consumed. Subjects received either aspartame® or placebo on Day 2 or 4 in random order. There was no statistical difference in the incidence of positive reactions between aspartame® and placebo. Even though several individuals have reported an exacerbation of urticaria symptoms after aspartame® consumption, these claims have not been validated.

SIGNIFICANCE OF THE PRESENT STUDY

Diet may exacerbate urticaria and angioedema by increasing histamine levels in the body through exogenous or endogenous mechanisms. The control of urticaria and angioedema through dietary manipulation would lead to a reduction in medication use and an improvement in the quality of life for these patients. The effectiveness of dietary manipulation in chronic urticaria and angioedema should be evaluated in a controlled study.
EXPERIMENTAL DESIGN

The study was a randomized, prospective design. Subjects with chronic urticaria and/or angioedema were recruited and randomized to a treatment or control diet. The treatment diet eliminated food which was high in histamine and food additives which may increase endogenous release of histamine. The control diet was based on Canada's Food Guide and eliminated artificial sweeteners and sugar alcohols. The diets were to be followed for 56 days (8 weeks). Three-day food records were analyzed every 14 days (2 weeks) to ensure nutritional adequacy and dietary compliance. Subjects evaluated their urticaria and angioedema symptoms on a daily basis, as instructed, beginning fourteen days prior to the start of the diet and continuing throughout the study period. Antihistamine medication intake, number of wheals, severity of pruritus and angioedema were recorded. The data were analyzed using a 2x2 (group x time) repeated measures ANOVA.
METHODS

Sample size

A sample size of 15 to 20 subjects per group has been shown to be adequate for statistical significance in antihistamine medication clinical trials (Shareeah, 1992; Sussman, 1991; Bernstein, 1988). The number of antihistamine tablets taken by the first ten subjects, during the 14 days before starting the diet, was used to calculate sample size (Cheney & Boushey, 1992). The mean number of tablets taken was 9.5 with a standard deviation of 7.2. A 50% change in this measure was considered meaningful; therefore, a change of 5 tablets. A two-tailed test was used; α was set at 0.05 and β was set at 0.02.

Figure 3: SAMPLE SIZE CALCULATION

\[
n = \frac{(Z_{1-\beta} + Z_{1-\alpha}) \times SD_{diff}^2}{|\mu_1 - \mu_0|} + 1
\]

\[
n = \frac{(0.84 + 1.96) \times 7.2^2}{5}
\]

n= 16.25 or 17 subjects per group
Thus, as shown in Figure 3, the required sample size was calculated to be 17 subjects per group.

Subject Recruitment

Recruitment posters were placed in the waiting rooms at five medical clinics and six pharmacies in North Vancouver (Appendix A). The dermatologists in the lower mainland were contacted by telephone, and the investigator attempted to make an appointment to promote the study. According to each dermatologist's response, a personal visit was made, information was mailed or no further action was taken. The chairperson of the British Columbia Allergy Association was contacted by telephone and sent information about the study. The regional coordinator of the Allergy Asthma Information Association and the nine activators in the lower mainland were contacted by telephone and sent written information about the study. The Allergy Asthma Information Association activators provide telephone support to individuals with allergic diseases. Recruitment notices were placed in the British Columbia Dietitians' and Nutritionists' Association newsletter, British Columbia Pharmacy Newsletter (the Bulletin) and Rogers Cable community channel. Recruitment notices were placed in the
Methods

Vancouver Sun or the Province newspapers on January 21/22, April 22/23 and June 10/11, 1995.

Individuals were invited to participate if they had urticaria and/or angioedema symptoms for at least six weeks and had greater than one episode of urticaria and/or angioedema symptoms per week. Subjects were to be nineteen years of age or older. Younger subjects may be less compliant to diet therapy, and urticaria is most frequently reported in middle-aged women (Burrall, 1990; Soter, 1991). Exclusion criteria included those subjects who were changing medications to control symptoms, were pregnant or had urticarial vasculitis, mastocytosis, dermatophyte infection, candida infection, mononucleosis, rheumatoid arthritis or lupus erythematosus. Individuals were not excluded if they were taking medication that might exacerbate urticaria and angioedema. Many common drugs may exacerbate this disease, and excluding all subjects taking these drugs would have greatly limited subject recruitment. The subjects' physicians confirmed the diagnosis and gave verbal or written consent for their patients' participation in the study.
Dietary Intervention

Treatment Diet (Appendix B)

The treatment diet eliminated food which was potentially high in histamine and food additives which may increase endogenous release of histamine. The foods that were restricted due to potentially high histamine content were: spinach, tomato and tomato products, fish, processed meat, leftover meat, cheese products, yoghurt, sour cream, fermented soy products, fermented foods and alcohol. Subjects were instructed to follow hygienic procedures for food storage and preparation to decrease microbiological growth and histamine formation in food. Food products containing tartrazine, artificial food colour, benzoic acid, sodium benzoate, benzoyl peroxide, butylated hydroxyanisole and butylated hydroxytoluene were also eliminated because these additives may increase endogenous release of histamine.

Cranberries, strawberry, raspberry, prunes, cinnamon, anise, cloves and nutmeg were eliminated due to potentially high benzoate content. Pineapple, dates, currants, raisins, prunes, curry powder and hot paprika were eliminated due to potentially high salicylate content. Strawberries, pineapple, tomato and tomato products, seafood, uncooked egg white, and chocolate were eliminated due to potential "histamine releasing" properties of these foods.
Methods

The rationale for the diet was discussed with the treatment subjects. Subjects were taught to read ingredient labels. A written list of acceptable food products was given to each subject, and meal planning suggestions were discussed.

Control Diet (Appendix C)

The control diet was designed to eliminate food which would not influence urticaria and angioedema symptoms, but would appear to be a plausible treatment. The control subjects followed a diet which was based on Canada's Food Guide and eliminated aspartame®, splenda®, sunett®, saccharin, cyclamate, mannitol, xylitol and sorbitol.

The control subjects had diet instruction similar to the treatment group. The importance of a balanced intake for proper immune system function and health was discussed as part of the rationale for the control diet. The single documented case of exacerbation of urticaria after a blinded aspartame challenge was discussed (Kulczycki, 1986). Subjects were taught to read ingredient labels and follow Canada's Food Guide. Alternatives to unacceptable food products were discussed.
Urticaria and Angioedema Assessment Scale (Appendix D)

A validated measurement scale for urticaria and angioedema has not been developed (personal correspondence: Dr. Morton, MD and Dr. G. Sussman, MD). The scale developed for this study was pretested with urticaria and angioedema patients. Previous urticaria and angioedema patients who had attended the Vancouver Hospital Allergy Nutrition Clinic were contacted by telephone and asked to critique the urticaria and angioedema symptom assessment scale. The patients were asked to suggest changes which would make the scale easier to complete and more reflective of the severity of their symptoms. The assessment scale was revised based on these comments.

The urticaria and angioedema assessment scale included four variables.

(1) Antihistamine medication intake: The subjects recorded the number of tablets taken each day. Drug efficacy and effect varies among patients (Juhlin, 1992); therefore, it was necessary that each patient be consistent with respect to antihistamine medication brand throughout the study. The specific antihistamines and the doses were recorded each day to identify changes in this variable.
Methods

(2) Number of wheals: The subjects recorded the total number of wheals each day, and they specified whether they counted the wheals or guessed.

(3) Severity of itchiness: The subjects recorded the overall severity of itchiness each day on a scale of 0 to 3, where the numbers represented the following degrees of severity:
0=symptoms absent; 1=symptoms are present, but barely noticable; 2=symptoms are definitely noticable, but are tolerable; 3=symptoms are definitely noticable, and are not tolerable.

(4) Severity of angioedema: The subjects recorded the overall severity of angioedema each day on a scale of 0 to 3, where the numbers represented the following degrees of severity: 0=symptoms absent; 1=symptoms are present, but barely noticable; 2=symptoms are definitely noticable, but are tolerable; 3=symptoms are definitely noticable, and are not tolerable.

The subjects were instructed to complete the assessments at the same time each day for the previous 24 hours. Consistency of symptom assessment was stressed throughout the study.

Three-Day Food Records (Appendix E)

The purpose of recording dietary intakes was to assess nutrient intake before the diets were initiated (Days -3 to -5) and every two weeks after the diets were initiated.
Methods

(Days 11,12,13, 25,26,27, 39,40,41, 53,54 and 55). Additionally, the food records were used to provide feedback to the subjects with respect to dietary compliance. Food records were chosen as the method to evaluate dietary intake because dietary information was required for specific days. The subjects may not have been able to accurately recall their dietary intake if questioned retrospectively.

The subjects were instructed to record the type and quantity of all food and beverages consumed and the preparation methods used. A written example of a meal recorded accurately was provided.

The completed food records were reviewed for accuracy and dietary compliance at each appointment. The food records were analyzed using the software PC Nutricom Version 5.03 (Delta Nutrition Systems; Vancouver, B.C.). The results of the nutritional analyses were returned to the subjects at the next appointment. If the analyses indicated an inadequate intake, a handout entitled Food Sources of Selected Nutrients was provided and discussed with the subject (Appendix F). The handout lists the major food sources of each nutrient.
Control of Confounding Variables

A variety of medications have been suspected to contribute to urticaria and angioedema. Anti-inflammatory drugs, such as acetylsalicylic acid, fenoprofen, indomethacin, ketoprofen, mefenamic acid, naproxen, acetaminophen, phenylbutazone, are commonly suspected. Angiotensin converting enzyme inhibitors have also been suspected (Armenaka, 1992; Holgate, 1993). Isoniazid ingestion has been shown to potentiate histamine poisoning, and may be relevant in urticaria and angioedema (Uragoda & Kottegoda, 1977). From the literature, it appears that a variety of medications may exacerbate urticaria and angioedema. Therefore, consistency of all medications during the research study was stressed. Any changes in medication from baseline were documented.

Changes in bacterial, viral or parasitic infections; use of soaps, creams, cosmetics or laundry detergents; environmental allergens and stress may affect urticaria and angioedema (Burrall, 1990; Armenaka, 1992). Subjects were instructed to keep these factors consistent and to record changes in any of these variables on the assessment scale.
Methods

Subject Appointments

The subject appointments were conducted at the Vancouver Hospital and Health Sciences Centre, Heather Pavilion or at the business office of the investigator, #9, 106 East 14th Street, North Vancouver.

Eligible subjects were invited to an initial interview. The study was fully explained and the subjects were asked to read and sign the consent form (Appendix G). Self-reported weight, height and frequency of gastrointestinal disturbances, atopic symptoms or migraine headaches were recorded. A weight and height scale was not available at the study site. Study booklets containing daily urticaria and angioedema assessment scales and bi-monthly three day food record forms were given to the subjects. The four variables on the urticaria and angioedema assessment scale were discussed.

Prior to beginning the dietary intervention, subjects returned for a follow-up appointment. Urticaria and angioedema assessment scales and food records were reviewed. The subjects were randomized to the control or treatment diet. The first subject chose one of four pieces of paper. The letter "o" (control) was written on two of the papers, and the letter "r" (treatment) was written on the other two papers. The second subject chose from the three remaining pieces of paper. After
four subjects had been randomized, the procedure began again. The subjects were instructed on the appropriate diet. The diets began on Day 0 of the study.

Follow-up appointments were conducted every two weeks. The symptom assessment scales were reviewed, and any variable changes or dietary problems over the previous two weeks were discussed. The current food records were reviewed for accuracy and dietary compliance. The nutrient analyses of the previous food records were discussed.

A final appointment was held after the study had been completed. Self-reported weight changes over the study were recorded. A weight change of 5% or more was considered significant. Changes in gastrointestinal distress, atopic symptoms or migraine headaches were recorded.

Statistical Analysis

The SPSS for Windows Release 6.0 (SPSS Inc., Chicago, Illinois, 1993) was used to perform the statistical analysis. The acceptable level of significance was set at $p < 0.05$.

Treatment and Control Group Comparisons

The age of the two groups was compared with an independent samples t-test. Gender distribution was analyzed with a Mann-
Methods

Whitney U test. Duration of disease was analyzed with a Wilcoxon Signed-Rank test because the data was not normally distributed. These variables are compared in most antihistamine clinical trials (Sussman, 1991; Belaich, 1990).

Urticaria and Angioedema Assessment Scale

The planned time periods were: Days -14 to -1 (time 1), 0 to 13 (time 2), 14 to 27 (time 3), 28 to 41 (time 4) and 42 to 55 (Time 5). The total number of antihistamine tablets and wheals were calculated for each time period. When the subjects expressed the number of wheals as a range, the lowest number of wheals was used. For example, >100 was considered to be 100 and 50 - 60 was considered to be 50. The total itchiness and angioedema severity scores were calculated. If data was missing on a particular day, the average of the other days in the time period was used as the value for that day. The total number of days that antihistamine tablets were taken, and the number of days that wheals, itchiness and angioedema symptoms were reported were calculated for each time period. The symptom variables were analyzed with a 2x2 (group x time) RM ANOVA (with repetition on the time factor). The time 1 scores for each variable were compared with an independent samples t-test to identify significant baseline differences between the control and the treatment groups. For variables with
Methods

a significant difference, the data were also analyzed with a 2x2 (group x time) RM ANCOVA (with repetition on the time factor) using the time 1 value as the covariate. The symptom data did not satisfy the assumption of sphericity. Therefore, an adjusted critical F value was calculated using the Huynh-Feldt epsilon. The adjusted critical F value was compared to the F value calculated by SPSS to determine significant effects and interactions. The significant time effect was followed by a comparison of the combined means for each time period with a paired t-test. To account for multiple comparisons, a p<0.008 was considered significant.

In addition to the RM ANOVA which assessed the change in antihistamine intake over the entire study period, a paired samples t-test was used to compare the number of antihistamine tablets taken by the treatment group during time 1 and time 2. A separate comparison of the control group was completed. This was done because of the assumption that if the treatment diet is effective, symptoms will improve within a few days of the dietary intervention.

Nutrient Analysis

The food records were analyzed for kilocalories, protein, carbohydrate, fat, calcium, iron, magnesium, phosphorus, zinc and
vitamins A, B1, B2, B3, B6, B12, C and folacin. The mean and standard deviation for both groups at time 1, time 2, time 3 and time 4 were compared to the 1990 Recommended Nutrient Intakes (RNI) for Canadians (Health and Welfare Canada, 1990). For each nutrient and each group, a weighted RNI was calculated based on the number of male and female subjects in each group. A mean intake less than 70% of the weighted RNI was considered a significant deficiency. The nutrient data were analyzed with a 2x2 (group x time) RM ANOVA (with repetition on the time factor). The time 1 values were compared with an independent samples t-test to identify significant baseline differences between the control and the treatment groups. For nutrients with a significant difference, the data were also analyzed with a 2x2 (group x time) RM ANCOVA (with repetition on the time factor) using the time 1 value as the covariate. For the nutrients that did not satisfy the assumption of sphericity, an adjusted critical F value was calculated using the Huynh-Feldt epsilon. Significant group x time interactions were followed by a comparison of the control and treatment groups at each time with an independent samples t-tests. To account for multiple comparisons, a p<0.0125 was considered significant. The significant time effects were followed by comparison of the combined means at each time period with a paired t-test. To
account for multiple comparisons, a \( p < 0.008 \) was considered significant.

**Ethical Approval (Appendix H)**

This study received approval from the University of British Columbia Clinical Screening Committee for Research and Other Studies involving Human Subjects.
CHAPTER 4

RESULTS

URTICARIA AND ANGIOEDEMA ASSESSMENT SCALE PRETEST

Ten previous urticaria and angioedema patients of the Vancouver Hospital Allergy Nutrition Clinic commented on the urticaria and angioedema assessment scale. Based on the comments, "pruritus" was changed to "itchiness". Three patients were not able to count their wheals. This was because there were too many wheals to count accurately or the wheals tended to join together and it was difficult to differentiate between a single wheal and a group of wheals. Thus, a space to indicate if the wheals had been counted or guessed was included in the assessment scale.

RECRUITMENT

There was no response to the recruitment posters in the medical offices and pharmacies. Thirty-eight dermatologists were contacted by telephone and appointments with two dermatologists were obtained. Information and recruitment posters were mailed to several dermatologists. One dermatologist referred one patient to the study. The British Columbia Allergy Association allergists did not support the study because it was not supervised by a
medical doctor. However, one member of the British Columbia Allergy Association referred three patients to the study. Eighty-three individuals inquired about the study (Table 8). The most common reason for not entering the study was distance from the potential subject's residence to the study centre (Appendix I).

Table 8: NUMBER OF SUBJECTS INQUIRING ABOUT AND ENTERING THE STUDY

<table>
<thead>
<tr>
<th>RECRUITMENT EFFORT</th>
<th>Total Inquires</th>
<th>Subjects Entering Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newspaper Ad: Jan 21/22</td>
<td>56</td>
<td>12</td>
</tr>
<tr>
<td>Newspaper Ad: April 22/23</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Newspaper Ad: June 10/11</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Referral to ANC</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Pharmacy newsletter</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>AAIA referral</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Community Channel Ad</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>BCDNA newsletter</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Ad = Advertisement
ANC = Allergy Nutrition Clinic
AAIA = Allergy Asthma Information Association
BCDNA = British Columbia Dietitians' and Nutritionists' Association
SUBJECTS

Twenty subjects started the study, but one subject withdrew from the study on approximately Day 30. The subject had not been completing the food records consistently, and she lacked motivation to continue with the study. Another subject withdrew from the study on Day 42, but the data were considered in the analysis. Originally, the study had been designed for 56 days of follow-up, however, to retain this subject's data the study was considered complete at 42 days. All analyses are based on data up to 42 days even though the remainder of the subjects continued with the study until day 56. Data from 19 subjects and four time periods (Days -14 to 41) were used for the statistical analysis. The pre-determined sample size was not achieved.

There were 10 subjects in the control group and nine subjects in the treatment group. There were no significant differences in age, duration of disease or gender between the two groups (Table 9). Thus, the results from the treatment and control groups will not be differentiated by gender.
Table 9: SUBJECT CHARACTERISTICS

<table>
<thead>
<tr>
<th>GROUP</th>
<th>Age (years)</th>
<th>Gender</th>
<th>Duration of Disease (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>42±21*</td>
<td>6 female</td>
<td>13 ± 18</td>
</tr>
<tr>
<td>(n=9)</td>
<td></td>
<td>3 male</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>46±16</td>
<td>8 female</td>
<td>3 ± 6</td>
</tr>
<tr>
<td>(n=10)</td>
<td></td>
<td>2 male</td>
<td></td>
</tr>
</tbody>
</table>

* mean ± SD
No significant differences

COMPLIANCE TO STUDY PROTOCOL

Sixteen out of 560 urticaria and angioedema assessment scales were not completed in the control group, and 3 out of 504 assessment scales were not completed in the treatment group (Appendix J).

Three subjects in the control group did not start the diet immediately after day -1. There were 7, 9 and 26 day delays between day -1 and day 0 (Appendix K).

All food records were completed. The control group reported dietary noncompliance on 5 out of 420 days. The treatment group reported dietary noncompliance on 11 out of 378 days (Appendix L).

One subject in the control group experienced a weight gain of 8% over her initial body weight. There were no other weight changes greater than 5%. One of the 10 control subjects lost weight, and five of the nine treatment subjects lost weight (Appendix M).
One subject in the control group reported a cold with fever on Days 32 - 38. Tylenol®, robitussin® AC cough syrup and ceclor® were taken throughout this period. The subject took one antihistamine tablet on Days 32 and 33 for sneezing and rhinitis. The illness and/or medication intake appeared to slightly exacerbate the urticaria symptoms during this period.

STATISTICAL ANALYSIS

Urticaria and Angioedema Assessment Scale

Antihistamine Tablets

There was a trend toward a significant decrease in the number of antihistamine tablets taken over the four time periods in the treatment group compared to the control group (significant group x time interaction F = 3.46; calculated F = 3.15) as shown in Table 10 and 20. There were no significant differences between groups or time periods in the number of days that antihistamine tablets were taken as shown in Table 11 and 20.

<table>
<thead>
<tr>
<th>GROUP</th>
<th>Time 1</th>
<th>Time 2</th>
<th>Time 3</th>
<th>Time 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>17.5±11.5*</td>
<td>11.5±13.0</td>
<td>11.0±13.0</td>
<td>11.5±14.0</td>
</tr>
<tr>
<td>Control</td>
<td>7.5±6.5</td>
<td>7.5±5.0</td>
<td>7.0±6.0</td>
<td>7.5±4.5</td>
</tr>
</tbody>
</table>

* mean ± SD
No significant differences (see table 20 for F ratio)
Table 11: NUMBER OF DAYS ANTIHISTAMINE TABLETS WERE TAKEN

<table>
<thead>
<tr>
<th>GROUP</th>
<th>Time 1</th>
<th>Time 2</th>
<th>Time 3</th>
<th>Time 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>12±3*</td>
<td>9±6</td>
<td>8±7</td>
<td>8±7</td>
</tr>
<tr>
<td>Control</td>
<td>7±5</td>
<td>7±5</td>
<td>7±6</td>
<td>6±4</td>
</tr>
</tbody>
</table>

* mean ± SD
No significant differences (see table 20 for F ratio)

The treatment group took significantly more antihistamine tablets and took antihistamine tablets on more days during time 1 than the control group. When time 1 was used as a covariate for the RM ANCOVA of the number of antihistamine tablets taken and the number of days that antihistamine tablets were taken, there were no significant differences between groups.

The treatment subjects took significantly fewer antihistamine tablets during time 2 than time 1 (p=0.02). There were no differences between time 1 and time 2 in the control group (p=0.81) as shown in Table 12.
Table 12: TOTAL NUMBER OF ANTIHISTAMINE TABLETS TAKEN BEFORE THE CONTROL OR TREATMENT DIET (TIME 1) AND AFTER THE INITIATION OF THE DIET (TIME 2)

<table>
<thead>
<tr>
<th>GROUP</th>
<th>Total tablets taken</th>
<th>Time 1</th>
<th>Time 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>17.5±11.5*</td>
<td>11.5±13.0a</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>7.5±6.5</td>
<td>7.5±5.0</td>
<td></td>
</tr>
</tbody>
</table>

* mean ± SD
* p<0.05 (Time 1 vs Time 2)
No significant differences in the control group

Wheals

There were no significant differences between groups or time periods in the total number of wheals reported as shown in Table 13 and 20, and there were no significant differences between groups or time periods in the number of days that wheals were reported as shown in Table 14 and 20.

Table 13: TOTAL NUMBER OF WHEALS REPORTED

<table>
<thead>
<tr>
<th>GROUP</th>
<th>Time 1</th>
<th>Time 2</th>
<th>Time 3</th>
<th>Time 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>549±839*</td>
<td>225±410</td>
<td>298±602</td>
<td>191±230</td>
</tr>
<tr>
<td>Control</td>
<td>382±554</td>
<td>228±345</td>
<td>216±214</td>
<td>162±150</td>
</tr>
</tbody>
</table>

* mean ± SD
No significant differences (see table 20 for F ratio)
Results

Table 14: NUMBER OF DAYS WHEALS WERE REPORTED

<table>
<thead>
<tr>
<th>GROUP</th>
<th>Time 1</th>
<th>Time 2</th>
<th>Time 3</th>
<th>Time 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>9±6 *</td>
<td>8±7</td>
<td>8±6</td>
<td>9±7</td>
</tr>
<tr>
<td>Control</td>
<td>12±4</td>
<td>10±5</td>
<td>10±5</td>
<td>8±5</td>
</tr>
</tbody>
</table>

* mean ± SD

No significant differences (see table 20 for F ratio)

Itchiness

Averaged over group, there was a significant change over time for the severity of itchiness (significant time effect F=3.50, calculated F=4.00); however, the follow-up comparisons did not delineate differences between the time periods as shown in tables 15, 16 and 20. Observation of the results indicates that itchiness decreased after time 1. There were no significant differences between groups or time periods in the number of days that itchiness was reported as shown in table 17 and 20.

Table 15: TOTAL SEVERITY OF ITCHINESS SCORES

<table>
<thead>
<tr>
<th>GROUP</th>
<th>Time 1</th>
<th>Time 2</th>
<th>Time 3</th>
<th>Time 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>19±10*</td>
<td>12±9</td>
<td>12±9</td>
<td>13±11</td>
</tr>
<tr>
<td>Control</td>
<td>25±10</td>
<td>21±10</td>
<td>25±10</td>
<td>20±12</td>
</tr>
</tbody>
</table>

* mean ± SD

1 Severity of itchiness scale: 0=symptoms absent; 1=symptoms are present, but barely noticeable; 2=symptoms are definitely noticeable, but are tolerable; 3=symptoms are definitely noticeable, and are not tolerable. Over 14 days, a score of 0 would reflect absence of symptoms on all days. A score of 42 would reflect intolerable symptoms on all days.

* time effect *p<0.05 (see table 20 for F ratio) (follow-up comparisons did not delineate differences between the time periods)
Table 16: SEVERITY OF ITCHINESS OF INDIVIDUALS WITH URTICARIA AND ANGIOEDEMA

<table>
<thead>
<tr>
<th>Severity of Itchiness</th>
<th>Time 1</th>
<th>Time 2</th>
<th>Time 3</th>
<th>Time 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>22 ± 10*</td>
<td>17 ± 10</td>
<td>19 ± 11</td>
<td>16 ± 11(^a)</td>
</tr>
</tbody>
</table>

* mean ± SD

1 Severity of itchiness scale: 0=symptoms absent; 1=symptoms are present, but barely noticeable; 2=symptoms are definitely noticeable, but are tolerable; 3=symptoms are definitely noticeable, and are not tolerable. Over 14 days, a score of 0 would reflect absence of symptoms on all days. A score of 42 would reflect intolerable symptoms on all days.

\(^a\) time effect *p<0.05 (see table 20 for F ratio) (follow-up comparisons did not delineate differences between the time periods)

Table 17: NUMBER OF DAYS THAT ITCHINESS WAS REPORTED

<table>
<thead>
<tr>
<th>GROUP</th>
<th>Time 1</th>
<th>Time 2</th>
<th>Time 3</th>
<th>Time 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>11±5 *</td>
<td>9±5</td>
<td>9±5</td>
<td>9±6</td>
</tr>
<tr>
<td>Control</td>
<td>13±2</td>
<td>11±4</td>
<td>12±4</td>
<td>9±5</td>
</tr>
</tbody>
</table>

* mean ± SD

1 Severity of itchiness scale: 0=symptoms absent; 1=symptoms are present, but barely noticeable; 2=symptoms are definitely noticeable, but are tolerable; 3=symptoms are definitely noticeable, and are not tolerable. Over 14 days, a score of 0 would reflect absence of symptoms on all days. A score of 42 would reflect intolerable symptoms on all days. No significant differences (see table 20 for F ratio)

Angioedema

There were no significant differences between groups or time periods in the severity of angioedema as shown in Table 18 and 20. There were no significant differences between groups or time periods in the number of days angioedema was reported as shown in Table 19 and 20.
Results

Table 18: TOTAL SEVERITY OF ANGIOEDEMA SCORES

<table>
<thead>
<tr>
<th>GROUP</th>
<th>Time 1</th>
<th>Time 2</th>
<th>Time 3</th>
<th>Time 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>11±12*</td>
<td>9±11</td>
<td>8±10</td>
<td>10±11</td>
</tr>
<tr>
<td>Control</td>
<td>13±13</td>
<td>11±9</td>
<td>13±12</td>
<td>11±12</td>
</tr>
</tbody>
</table>

* mean ± SD

1 Severity of angioedema scale: 0=symptoms absent; 1=symptoms are present, but barely noticeable; 2=symptoms are definitely noticeable, but are tolerable; 3=symptoms are definitely noticeable, and are not tolerable. Over 14 days, a score of 0 would reflect absence of symptoms on all days. A score of 42 would reflect intolerable symptoms on all days. No significant differences (see table 20 for F ratio).

Table 19: NUMBER OF DAYS THAT ANGIOEDEMA WAS REPORTED

<table>
<thead>
<tr>
<th>GROUP</th>
<th>Time 1</th>
<th>Time 2</th>
<th>Time 3</th>
<th>Time 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>6±6*</td>
<td>6±7</td>
<td>6±6</td>
<td>7±7</td>
</tr>
<tr>
<td>Control</td>
<td>6±6</td>
<td>6±5</td>
<td>7±6</td>
<td>5±6</td>
</tr>
</tbody>
</table>

* mean ± SD

1 Severity of angioedema scale: 0=symptoms absent; 1=symptoms are present, but barely noticeable; 2=symptoms are definitely noticeable, but are tolerable; 3=symptoms are definitely noticeable, and are not tolerable. Over 14 days, a score of 0 would reflect absence of symptoms on all days. A score of 42 would reflect intolerable symptoms on all days. No significant differences (see table 20 for F ratio).
### Table 20: ADJUSTED CRITICAL F\(^1\) AND CALCULATED F\(^2\) FOR EIGHT URTICARIA AND ANGIOEDEMA VARIABLES

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>Effect of Time</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Effect of Group</td>
<td></td>
<td>Group x Time Interaction</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Adjusted</td>
<td>Calculated F</td>
<td>Adjusted Critical F</td>
<td>Calculated F</td>
<td>Adjusted Critical F</td>
<td>Calculated F</td>
</tr>
<tr>
<td>Total antihistamine tablets taken</td>
<td>3.46</td>
<td>2.39</td>
<td>6.55</td>
<td>1.90</td>
<td>3.46</td>
<td>3.15</td>
</tr>
<tr>
<td>Number of days antihistamine tables were taken</td>
<td>3.46</td>
<td>1.14</td>
<td>6.55</td>
<td>1.67</td>
<td>3.46</td>
<td>2.22</td>
</tr>
<tr>
<td>Total number of wheals reported</td>
<td>3.59</td>
<td>2.74</td>
<td>7.21</td>
<td>0.13</td>
<td>3.59</td>
<td>0.37</td>
</tr>
<tr>
<td>Number of days wheals were reported</td>
<td>3.40</td>
<td>1.80</td>
<td>6.20</td>
<td>0.32</td>
<td>3.40</td>
<td>1.79</td>
</tr>
<tr>
<td>Total severity of itchiness</td>
<td>3.50</td>
<td>4.00</td>
<td>6.55</td>
<td>4.65</td>
<td>3.50</td>
<td>1.44</td>
</tr>
<tr>
<td>Number of days itchiness was reported</td>
<td>3.40</td>
<td>2.95</td>
<td>6.20</td>
<td>0.82</td>
<td>3.40</td>
<td>1.09</td>
</tr>
<tr>
<td>Total severity of angioedema</td>
<td>3.59</td>
<td>1.08</td>
<td>6.72</td>
<td>0.24</td>
<td>3.59</td>
<td>0.67</td>
</tr>
<tr>
<td>Number of days angioedema was reported</td>
<td>3.46</td>
<td>0.21</td>
<td>6.20</td>
<td>0</td>
<td>3.46</td>
<td>1.13</td>
</tr>
</tbody>
</table>

\(^1\)Critical F statistic after adjustment with Huynh-Feldt Epsilon for p < 0.05

\(^2\)Calculated from SPSS
Nutrient Analysis

Adequacy of Nutrient Intake

The nutrient intake of the treatment group did not meet the weighted RNI for: energy during time 2, 3 and 4; calcium during time 2, 3 and 4 and zinc during time 2 as shown in tables 21 - 22. There were no intakes that were less than 70% of the weighted RNI.

The nutrient intake of the control group did not meet the weighted RNI for: energy during all four time periods; calcium during all four time periods; iron during time 2; magnesium during time 2; zinc during time 1, 2 and 4 and folate during time 4 as shown in tables 21 - 23. There were no intakes that were less than 70% of the weighted RNI.

Significant Changes in Nutrient Intake

The treatment group consumed significantly more carbohydrate than the control group (significant group effect F=6.55, calculated F=8.66) as shown in tables 21 and 26. Averaged over group, there was a significant change over time for calcium (p=0.03) and vitamin C (p=0.04) as shown in Tables 22, 23 and 25. However, follow-up comparisons did not delineate differences between time periods as shown in Table 24. Observation of the results indicates that the calcium intake decreased after initiation of the diet. In time period 4, the calcium intake
Results

increased, but did not reach the baseline value. Vitamin C intake increased after initiation of the diet. In time period 4, the vitamin C intake decreased slightly, but was still above the baseline value.

There was a different pattern of change between groups when considering time for fat, calcium, vitamin B12 and vitamin C as shown in Tables 21, 22, 23, 25 and 26 and Figures 4-7. However, the control and treatment groups were not significantly different at any time periods. Observation of the results indicates that the control group's intake of fat, calcium and vitamin C was consistent over time. In the treatment group, fat intake decreased after initiation of the treatment diet and remained decreased for the remainder of the study. The calcium intake initially decreased after initiation of the treatment diet and increased somewhat during time 4, but was still below the baseline value. The vitamin C intake increased after initiation of the treatment diet and remained increased for the remainder of the study. The vitamin B12 intake increased after initiation of the control diet and decreased after initiation of the treatment diet.

The treatment group consumed significantly more energy and carbohydrate (p<0.05) during time period 1 than the control group. When time 1 was used as a covariate for the RM ANCOVA of
Results

kilocalories and carbohydrate, there were no differences between groups or time periods.

Table 21: MACRONUTRIENT INTAKE OF INDIVIDUALS WITH URTICARIA AND ANGIOEDEMA COMPARED TO THE RECOMMENDED NUTRIENT INTAKES

<table>
<thead>
<tr>
<th>NUTRIENT</th>
<th>RNI</th>
<th>Group</th>
<th>Time 1</th>
<th>Time 2</th>
<th>Time 3</th>
<th>Time 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kilocalories</td>
<td>2230</td>
<td>Treatment</td>
<td>2310±626*</td>
<td>1738±440</td>
<td>1932±383</td>
<td>1928±215</td>
</tr>
<tr>
<td></td>
<td>2140</td>
<td>Control</td>
<td>1677±453</td>
<td>1793±350</td>
<td>1711±576</td>
<td>1669±636</td>
</tr>
<tr>
<td>Protein</td>
<td>50</td>
<td>Treatment</td>
<td>83±27</td>
<td>68±25</td>
<td>69±22</td>
<td>75±18</td>
</tr>
<tr>
<td>(grams)</td>
<td>47</td>
<td>Control</td>
<td>78±24</td>
<td>75±25</td>
<td>74±31</td>
<td>74±28</td>
</tr>
<tr>
<td>Carbohydrate</td>
<td>none</td>
<td>Treatment</td>
<td>308±108</td>
<td>247±59</td>
<td>279±48</td>
<td>279±78 a</td>
</tr>
<tr>
<td>(grams)</td>
<td>none</td>
<td>Control</td>
<td>205±61</td>
<td>209±50</td>
<td>220±72</td>
<td>206±74</td>
</tr>
<tr>
<td>Fat</td>
<td>none</td>
<td>Treatment</td>
<td>86±33</td>
<td>58±26</td>
<td>60±16</td>
<td>63±18 c</td>
</tr>
<tr>
<td>(grams)</td>
<td>none</td>
<td>Control</td>
<td>61±29</td>
<td>70±24</td>
<td>60±31</td>
<td>62±33</td>
</tr>
</tbody>
</table>

For each nutrient and each group, a weighted RNI was calculated based on the number of male and female subjects in each group.

* mean ± SD
* group effect (treatment vs control) *p<0.05 (see table 26 for F ratios)
* group by time interaction *p<0.05 (see table 25 for P values)
### Table 22: MINERAL INTAKE OF INDIVIDUALS WITH URTICARIA AND ANGIOEDEMA COMPARED TO THE RECOMMENDED NUTRIENT INTAKES\(^1\)

<table>
<thead>
<tr>
<th>NUTRIENT</th>
<th>RNI</th>
<th>Group</th>
<th>Time 1</th>
<th>Time 2</th>
<th>Time 3</th>
<th>Time 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium</td>
<td>733</td>
<td>Treatment</td>
<td>955±408*</td>
<td>544±279</td>
<td>545±338</td>
<td>644±174</td>
</tr>
<tr>
<td>(milligrams)</td>
<td>720</td>
<td>Control</td>
<td>682±307</td>
<td>687±278</td>
<td>674±317</td>
<td>680±325</td>
</tr>
<tr>
<td>Iron</td>
<td>12</td>
<td>Treatment</td>
<td>17±4</td>
<td>13±4</td>
<td>14±6</td>
<td>14±5</td>
</tr>
<tr>
<td>(milligrams)</td>
<td>12</td>
<td>Control</td>
<td>12±4</td>
<td>10±2</td>
<td>12±5</td>
<td>12±4</td>
</tr>
<tr>
<td>Magnesium</td>
<td>217</td>
<td>Treatment</td>
<td>295±136</td>
<td>265±87</td>
<td>291±122</td>
<td>295±63</td>
</tr>
<tr>
<td>(milligrams)</td>
<td>210</td>
<td>Control</td>
<td>259±73</td>
<td>207±30</td>
<td>237±67</td>
<td>220±65</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>900</td>
<td>Treatment</td>
<td>1420±481</td>
<td>1059±385</td>
<td>1068±466</td>
<td>1218±217</td>
</tr>
<tr>
<td>(milligrams)</td>
<td>880</td>
<td>Control</td>
<td>1137±292</td>
<td>1083±226</td>
<td>1170±474</td>
<td>1160±373</td>
</tr>
<tr>
<td>Zinc</td>
<td>10</td>
<td>Treatment</td>
<td>10±5</td>
<td>9±4</td>
<td>10±4</td>
<td>10±3</td>
</tr>
<tr>
<td>(milligrams)</td>
<td>10</td>
<td>Control</td>
<td>9±3</td>
<td>8±3</td>
<td>10±5</td>
<td>9±3</td>
</tr>
</tbody>
</table>

\(^1\)For each nutrient and each group, a weighted RNI was calculated based on the number of male and female subjects in each group.

\(^*\) mean ± SD

\(^b\) time effect \(^*\)p<0.05 (follow-up comparisons did not delineate differences between the time periods) (see table 25 for P values)

\(^c\) group by time interaction \(^*\)p<0.01 (see table 25 for P values)
Table 23: VITAMIN INTAKE OF INDIVIDUALS WITH URTICARIA AND ANGIOEDEMA COMPARED TO THE RECOMMENDED NUTRIENT INTAKES

<table>
<thead>
<tr>
<th>NUTRIENT</th>
<th>RNI</th>
<th>Group</th>
<th>Time 1</th>
<th>Time 2</th>
<th>Time 3</th>
<th>Time 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Folate</td>
<td>190</td>
<td>Treatment</td>
<td>253±107*</td>
<td>269±87</td>
<td>244±75</td>
<td>283±67</td>
</tr>
<tr>
<td>(micrograms)</td>
<td>184</td>
<td>Control</td>
<td>204±115</td>
<td>210±53</td>
<td>307±232</td>
<td>172±70</td>
</tr>
<tr>
<td>Niacin</td>
<td>16</td>
<td>Treatment</td>
<td>32±11</td>
<td>30±9</td>
<td>32±11</td>
<td>33±10</td>
</tr>
<tr>
<td>(NE)</td>
<td>15</td>
<td>Control</td>
<td>29±15</td>
<td>32±13</td>
<td>31±11</td>
<td>31±13</td>
</tr>
<tr>
<td>Riboflavin</td>
<td>1.1</td>
<td>Treatment</td>
<td>1.9±0.8</td>
<td>1.5±0.5</td>
<td>1.4±0.5</td>
<td>1.5±0.4</td>
</tr>
<tr>
<td>(milligrams)</td>
<td>1.1</td>
<td>Control</td>
<td>1.4±0.5</td>
<td>1.4±0.4</td>
<td>1.4±0.5</td>
<td>1.4±0.6</td>
</tr>
<tr>
<td>Thiamin</td>
<td>0.9</td>
<td>Treatment</td>
<td>1.8±1.1</td>
<td>1.4±0.4</td>
<td>1.7±0.9</td>
<td>1.6±0.6</td>
</tr>
<tr>
<td>(milligrams)</td>
<td>0.9</td>
<td>Control</td>
<td>1.2±0.8</td>
<td>1.1±0.3</td>
<td>1.1±0.4</td>
<td>1.4±1.2</td>
</tr>
<tr>
<td>Vitamin A</td>
<td>867</td>
<td>Treatment</td>
<td>3654±2363</td>
<td>4335±2700</td>
<td>5385±5455</td>
<td>4604±3965</td>
</tr>
<tr>
<td>(RE)</td>
<td>840</td>
<td>Control</td>
<td>2451±1586</td>
<td>3590±2433</td>
<td>3859±2772</td>
<td>3459±3620</td>
</tr>
<tr>
<td>Vitamin B6</td>
<td>0.8</td>
<td>Treatment</td>
<td>1.7±0.8</td>
<td>1.7±0.7</td>
<td>1.9±0.9</td>
<td>2.2±0.7</td>
</tr>
<tr>
<td>(milligrams)</td>
<td>0.7</td>
<td>Control</td>
<td>1.6±0.7</td>
<td>1.6±0.6</td>
<td>1.6±0.5</td>
<td>1.5±0.6</td>
</tr>
<tr>
<td>Vitamin B12</td>
<td>2</td>
<td>Treatment</td>
<td>3.7±2.9</td>
<td>2.7±1.7</td>
<td>2.1±1.7</td>
<td>2.6±1.3</td>
</tr>
<tr>
<td>(micrograms)</td>
<td>2</td>
<td>Control</td>
<td>3.0±1.4</td>
<td>3.2±0.9</td>
<td>4.6±3.5</td>
<td>3.7±1.5</td>
</tr>
<tr>
<td>Vitamin C</td>
<td>37</td>
<td>Treatment</td>
<td>93±54</td>
<td>175±91</td>
<td>147±62</td>
<td>170±94</td>
</tr>
<tr>
<td>(milligrams)</td>
<td>38</td>
<td>Control</td>
<td>105±96</td>
<td>103±85</td>
<td>126±70</td>
<td>90±69</td>
</tr>
</tbody>
</table>

1 For each nutrient and each group, a weighted RNI was calculated based on the number of male and female subjects in each group.
2 Based on a requirement of 0.015mg/gram dietary protein
* mean ± SD
* time effect *p<0.05 (follow-up comparisons did not delineate differences between the time periods) (see table 25 for P values)
* group by time interaction *p<0.05 (see tables 25 and 26 for P values and F ratios)
Table 24: CALCIUM AND VITAMIN C INTAKE OF INDIVIDUALS WITH URTICARIA AND ANGIOEDEMA

<table>
<thead>
<tr>
<th>NUTRIENT</th>
<th>Time 1</th>
<th>Time 2</th>
<th>Time 3</th>
<th>Time 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium</td>
<td>831±383*</td>
<td>619±280</td>
<td>613±325</td>
<td>663±258b</td>
</tr>
<tr>
<td>Vitamin C</td>
<td>99±77</td>
<td>137±93</td>
<td>136±65</td>
<td>128±90b</td>
</tr>
</tbody>
</table>

* mean ± SD  
* time effect *p<0.05 (follow-up comparisons did not delineate differences between the time periods)

Table 25: P AND F VALUES FOR NUTRIENTS THAT SATISFY THE ASSUMPTION OF SPHERICITY

<table>
<thead>
<tr>
<th>NUTRIENT</th>
<th>Effect of Time</th>
<th>Effect of Group</th>
<th>Group x Time Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F value</td>
<td>P value</td>
<td>F value</td>
</tr>
<tr>
<td>Protein</td>
<td>1.457</td>
<td>0.266</td>
<td>0.03</td>
</tr>
<tr>
<td>Fat</td>
<td>1.31</td>
<td>0.308</td>
<td>0.14</td>
</tr>
<tr>
<td>Calcium</td>
<td>3.85</td>
<td>0.032</td>
<td>0</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>1.943</td>
<td>0.166</td>
<td>0.18</td>
</tr>
<tr>
<td>Riboflavin</td>
<td>1.877</td>
<td>0.177</td>
<td>1.16</td>
</tr>
<tr>
<td>Vitamin C</td>
<td>3.59</td>
<td>0.039</td>
<td>1.74</td>
</tr>
<tr>
<td>Vitamin A</td>
<td>0.964</td>
<td>0.435</td>
<td>1.05</td>
</tr>
<tr>
<td>Vitamin B6</td>
<td>0.995</td>
<td>0.422</td>
<td>2.05</td>
</tr>
<tr>
<td>Zinc</td>
<td>0.853</td>
<td>0.487</td>
<td>0.47</td>
</tr>
</tbody>
</table>

72
### Table 26: ADJUSTED CRITICAL F\(^1\) AND CALCULATED F\(^2\) FOR EIGHT NUTRIENTS THAT DID NOT SATISFY THE ASSUMPTION OF SPHERICITY

<table>
<thead>
<tr>
<th>NUTRIENT</th>
<th>Effect of Time</th>
<th>Effect of Group</th>
<th>Group x Time Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adjusted Critical F</td>
<td>Calculated F</td>
<td>Adjusted Critical F</td>
</tr>
<tr>
<td>Kilocalories</td>
<td>3.52</td>
<td>1.89</td>
<td>6.55</td>
</tr>
<tr>
<td>Carbohydrate</td>
<td>3.52</td>
<td>2.3</td>
<td>6.55</td>
</tr>
<tr>
<td>Folate</td>
<td>3.46</td>
<td>0.95</td>
<td>6.55</td>
</tr>
<tr>
<td>Iron</td>
<td>3.72</td>
<td>2.31</td>
<td>7.21</td>
</tr>
<tr>
<td>Magnesium</td>
<td>3.46</td>
<td>1.61</td>
<td>6.55</td>
</tr>
<tr>
<td>Niacin</td>
<td>3.46</td>
<td>0.17</td>
<td>6.2</td>
</tr>
<tr>
<td>Thiamin</td>
<td>3.46</td>
<td>0.87</td>
<td>6.2</td>
</tr>
<tr>
<td>Vitamin 12</td>
<td>3.46</td>
<td>0.08</td>
<td>6.2</td>
</tr>
</tbody>
</table>

\(^1\) Critical F statistic after adjustment with Huynh-Feldt Epsilon for \(p<0.05\)

\(^2\) Calculated by SPSS
Figure 4: GROUP X TIME INTERACTION

Fat

Figure 5: GROUP X TIME INTERACTION

Calcium
Figure 6: GROUP X TIME INTERACTION

Vitamin B12

![Graph showing Vitamin B12 levels over time with two lines for Treatment and Control groups.]

Legend
- Treatment
- Control

Time Periods:
1 2 3 4

Time 1 Time 2 Time 3 Time 4

Figure 7: GROUP X TIME INTERACTION

Vitamin C

![Graph showing Vitamin C levels over time with two lines for Treatment and Control groups.]

Legend
- Treatment
- Control

Time Periods:
1 2 3 4

Time 1 Time 2 Time 3 Time 4
CASE ANALYSIS OF TREATMENT GROUP SUBJECTS WITH IMPROVEMENT IN SYMPTOMS

Subject 11 (Table 27) entered the study with an 8 month history of urticaria and facial angioedema. The wheals and angioedema were controlled by antihistamine medication and topical corticosteroid. Pruritus was the only symptom remaining when the subject entered the study. The subject had relief from pruritus on day 1 of the treatment diet. Mild pruritus was reported from day 9 to the end of the study. Thirteen antihistamine tablets were taken in time 1, and two tablets were taken in time 2, 3 and 4. Additionally, the subject discontinued the use of a topical corticosteroid on Day 0. The subject had a long history of rhinitis which improved on the histamine-reducing diet. At the end of the study, the subject wrote, "very interesting and satisfactory results."

Subject 13 (table 29) entered the study with a 20 year history of urticaria and occasional facial angioedema. The symptoms began at 6 years of age and were in remission between 15 and 21 years of age. The angioedema, wheals and itching disappeared on Day 4 of the treatment diet. The symptoms were reported on Day 14, but only lasted a few hours. Antihistamine tablets were discontinued on Day 4. On Day 2 the subject wrote "I have much more energy - feel great". The subject had a long history of rhinitis, bloating and gas and migraine headache which

76
Results

improved on the histamine-reducing diet.

Subject 17 (table 30) entered the study with a five year history of urticaria without angioedema. A partial reduction in the number of antihistamine tablets, wheals and severity of pruritus occurred on Day 1 of the histamine-reducing diet. The number of days that symptoms occurred and antihistamine tablets were taken did not change, but the severity of symptoms and the number of antihistamine tablets taken decreased. The subject indicated that she felt in better health overall on the histamine-reducing diet. The subject had a history of gas, abdominal bloating and constipation. These symptoms improved on the histamine-reducing diet.

Subject 12 (table 28) entered the study with a five year history of urticaria and facial and body angioedema. The number of wheals and the severity of pruritus and angioedema appeared to remain stable throughout the study, but the number of antihistamine tablets taken decreased. Thirteen antihistamine tablets were taken during time 1, and four tablets were taken during time 2, 3 and 4.
Table 27: THE EFFECT OF THE TREATMENT DIET ON URTICARIA AND ANGIOEDEMA SYMPTOMS (SUBJECT 11)

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>Time 1</th>
<th>Time 2</th>
<th>Time 3</th>
<th>Time 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total number</td>
<td>Days</td>
<td>Total number</td>
<td>Days</td>
</tr>
<tr>
<td>Antihistamine Intake</td>
<td>13.0</td>
<td>13</td>
<td>2.0</td>
<td>2</td>
</tr>
<tr>
<td>Number of Wheals</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Severity of Itchiness^1</td>
<td>22</td>
<td>14</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Severity of Angioedema^1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

^1 Severity of itchiness/angioedema scale: 0 = symptoms absent; 1 = symptoms are present, but barely noticeable; 2 = symptoms are definitely noticeable, but are tolerable; 3 = symptoms are definitely noticeable, and are not tolerable. Over 14 days, a score of 0 would reflect absence of symptoms on all days. A score of 42 would reflect intolerable symptoms on all days.

Table 28: THE EFFECT OF THE TREATMENT DIET ON URTICARIA AND ANGIOEDEMA SYMPTOMS (SUBJECT 12)

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>Time 1</th>
<th>Time 2</th>
<th>Time 3</th>
<th>Time 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total number</td>
<td>Days</td>
<td>Total number</td>
<td>Days</td>
</tr>
<tr>
<td>Antihistamine Intake</td>
<td>13.0</td>
<td>12</td>
<td>3.0</td>
<td>3</td>
</tr>
<tr>
<td>Number of Wheals</td>
<td>335</td>
<td>12</td>
<td>220</td>
<td>14</td>
</tr>
<tr>
<td>Severity of Itchiness^1</td>
<td>18</td>
<td>11</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>Severity of Angioedema^1</td>
<td>19</td>
<td>11</td>
<td>14</td>
<td>14</td>
</tr>
</tbody>
</table>

^1 Severity of itchiness/angioedema scale: 0 = symptoms absent; 1 = symptoms are present, but barely noticeable; 2 = symptoms are definitely noticeable, but are tolerable; 3 = symptoms are definitely noticeable, and are not tolerable. Over 14 days, a score of 0 would reflect absence of symptoms on all days. A score of 42 would reflect intolerable symptoms on all days.
Table 29: THE EFFECT OF THE TREATMENT DIET ON URTICARIA AND ANGIOEDEMA SYMPTOMS (SUBJECT 13)

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>Time 1</th>
<th></th>
<th>Time 2</th>
<th></th>
<th>Time 3</th>
<th></th>
<th>Time 4</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td>Days</td>
<td>Total</td>
<td>Days</td>
<td>Total</td>
<td>Days</td>
<td>Total</td>
<td>Days</td>
</tr>
<tr>
<td>Antihistamine Intake</td>
<td>14.0</td>
<td>11</td>
<td>1.0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Number of Wheals</td>
<td>24</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>11</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Severity of Itchiness(^1)</td>
<td>19</td>
<td>12</td>
<td>4</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Severity of Angioedema(^1)</td>
<td>4</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

\(^1\) Severity of itchiness/angioedema scale: 0=symptoms absent; 1=symptoms are present, but barely noticeable; 2=symptoms are definitely noticeable, but are tolerable; 3=symptoms are definitely noticeable, and are not tolerable. Over 14 days, a score of 0 would reflect absence of symptoms on all days. A score of 42 would reflect intolerable symptoms on all days.

Table 30: THE EFFECT OF THE TREATMENT DIET ON URTICARIA AND ANGIOEDEMA SYMPTOMS (SUBJECT 17)

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>Time 1</th>
<th></th>
<th>Time 2</th>
<th></th>
<th>Time 3</th>
<th></th>
<th>Time 4</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Days</td>
<td>Total</td>
<td>Days</td>
<td>Total</td>
<td>Days</td>
<td>Total</td>
<td>Days</td>
</tr>
<tr>
<td>Antihistamine Intake</td>
<td>12.0</td>
<td>14</td>
<td>6.5</td>
<td>13</td>
<td>6.5</td>
<td>13</td>
<td>6.0</td>
<td>12</td>
</tr>
<tr>
<td>Number of Wheals</td>
<td>1385</td>
<td>14</td>
<td>395</td>
<td>14</td>
<td>365</td>
<td>13</td>
<td>285</td>
<td>12</td>
</tr>
<tr>
<td>Severity of Itchiness(^1)</td>
<td>33</td>
<td>14</td>
<td>19</td>
<td>12</td>
<td>17</td>
<td>13</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Severity of Angioedema(^1)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

\(^1\) Severity of itchiness/angioedema scale: 0=symptoms absent; 1=symptoms are present, but barely noticeable; 2=symptoms are definitely noticeable, but are tolerable; 3=symptoms are definitely noticeable, and are not tolerable. Over 14 days, a score of 0 would reflect absence of symptoms on all days. A score of 42 would reflect intolerable symptoms on all days.
MAJOR FINDINGS

The study was conducted to evaluate the effect of a histamine-reducing diet in chronic urticaria and angioedema, and to evaluate the effect of the diet on nutrient intake. The major findings were as follows: A histamine-reducing diet did not improve chronic urticaria and angioedema. There were no differences between groups over time in the number of antihistamine tablets taken, the number of wheals, the severity of urticaria and angioedema, the number of days that antihistamine tablets were taken or the number of days wheals, pruritus or angioedema were reported. However, the treatment group took significantly more antihistamine tablets during the two weeks prior to the treatment diet than during the two weeks after the initiation of the treatment diet.

Adherence to the histamine-reducing diet resulted in a decreased intake of fat, calcium and vitamin B12 and an increased intake of vitamin C. The treatment group met the weighted RNI for energy and calcium during time period 1, but failed to meet the recommendations for these nutrients during time periods 2, 3 and 4.
Discussion

The follow-up comparisons for the significant time effects and group x time interactions were not significant. This may have been due to the strict α levels used for multiple comparisons and the small sample size.

COMPARISON TO CLINICAL FINDINGS

The histamine-reducing diet has been used in patient counselling at the Allergy Nutrition Clinic at the Vancouver Hospital and Health Sciences Centre since October 1991. As of January 1994, 16 patients with urticaria, angioedema or pruritus have been instructed to follow the histamine-reducing diet. The effect of dietary intervention on the disease symptoms was evaluated through follow-up interview notes in the patients' clinical charts. If a follow-up appointment was not held, the investigator contacted the patient by telephone. Three patients could not be reached, and one patient changed medication and diet at the same time. Four (33%) patients had a complete or partial remission of symptoms on the histamine-reducing diet. The diet did not improve symptoms in eight (67%) patients.

Of the nine treatment subjects in the present study, one (11%) subject had complete remission of symptoms and discontinued antihistamine medication. One subject (11%) had a decrease in itching (the only symptom present during time 1) and discontinued antihistamine medication and topical corticosteroid. Another 2 (22%) subjects had partial remission of symptoms and a reduction
Discussion

in antihistamine medication intake, and the remaining five subjects did not benefit from the histamine-reducing diet.

The clinical findings from the Allergy Nutrition Clinic are similar to the treatment group finding from the present study (33% versus 44% complete or partial remission of symptoms, respectively).

COMPARISON TO OTHER STUDIES

The present study is the only dietary manipulation study in chronic urticaria and angioedema with statistical analyses of a control and treatment diet. Several studies have evaluated the effect of food-additive free diets in open designs. The results from the treatment group (n=9) will be compared to these studies.

The effect of a food-additive free and low-tyramine diet in chronic urticaria was evaluated by Verschave et al. (1983). The diet eliminated food additives, alcohol, stone fruit, oranges, nuts, strawberries, tomatoes, peas, beans, shellfish, bananas, pineapple and old and fermented cheese. This diet was similar to the histamine-reducing diet. Fifty-five percent (37/67) of the subjects had complete or partial remission of symptoms while following the low-tyramine diet. These findings are similar to the 44% complete or partial remission of symptoms on the histamine-reducing diet. The length of the diet or the method and timing of symptom evaluation were not described. This brings the
results of the low-tyramine diet into question, and impedes detailed comparison between the two studies.

Several food-additive free diets have reported a range of 32 to 90% complete or partial remission of urticaria symptoms (Table 5). Six of the seven studies reviewed, had 60% or greater complete or partial remission of symptoms. However, these studies have several limitations. The method of symptom assessment and length of the diet was not described. The time between the initial and the final evaluation of symptoms ranged from 6 months to 2 years. The large number of subjects free from symptoms were likely due to placebo effect and natural remission of symptoms. However, the beneficial effects may have been partially due to the treatment diet.

Comparison between the findings from the present study and the food-additive free studies is difficult due to the nonspecific methods and the small sample size of the present study. The higher percentages of subjects with complete or partial remission of symptoms on the food-additive free diets may have resulted from the long periods of time between initial and final symptom assessment and placebo effect.

**TREATMENT GROUP SUBJECTS WITH IMPROVEMENT IN SYMPTOMS**

Four subjects on the treatment diet (n=9) had an improvement in urticaria and angioedema symptoms (Tables 27-30). There were no features which distinguished the subjects who improved on the
treatment diet from the subjects who did not improve. A larger sample size and detailed clinical evaluation by a dermatologist may have identified features which distinguished the two groups.

Subject 11, 12 and 13 were contacted by telephone five months after finishing the study. Subject 11 was following the treatment diet, and his symptoms were controlled. Subject 12 was not following the treatment diet because her symptoms had improved. Subject 13 was following the treatment diet, and her symptoms were controlled. Subject 17 was contacted by telephone two months after finishing the study. She was not following the treatment diet because she did not have time to prepare food without preservatives and found it difficult to eliminate cheese and tomatoes from her diet. The urticaria and angioedema symptoms became worse when the treatment diet was discontinued. She took one half of an antihistamine tablet per day when she was adhering to the histamine-reducing diet. The subject increased her intake to one tablet per day after the diet was discontinued.

TREATMENT GROUP SUBJECTS WITHOUT IMPROVEMENT IN SYMPTOMS

Many factors have been identified in the pathogenesis of chronic urticaria and angioedema. Diet may be the primary cause or a contributing factor in some individuals. The treatment diet is based on the theory that some individuals with chronic
urticaria and angioedema have reduced diamine oxidase activity (DAO) in the intestinal mucosa (Lessof et al., 1990). Plasma histamine and urticaria symptoms may increase after consumption of histamine rich foods. Additionally, food additives may increase endogenous release of histamine in some individuals.

The post-heparin plasma DAO curve was decreased in a sample of nine subjects with urticaria, indicating an overall decrease in intestinal mucosa DAO activity (Lessof et al., 1990). However, there was a large variation among individuals. Two subjects had a minimal DAO response, three subjects had a low normal response, three subjects had a normal response and one subject had an above normal response. Intraduodenal administration of histamine did not alter plasma histamine in eight control subjects, and there was little variation in plasma histamine within the sample. The urticaria group (n=25) had a significant rise in plasma histamine after intraduodenal histamine administration. Moreover, there was a large variation in the plasma histamine levels. Based on these observations, the effect of dietary histamine on urticaria and angioedema would be expected to differ among individuals.

Plasma and urinary histamine increase in some subjects after oral administration of food additives. Three subjects who were asymptomatic on an additive-free diet and had an exacerbation of urticaria after a double-blind food additive challenge were
enrolled in a study to measure biochemical changes during food additive challenge. Plasma histamine and urticaria symptoms increased in two of the three subjects. However, the subjects' responses to the challenges differed dramatically.

The activity of DAO and the endogenous release of histamine after food additive consumption varies between individuals. As a result, dietary manipulation will not benefit all subjects with urticaria and angioedema.

NUTRITIONAL ADEQUACY OF THE HISTAMINE-REDUCING DIET

Adherence to the treatment diet was initially difficult as the subjects had to change their eating patterns in order to abide by the dietary restrictions. The subjects became accustomed to the dietary restrictions and established new eating patterns during time 3 and 4. This trend concurs with the observation that the nutrient intakes tended to decrease in the treatment group during time 2 but subsequently increased during time 3 and 4.

Five of the nine treatment subjects had a marginal weight loss while only one control subject lost weight. Fluid loss has been observed to occur when the histamine-reducing diet is first initiated (personal correspondence, Dr. Janice Joneja). However, the weight loss in the treatment group was likely due to an energy restriction because subjects appeared to lose weight
gradually over the study rather than immediately preceding the
initiation of the diet. The energy intake met the weighted RNI of
the treatment group during time 1, but failed to do so during
time 2, 3 and 4. The energy intake of the treatment group in time
period 2 was 75% of the energy intake in time period 1.
Approximately 45% of this decrease was due to a reduction in fat,
45% due to a reduction in carbohydrate and 10% due to a reduction
in protein. The energy intake increased in time periods 3 and 4.
For the eight subjects in the treatment group who completed the
entire 56 days of the study, the mean energy intake was 2150
kilocalories/day (data not shown), which was slightly less than
the weighted RNI (2230 kilocalories/day) for the treatment group.
The decreased caloric intake was likely a temporary adaptation to
the dietary restrictions and did not appear to put the treatment
subjects at nutritional risk.

The calcium intake of the treatment group met the weighted
RNI during time period 1, but failed to do so during time periods
2, 3 and 4. For the eight subjects in the treatment group who
completed the entire 56 days of the study, the mean calcium
intake was 731 mg/day (data not shown), which was slightly less
than the weighted RNI (733 mg/day) for the treatment group. The
decreased calcium intake was likely a temporary adaptation to the
dietary restrictions and did not appear to put the treatment subjects at nutritional risk.

There were no other nutrient intakes that met the weighted RNI of the treatment group during time period 1, but failed to do so during time 2, 3 and 4.

The histamine-reducing diet did not significantly limit any nutrients, and an adequate nutrient intake was achieved while following the diet. Nutritional deficiency is possible especially during the initial adaptation to the diet; therefore, dietary follow-up and counselling is an essential component of dietary intervention. The potential benefits of the histamine-reducing diet outweigh the possibility of nutritional deficiencies.

**LIMITATIONS OF THE STUDY**

The limitations to the study were the small sample size, large within- and between-subject variation, group differences, lack of a standardized method to assess urticaria and angioedema, lack of a biochemical marker for plasma histamine, potential for placebo effect and potential for bias due to a single-blind design.

Prior to initiation of the study, a sample size of 34 subjects was estimated to be necessary for statistical significance. Due to difficulty with subject recruitment, data
from 19 subjects were used in the statistical analysis. Significant findings would not be anticipated based on the small sample size.

The symptom data failed the assumption of sphericity indicating that there was a lot of variation in the data. This decreased the power of the study.

The treatment group took significantly more antihistamine tablets and consumed more energy during time 1 than the control group. Even though not statistically significant, the treatment group appeared to have more wheals during time 1 and entered the study with a longer duration of disease than the control group. The control and treatment groups may not have been comparable.

In the absence of a standardized method to assess the severity of urticaria and angioedema, an assessment scale was developed based on variables that were commonly evaluated in antihistamine medication clinical trials. Antihistamine medication intake was the most reliable indicator because it was an objective variable and was congruent with the rationale for the treatment diet.

Antihistamine medication intake was an important indicator for the study because the need to take this medication likely reflects increased body histamine. However, there were circumstances in which alteration of antihistamine medication did
Discussion

not reflect changes in urticaria and angioedema symptoms. Antihistamine medication was also taken during the study to control rhinitis. Some subjects took antihistamine medication even though it did not noticeably improve their symptoms. The antihistamine medication intake was variable in these subjects. The effectiveness of antihistamine medications may decrease with use, and the individual may need to change the type of antihistamine or increase the dose to control symptoms.

The severity of pruritus was an important indicator for the study because histamine is solely responsible for pruritus. However, it was a subjective variable and this decreased its reliability.

Histamine is one of many inflammatory mediators that produce wheals. The number of wheals may not be a good indicator of body histamine, and therefore, may not be a good indicator of the effectiveness of a histamine-reducing diet. Counting the number of wheals was difficult for most subjects. The number of wheals was applicable to 16 subjects, and 11 subjects guessed the number of wheals at certain times. The reasons given for guessing were, that there were too many wheals to count, wheals were on body parts that could not be seen, and wheals were difficult to distinguish especially if they tended to coalesce. The number of wheals was a questionable variable for use in this study.
Histamine is one of many inflammatory mediators that produce angioedema. The severity rating of this variable was subjective, and therefore, not reliable. The severity of angioedema was a questionable variable for use in this study.

Although the latter three measures are subjective, consistency of symptom assessment was stressed throughout the study. Therefore, the within-subject variation should have been minimized. Significant changes over time would have been detected.

The ability to measure plasma histamine would have added an important variable in this study. Several techniques to measure blood histamine have been developed. These include gas chromatographic-mass-spectrometric technique, single isotope assay, fluorometric-fluoroenzyme assay, radioimmunoassay and high performance liquid chromatography. In a European external quality control study, seven out of ten laboratories measuring samples with known blood histamine levels were accurate and precise. Inaccurate results were due to human error rather than the method (Neugebauer et al., 1990). Despite reasonable accuracy of determination, practical application of these methods may be limited. Frequent fluctuations in plasma histamine make the interpretation of plasma histamine levels difficult (Keyzer et al., 1984). Histamine has five urinary metabolites, of which N-
Discussion

methylhistamine and N-methylimidazole acetic acid are unique metabolites. Levels of N-methylimidazole acetic acid are greatly influenced by the amount of histamine in the diet (Keyzer et al., 1984). Measurement of this metabolite has not been clearly defined to make it a valid clinical test. Further research is required to find a valid and reliable marker for blood histamine levels.

Placebo effect is a potential concern in the present study. Significant time effects, with a decrease in symptoms over time, would have indicated a strong placebo effect. There was a significant time effect for the severity of itchiness which decreased over time as shown in table 16. The effect of placebo was minimized by comparing the outcome of the histamine-reducing and the control diet over time.

The researcher conducting the study and educating the treatment and control subjects was aware of the difference between the diets. A conscientious effort to treat both groups the same was made; however, the potential for bias was present.
Discussion

THE VALIDITY OF USING A CROSSOVER DESIGN TO EVALUATE THE EFFECT OF DIETARY MANIPULATION IN CHRONIC URTICARIA AND ANGIOEDEMA

In a crossover design the subjects follow both the treatment and the control diet in a random order. Fewer subjects are required for a crossover design because the within-subject variation is less than the between-subject variation (Monsen & Cheney, 1992; Louis et al., 1984). In the present study, the small sample size and large within- and between-subject variation decreased the power of the study. If the study had been conducted as a crossover design, statistical significance may have been found.

However, the findings of a crossover design would not be valid for three reasons. First, the subjects must enter the control diet and the treatment diet in an identical state. The symptoms of chronic urticaria and angioedema fluctuate over time, and the above assumption could not be guaranteed. Second, a carry-over effect from each diet period may occur. If a subject's symptoms were relieved on the first diet, he would likely continue the dietary restriction during the second diet period. Finally, blinding would be difficult with a crossover design. In the present study, the subjects were given either the treatment diet or the control diet and did not compare the diets until the study was complete. If the diets are compared, it is obvious that the treatment diet is much more rigorous than the control diet.
In a crossover design, the subjects may believe that the control diet is not effective.

**FUTURE RESEARCH**

The results of this study were not conclusive and further studies are required to clarify the findings. If dietary manipulation is shown to be effective in the management of urticaria and angioedema, additional research will be required to determine which aspects of the diet were effective and which subjects are most likely to benefit from a histamine-reducing diet. Finally, the food handling conditions which lead to histamine formation must be further investigated.

Food additives and histamine-rich food were eliminated in the histamine-reducing diet. If the diet is effective in urticaria and angioedema, it will be important to determine which of the restrictions are responsible for the beneficial effect.

The activity of DAO and the pattern of histamine metabolism can be measured (Lessof et al., 1990 and Kanny et al., 1993, respectively). If urticaria subjects with decreased DAO activity or delayed histamine catabolism follow a histamine-reducing diet, all subjects should improve. A study of this nature would test the rationale of the treatment diet. Moreover, the correlation between effectiveness of the diet and the DAO activity could be
determined. Diamine oxidase activity and/or indicators of histamine metabolism may be useful clinical tests to determine which subjects may benefit from a histamine-reducing diet.

Further research is required to determine the food preparation conditions that lead to histamine formation. Presence of histidine decarboxylase-producing microorganisms, free histidine and conditions that allow for microbiological growth result in histamine formation. There is evidence that poor hygiene in the fish canning industry may result in histamine formation (Kim & Bjeldanes, 1978). However, there have not been any studies to determine the prevalence of histamine formation from poor hygiene in other food manufacturing industries, restaurants and the home. Education on hygienic food handling may be necessary for histamine sensitive individuals.

CLINICAL APPLICATION OF STUDY FINDINGS

Chronic urticaria and angioedema can be very troublesome for those afflicted with this condition. Patients are often frustrated because the inciting agent remains unknown in 75% of cases (Burrall et al., 1990). This frustration was apparent in the urgent response to the January 21 and 22, 1995 newspaper ad. Many subjects stated that they would try anything to alleviate their suffering. A histamine-reducing diet may improve symptoms
in some subjects with chronic urticaria. The symptoms will improve within two weeks, if the diet is effective. The histamine-reducing diet should be considered for treatment of chronic urticaria and angioedema at least for a trial period. The results of the study and the details of the diet, should be disseminated to health care professionals who provide treatment for these patients.

The results of this study demonstrated that the histamine-reducing diet can also result in a decreased intake of energy and some nutrients and subsequent weight loss in some individuals. It is imperative that dietary counselling and adequate follow-up be provided for patients wishing to modify their diets.
REFERENCES


APPENDICES
APPENDIX B: HISTAMINE-REDUCING DIET

DIETARY GUIDELINES

FRUIT/VEGETABLE
- Cranberries
- Strawberries
- Pineapple
- Raspberry
- Dates
- Currants
- Raisins
- Spinach
- Tomato and tomato products
- Prunes

MEAT/ALTERNATES
- any seafood (shell fish, fin fish which is canned, fresh, frozen)
- uncooked egg white (egg nog, some milkshakes)
- processed meat (luncheon meat, sausage, wiener)
- leftover meat, EAT fresh prepared meat only

MILK/MILK PRODUCTS
- cheese products (block, processed, slices)
- yoghurt
- sour cream

FOOD ADDITIVES
- read all food labels carefully, do not eat food which contains: tartrazine, artificial food color, benzoic acid, sodium benzoate, benzyol peroxide, BHT, BHA
- many medications, vitamin pills etc. contain these additives; ask your pharmacist

SEASONING
- cinnamon
- cloves
- hot paprika
- anise
- curry powder
- nutmeg

MISCELLANEOUS
- fermented soy products (soy sauce, miso)
- fermented food (sauerkraut)
- tea (herbal or regular)
- chocolate
- alcohol (beer, wine, hard liquor)

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1 Benzoates (Jacobson, 1987; Heimhuber, 1990)
2 Salicylates (Swain, 1985)
3 Food Additives
4 Histamine releasing food (Finn, 1987)
5 Histamine rich food (Stratton et al., 1991; ten Brink et al., 1990)
APPENDIX C: CONTROL DIET

DIETARY GUIDELINES

Please **DO NOT** eat or drink any of the following artificial sweeteners or sugar alcohols during the research study.

- Aspartame®
- Splenda®
- Saccharin
- Cyclamate
- Mannitol
- Xylitol
- Sorbitol

These sweeteners are added to food and may be found in:

**FRUIT**
- canned fruit
- fruit drink

**MEAT/ALTERNATES**
- peanut butter

**MILK/MILK PRODUCTS**
- yoghurt
- ice cream

**DESSERTS/SWEETS**
- popsicles
- chocolate bars
- candies
- soda pop
- pudding
- hot chocolate
- cake
- syrup

Many commercial desserts contain artificial sweeteners.

**MEDICATION**
- cough syrup
- Neo Citran™
- cough lozenge

**MISCELLANEOUS**
- barbeque sauce
- ketchup
- chewing gum
- cold and hot cereal

**READ THE LABELS CAREFULLY**

Artificial sweeteners may be purchased in a liquid or a granulated form. The brand names are Equal, Sucaryl, Sugar Twin, Sweet n' Low and Splenda. Please do not consume these products.
Please complete the assessment at the same time each day. Complete the assessment for the previous 24 hours.

1. Number of antihistamine tablets taken: ______
   Name of tablet: __________________
   Dose of tablet: ________ mg

2. Total number of wheals (hives): ______
   Did you ___ count your wheals or ___ guess?

3. Severity of itchiness: Please check one.
   ___ symptoms absent
   ___ symptoms are present, but barely noticeable
   ___ symptoms are definitely noticeable, but are tolerable
   ___ symptoms are definitely noticeable, and are not tolerable

4. Severity of angioedema: Please check one.
   ___ symptoms absent
   ___ symptoms are present, but barely noticeable
   ___ symptoms are definitely noticeable, but are tolerable
   ___ symptoms are definitely noticeable, and are not tolerable

5. Comments: ________________________________

6. Changes in medications (including hormonal therapy), creams, laundry detergent, stress, lifestyle, and other factors which affect your symptoms or dietary problems: ________________________________

__________________________________________________________________
__________________________________________________________________

Day of Study: ___ Date: ___________ Name: _________________________

108
### APPENDIX E: THREE DAY FOOD RECORD

#### FOOD RECORD

| Day of Study: 1 | Date: | Name: |

Please list everything you eat and drink from 12:00 am to 11:59 pm. Include any medication, vitamins or supplements. Please be specific. Indicate how the food was prepared, brand names, and quantities.

<table>
<thead>
<tr>
<th>TIME</th>
<th>FOOD</th>
<th>QUANTITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Example</td>
<td>Fried eggs</td>
<td>2</td>
</tr>
<tr>
<td>8:00am</td>
<td>Margarine</td>
<td>2 teaspoon</td>
</tr>
<tr>
<td></td>
<td>Whole wheat toast</td>
<td>1 slice</td>
</tr>
<tr>
<td></td>
<td>Jam</td>
<td>1 tsp</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TIME</th>
<th>FOOD</th>
<th>QUANTITY</th>
</tr>
</thead>
<tbody>
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<tr>
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<td></td>
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</tbody>
</table>

109
## Appendix F: Food Sources of Selected Nutrients

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Meat, Fish, Poultry and Alternates</th>
<th>Milk and Milk Products</th>
<th>Fruits and Vegetables</th>
<th>Breads and Cereals</th>
<th>Miscellaneous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin A</td>
<td>Eggs, fish, liver</td>
<td>Fortified milk and margarine, butter</td>
<td>Dark green and yellow vegetables, sweet potato, tomato</td>
<td>Fish liver oils</td>
<td></td>
</tr>
<tr>
<td>Vitamin B₁ (Thiamin)</td>
<td>Meats, dried peas, legumes</td>
<td>Milk, cheese, yogurt, cottage cheese</td>
<td>Green vegetables</td>
<td>Whole grains, enriched flour and cereals</td>
<td>Nutritional yeast, wheat germ</td>
</tr>
<tr>
<td>Vitamin B₂ (Riboflavin)</td>
<td>Meats, especially organ meats, legumes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Niacin</td>
<td>Meats, especially organ meats, poultry, fish, peanuts, legumes</td>
<td>Corn</td>
<td>Whole grains, enriched flour and cereals</td>
<td>Nutritional yeast</td>
<td></td>
</tr>
<tr>
<td>Vitamin B₆ (Pyridoxine)</td>
<td>Meats, especially organ meats, eggs, fish, legumes</td>
<td>Green leafy vegetables, banana, carrot, potato</td>
<td>Whole grains</td>
<td>Nutritional yeast, wheat germ</td>
<td></td>
</tr>
<tr>
<td>Vitamin B₁₂</td>
<td>Meats, especially organ meats, eggs, fish, shellfish</td>
<td>Cheese, yogurt</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin C (Ascorbic Acid)</td>
<td></td>
<td>Fruits, especially citrus fruits and juices, strawberries, cabbage, tomato, potato</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin D</td>
<td>Eggs, liver</td>
<td>Fortified milk and margarine, butter</td>
<td></td>
<td>Fish liver oils</td>
<td></td>
</tr>
<tr>
<td>Vitamin E</td>
<td>Eggs, nuts, liver, legumes</td>
<td>Milk, butter</td>
<td>Green leafy vegetables</td>
<td>Whole grains, fortified cereals</td>
<td>Vegetable oils, wheat germ</td>
</tr>
<tr>
<td>Vitamin K</td>
<td>Liver, egg yolk</td>
<td>Butter, cheese</td>
<td>Green leafy vegetables, potato</td>
<td>Wheat, oats</td>
<td>Vegetable oils</td>
</tr>
<tr>
<td>Folic acid</td>
<td>Organ meats, nuts, legumes</td>
<td></td>
<td>Green leafy vegetables, asparagus, banana, strawberries</td>
<td>Whole grains</td>
<td>Nutritional yeast</td>
</tr>
<tr>
<td>Pantothenic acid</td>
<td>Eggs, organ meats, peanuts, walnuts</td>
<td></td>
<td>Fresh vegetables</td>
<td>Whole grains, rice bran</td>
<td>Nutritional yeast</td>
</tr>
<tr>
<td>Calcium</td>
<td>Oysters, scallops, salmon and sardines with bones, tofu</td>
<td>All</td>
<td>Green leafy vegetables, broccoli, dates</td>
<td>Blackstrap molasses</td>
<td></td>
</tr>
<tr>
<td>Iron</td>
<td>Meats, liver, eggs, shellfish, nuts, sardines, legumes</td>
<td>Broccoli, peas, spinach, prunes, raisins</td>
<td>Bran, enriched cereals</td>
<td>Blackstrap molasses, wheat germ</td>
<td></td>
</tr>
<tr>
<td>Magnesium</td>
<td>Nuts, legumes</td>
<td>Peas</td>
<td>Whole grain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Potassium</td>
<td>Meats</td>
<td>Milk</td>
<td>Fruits, especially orange juice, bananas, dried fruits, potato</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zinc</td>
<td>Meat, liver, eggs, shellfish</td>
<td>Cheese</td>
<td>Green leafy vegetables, orange, prunes, strawberries</td>
<td>Whole grains</td>
<td>Chocolate syrup</td>
</tr>
</tbody>
</table>

Sources:

This appendix was written by:
- Cathy Hauchecorne, R.D.N.
- University Hospital
- Vancouver
Any information resulting from this research study will be kept strictly confidential. All documents will be identified only by code number and kept in a locked file cabinet. The subjects will not be identified by name in any reports of the completed study.

Your participation in this study is strictly voluntary. You are free to withdraw from the study at anytime without consequence to continued medical care.

Thank you for your interest in this study. If you have any questions or comments, please contact Wendy King at 875-5002. If you have any concerns about your treatment or rights as a research subject, contact the Director of Research Services at the University of British Columbia, Dr. Richard Spratley at 822-9252.

I consent to participate in the "Effect of Dietary Manipulation in Chronic Urticaria/Andioedema" Study, and have received a copy of this consent form.

Subject Signature Date

Witness Signature Date

Investigator's Signature Date
### APPENDIX I: REASONS GIVEN BY POTENTIAL SUBJECTS FOR NOT PARTICIPATING IN THE STUDY

<table>
<thead>
<tr>
<th>Reason</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distance</td>
<td>22</td>
</tr>
<tr>
<td>Unknown</td>
<td>12</td>
</tr>
<tr>
<td>Insufficient time to participate</td>
<td>7</td>
</tr>
<tr>
<td>Symptoms less frequent than once per week</td>
<td>5</td>
</tr>
<tr>
<td>Symptoms were not urticaria/angioedema</td>
<td>4</td>
</tr>
<tr>
<td>Subject began study, but stressful period during Time Period #1</td>
<td>2</td>
</tr>
<tr>
<td>Subject reported symptoms were too severe</td>
<td>2</td>
</tr>
<tr>
<td>Subject began study, but reported pregnancy during Time Period #1</td>
<td>1</td>
</tr>
<tr>
<td>Subject began study, but changed medication/health during Time Period #1</td>
<td>1</td>
</tr>
<tr>
<td>Does not want to follow a diet</td>
<td>1</td>
</tr>
<tr>
<td>Currently following a diet for urticaria</td>
<td>1</td>
</tr>
<tr>
<td>Does not think diet will help symptoms</td>
<td>1</td>
</tr>
<tr>
<td>Pregnant</td>
<td>1</td>
</tr>
<tr>
<td>Under 19 years of age</td>
<td>1</td>
</tr>
<tr>
<td>Physician did not approve</td>
<td>1</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>62</strong></td>
</tr>
</tbody>
</table>
APPENDIX J: URTICARIA AND ANGIOEDEMA SYMPTOM ASSESSMENT
SCALES WHICH WERE NOT COMPLETED

Subject #4 (Control Group)
Antihistamine Medication Intake: Day 27
Number of Wheals: Day 9
Severity of Itchiness: Day 9
Severity of Angioedema: Day 9

Subject #5 (Control Group)
Number of Wheals: Day 11

Subject #6 (Control Group)
Number of Wheals: Day 38
Severity of Itchiness: Day 3
Severity of Angioedema: Days 2, 10

Subject #7 (Control Group)
Antihistamine Medication Intake: Day -3
Severity of Angioedema: Day 34

Subject #8 (Control Group)
Number of Wheals: Day -1
Severity of Itchiness: Days 22, 24
Severity of Angioedema: Days 22, 24

Subject #11 (Treatment Group)
Number of Wheals: Day 25

Subject #14 (Treatment Group)
Number of Wheals: Day 23

Subject #15 (Treatment Group)
Number of Wheals: Days 7
### APPENDIX K: STARTING AND ENDING DATES FOR EACH SUBJECT

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</thead>
<tbody>
<tr>
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<td>02/12</td>
<td>04/22</td>
</tr>
<tr>
<td>2</td>
<td>C</td>
<td>01/05</td>
<td>03/17</td>
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<tr>
<td>3</td>
<td>C</td>
<td>01/10</td>
<td>03/20</td>
</tr>
<tr>
<td>4</td>
<td>C</td>
<td>02/05</td>
<td>04/23&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>5</td>
<td>C</td>
<td>02/14</td>
<td>04/24</td>
</tr>
<tr>
<td>6</td>
<td>C</td>
<td>02/01</td>
<td>04/11</td>
</tr>
<tr>
<td>7</td>
<td>C</td>
<td>01/28</td>
<td>04/17&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>8</td>
<td>C</td>
<td>02/13</td>
<td>05/18&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
<td>9</td>
<td>C</td>
<td>05/19</td>
<td>07/28</td>
</tr>
<tr>
<td>10</td>
<td>C</td>
<td>05/12</td>
<td>07/21</td>
</tr>
<tr>
<td>11</td>
<td>T</td>
<td>02/01</td>
<td>04/11&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>12</td>
<td>T</td>
<td>02/17</td>
<td>04/27</td>
</tr>
<tr>
<td>13</td>
<td>T</td>
<td>02/05</td>
<td>04/15</td>
</tr>
<tr>
<td>14</td>
<td>T</td>
<td>01/26</td>
<td>04/05</td>
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<tr>
<td>15</td>
<td>T</td>
<td>02/05</td>
<td>04/17&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>16</td>
<td>T</td>
<td>02/03</td>
<td>04/13</td>
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<td>17</td>
<td>T</td>
<td>06/03</td>
<td>08/15</td>
</tr>
<tr>
<td>18</td>
<td>T</td>
<td>06/23</td>
<td>09/05</td>
</tr>
<tr>
<td>19</td>
<td>T</td>
<td>03/10</td>
<td>05/18</td>
</tr>
</tbody>
</table>

<sup>a</sup>Day 0 was delayed because there was a delay in obtaining the physicians' approvals.

<sup>b</sup>Subject completed time 1 and went to Hawaii. She started the control diet when she returned from Hawaii.

<sup>c</sup>Subject did not complete an assessment on 02/12, 03/28 and 03/30.

<sup>d</sup>Subject withdrew from the study on Day 42.

**Note:** Only data up to Day 42 were used in the statistical analysis.
APPENDIX L: DIETARY NONCOMPLIANCE AND CONFOUNDING VARIABLE CHANGES

Subject #1 (Control Group)
1. Subject reported a cold with fever on Days 32 through 38.
2. Subject took one reactine® (antihistamine) on Day 32 and 33 for sneezing and rhinorrhea.
3. Subject took tylenol® (650mg) on Days 34 through 37 and tylenol® (325mg) on Day 38.
4. Subject took robitussin® AC (cough syrup) (40ml) Days 37 through 41.
5. Subject took ceclor® (antibiotic) (750 mg) on Days 38 through 43. The cold or the medication appeared to slightly exacerbate the urticaria symptoms during this period.

Subject #2 (Control Group)
1. Subject drank a diet coke® on Days 3, 9, 10 and 29.

Subject #3 (Control Group)
1. Subject took tylenol® (1000mg) on Days -3, 0 and 1. The change did not appear to affect the urticaria symptoms.
2. Subject reported congested sinus symptoms throughout the study.
3. Subject used habitol® (nicotine patch) on Days 2 through 19. The change did not appear to affect the urticaria symptoms.
4. Subject changed to Cheers® colorguard laundry detergent on Day 30. The change did not appear to affect the urticaria symptoms.

Subject #4 (Control Group)
1. Subject reported seasonal rhinitis on Days 38 through to the end of the study. Subject took a chlor-tripolon® (subject's usual antihistamine medication) (8 mg) every other day throughout this period.

Subject #5 (Control Group)
1. Subject reported sinus congestion periodically throughout the study.
2. Subject took benylin®-D-E Extra, Vitamin C (500 mg) and H2 blocker (histamine receptor 2) on Day -7. The change did not appear to affect the urticaria or angioedema symptoms.
3. Subject ate artificial sweetener on Day 1.

Subject #6 (Control Group)
1. Subject indicated an intention to withdraw from the study on Day 31 because of the amount of time attending appointments and because her doctor thought the urticaria was a side effect of dyazide® medication. The subject lived one hour from Vancouver Hospital. On Day 35, the subject indicated a desire to remain in
the study because discontinuation of dyazide® did not improve the symptoms. The subject had been compliant with the control diet and had been recording symptoms continuously.

Subject #7 (Control Group)
1. Subject took aspirin® (650 mg) on Day 10. The change did not appear to affect the urticaria or angioedema symptoms.

Subject #8 (Control Group)
1. Subject changed deodorant on Day -11. The change did not appear to affect the urticaria symptoms.

Subject #9 (Control Group)
1. Subject used reactine® alone everyday until Day 14. Subject used reactine® and benadryl® on Day 15, and benadryl® alone on Day 16. Subject used reactine® alone from Days 17 through 22, and benadryl® alone Days 23 and 24. Day 25 reactine® was used. Subject used atarax® alone Days 26 through 30. Reactine® alone was used Days 31 and 32, and atarax® and reactine® on Day 33. Reactine® alone was used everyday until the end of the study. The subject's symptoms were not controlled by medication, and the antihistamine medications did not have a significant impact on symptoms. Therefore, changes in medication do not reflect changes in disease severity.
2. Subject took 0, 1 or 2 tablets of prednisone® (5mg) consistently throughout the study.
3. Subject took a calcium supplement on Day 1 and throughout the remainder of the study.
4. Subject took Vitamin C (500mg) on Day 18.

Subject #10 (Control Group)
1. Subject doubled premarin® (hormone replacement therapy) the day before Day -14 and maintained the doubled dose throughout the study period. Premarin® often exacerbates urticaria (personal correspondence Janice Joneja, Ph.D.). However, the increased premarin® did not appear to exacerbate the subject's symptoms.

Subject #11 (Treatment Group)
1. Subject discontinued Vitamins C, E and B complex and lethicin supplements before Day-14.
2. Subject used sarna® HC 1% (topical corticosteroid) to control urticaria symptoms on Days -14 to 0. He discontinued the cream on Day 1.
3. Subject drank one can of pepsi® on Day 11.

Subject #12 (Treatment Group)
1. Subject used an new soap starting Day -9. The change did not appear to affect the urticaria or angioedema symptoms.
2. Subject reported flu symptoms on Days 11 through 15. The change did not appear to affect the urticaria or angioedema symptoms.
3. Subject ate one piece of leftover meat on Day 21.
Subject #14 (Treatment Group)
1. Subject took tylenol® (325 mg) on Days -14, -13, -12, -10, -8, -3, 1, 7, 9, 10, 11, 12, 14, 18, 36, 37, 38, 39 and 41. Eleven tablets were taken in time 1. Thirteen tablets were taken in time 2. Two tablets were taken in time 3. Five tablets were taken in time 4. The change did not appear to affect the urticaria or angioedema symptoms.
2. Subject reported a yeast infection on Days 2, 3 and 4. The change did not appear to affect the urticaria or angioedema symptoms.
3. Subject used diflucan® (antifungal agent) (150 mg) on Day 4. The change did not appear to affect the urticaria or angioedema symptoms.

Subject #15 (Treatment Group)
1. Subject reported cold symptoms Days 19 through 34.
2. Subject took novalhistine® DM (antitussive, decongestant) (45 ml) Days 21 and 22.
4. Subject took Halls® cough lozenges (3 lozenges) Day 23.
5. Subject took Tylenol® cold (1300 mg) Days 24 and 25, Tylenol® cold (975 mg) Days 26 and 27, Tylenol® cold (650 mg) Day 28 and Tylenol® cold (325 mg) Day 29.
6. Subject took Tylenol® (325 mg) Days 31 and 32. Neither the cold nor the medication appeared to affect the urticaria or angioedema symptoms.
7. Subject took Vitamin E (600 IU) Days 1, 2 and 3.
8. Subject drank tea on Day 1 and 39, ate small amount of chocolate brownie on Day 3, 1 glass of red wine on Day 5, ¼ cup chopped tomato on Day 6, 1 slice of pizza on Day 9, wine, tomato, tea, spinach and cheese on Day 16, small amount of yoghurt on Day 31 and Sprite® on Day 36.
9. Subject withdrew from the study on Day 42 because of difficulty following diet.

Subject #17
1. Subject ate 1 tablespoon of Parmesan cheese on Day 7.
2. Subject ate marshmallows on Days 9 and 10.

Subject #18
1. Subject drank one can of gingerale® on Day 26.
2. Subject ate one serving of cheese on Days 39 and 40.
### APPENDIX M: WEIGHT CHANGE OVER THE STUDY PERIOD³

<table>
<thead>
<tr>
<th>Subject</th>
<th>Group</th>
<th>Initial Weight (Day -14) (kg)</th>
<th>Final Weight (Day 56) (kg)</th>
<th>Percent Weight change</th>
<th>Initial Body Mass Index (Day -14)</th>
</tr>
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<tbody>
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<td>75</td>
<td>72⁵</td>
<td>-4%</td>
<td>24</td>
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<tr>
<td>2</td>
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<td>66</td>
<td>66</td>
<td>0%</td>
<td>23</td>
</tr>
<tr>
<td>3</td>
<td>C</td>
<td>71</td>
<td>77⁴</td>
<td>8%</td>
<td>25</td>
</tr>
<tr>
<td>4</td>
<td>C</td>
<td>64</td>
<td>64</td>
<td>0%</td>
<td>25</td>
</tr>
<tr>
<td>5</td>
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<td>95</td>
<td>2%</td>
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<tr>
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<td>C</td>
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<tr>
<td>7</td>
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<td>68</td>
<td>68</td>
<td>0%</td>
<td>24</td>
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<tr>
<td>8</td>
<td>C</td>
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<td>58</td>
<td>0%</td>
<td>21</td>
</tr>
<tr>
<td>9</td>
<td>C</td>
<td>63</td>
<td>64</td>
<td>2%</td>
<td>26</td>
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<td>10</td>
<td>C</td>
<td>98</td>
<td>102⁴</td>
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<td>34</td>
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<tr>
<td>11</td>
<td>T</td>
<td>87</td>
<td>85</td>
<td>-2%</td>
<td>29</td>
</tr>
<tr>
<td>12</td>
<td>T</td>
<td>91</td>
<td>88</td>
<td>-3%</td>
<td>36</td>
</tr>
<tr>
<td>13</td>
<td>T</td>
<td>55</td>
<td>54</td>
<td>-2%</td>
<td>21</td>
</tr>
<tr>
<td>14</td>
<td>T</td>
<td>75</td>
<td>75</td>
<td>0%</td>
<td>26</td>
</tr>
<tr>
<td>15</td>
<td>T</td>
<td>62</td>
<td>62</td>
<td>0%</td>
<td>24</td>
</tr>
<tr>
<td>16</td>
<td>T</td>
<td>130</td>
<td>130</td>
<td>0%</td>
<td>35</td>
</tr>
<tr>
<td>17</td>
<td>T</td>
<td>75</td>
<td>73</td>
<td>-3%</td>
<td>29</td>
</tr>
<tr>
<td>18</td>
<td>T</td>
<td>82</td>
<td>79</td>
<td>-4%</td>
<td>30</td>
</tr>
<tr>
<td>19</td>
<td>T</td>
<td>55</td>
<td>55</td>
<td>0%</td>
<td>21</td>
</tr>
</tbody>
</table>

* Based on self reported weight and height

b Subject was ill and lost weight.

c Subject stopped smoking one month before starting the study. The subject believes this may have contributed to the weight gain.

d Subject increased premarin® before Day -14. The subject believes this may have contributed to the weight gain.