

# Aspects of MSG Intolerance

A thesis presented for the degree of Honours  
by  
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## **DECLARATION**

I hereby declare that this submission is my own work and that, to the best of my knowledge and belief, it contains no material previously published or written by another person nor material which to a substantial extent has been accepted for the award of any other degree or diploma of the University or other institute of higher learning, except where due acknowledgement is made in the text.

Carmen María Pavía

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## **ABSTRACT**

MSG is the sodium salt of glutamic acid, the most common amino acid in nature. Glutamate, the active part of MSG, is naturally present in many foods, including tomatoes, mushrooms and Parmesan cheese. Manufactured monosodium glutamate is added to foods as a flavour enhancer (No. 621). The term “Chinese restaurant syndrome” (CRS) was first introduced in 1968. Numerous studies have been carried out to ascertain the validity of the existing evidence supporting this syndrome. These studies have not developed a conclusive position on CRS.

The present study explored some issues surrounding MSG intolerance by carrying out a database analysis, two clinical studies and a questionnaire. It was found that in the population assessed (at RPAH), MSG intolerance is a common disorder which is normally associated to other food intolerances. Isolated MSG intolerance was rare in this population. The prevalence of documented MSG intolerance in the community remains to be studied.

The method for food intolerance analysis in use at RPAH was found to give reproducible results. The importance of having a defined baseline diet is still to be confirmed.

From the MSG questionnaire it was concluded that the population knowledge about the nature of MSG was incomplete and in many instances incorrect. Furthermore people who self-report MSG intolerance often do not have a clear grasp of what MSG is and in which food products it is present.

## CHAPTER 1. INTRODUCTION

For most people the consumption of foods is a pleasant experience that, besides giving them certain emotional satisfaction, ensures their normal growth and development. However, for people with food allergies and intolerances this is not the case. For these people, the consumption of certain foods can be the cause of discomfort, illness and even death. True food allergies are mediated by the immune system. Food intolerances, on the other hand, are mediated by some metabolic or unknown disorder. Examples of food intolerance are sulphite, tartrazine and monosodium glutamate (MSG) sensitivities.

MSG consumption has been traditionally linked to the term “Chinese restaurant syndrome” (now called “MSG symptom complex”). Although MSG sensitivity is widely believed to be common in the community, this belief is not based on solid scientific evidence (Taylor & Hefle, 2000). Its prevalence is uncertain and food industry advocates (Tarasoff & Kelly, 1993) have questioned its very existence. Clinical experience at Royal Prince Alfred Hospital Allergy Unit (RPAHAU) indicates that MSG sensitivity is present among certain sensitive subjects who, almost always, also present clinical symptoms upon consumption of other food substances, such as amines, salicylates and preservatives (Loblay *et al*, 1991). MSG sensitivity is rarely an isolated event.

The most common clinical symptoms associated with the syndrome are recurrent urticaria/angioedema, migraine and irritable bowel syndrome. The spectrum or range of symptoms remains undocumented due to their diversity.

The assessment of food intolerances is carried out by food challenges. The “gold standard” for this is the double blind placebo controlled food challenge (DBPCFC).

Over the past twenty years, several thousand patients treated at the RPAHAU have undergone double-blind placebo controlled food challenges with MSG and other food substances. The investigation protocol involved a preliminary period (2-6 weeks) on a defined elimination diet. Upon improvement, patients were given a battery of blind challenges, which were expected to elicit symptoms if a sensitivity was present. Specific food intolerances were then identified and dietary modifications were introduced based on the individual's circumstances.

The diagnostic validity of this test has not been rigorously evaluated. Accordingly, there are no international standards, and the reproducibility of results remains low across studies. Reasons for disagreement include different challenge methodology, patient/subject selection, and diverse baseline diet. These and other reasons surround the controversial position of MSG among consumers, clinicians and the food industry. It is therefore essential that aspects regarding methodology and protocol be standardised.

In order to clear up some of the aspects surrounding the MSG debate, this study will aim to:

- Document the association between MSG and other food chemicals in patients previously assessed at RPAHAU. A database analysis will be carried out with the intention of documenting any association between MSG and other substances.
- Assess the reproducibility of MSG challenge reactions in food intolerant patients. This will be done by re-examining patients previously challenged (>1 year) at the RPAHAU. Patients will be selected upon certain exclusion criteria (such as asthma, laryngeal/tongue oedema or anaphylactoid reactions).

- Assess the influence of the defined elimination diet on MSG challenge reactivity. A small group of new patients presenting to RPAHAU will undergo two sets of challenges, one before (on their usual diet) and one after being on the standard defined elimination diet. This study will be designed and arranged by the author for future research projects. No results will be compiled from this study.
- Obtain community data on the knowledge of MSG as an additive as well as a natural component of foods; and on the perceived prevalence and symptomatology of MSG intolerance. A brief (5-10 min) anonymous questionnaire about MSG (self-administered) will be offered to: (a) patients presenting to the Allergy Clinic, (b) adult volunteers in suburban shopping centres, (c) adult volunteers undergoing clinical study and (d) adult volunteers at The University of New South Wales. Results from the four communities will be compared.

## CHAPTER 2 REVIEW OF EXISTING LITERATURE

### 2.1 INTRODUCTION

*Ut quod ali cibus est aliis fuit acre venenum*: “What is food to one is bitter poison to another” (Lucretius, II BC). Adverse food reactions are abnormal bodily responses caused by the consumption of food. Peanut allergy, lactose intolerance, seafood aversion and coeliac disease are all different kinds of adverse food reactions.

By convention, clinicians have classified adverse food reactions into two major groups: immunological food reactions and non-immunological food reactions (Figure 2.1). Immunological food reactions are also called inflammatory because, to a certain extent, they cause permanent effects on the body. True food allergies, enteropathies, and coeliac disease are all believed to be immune reactions to food.

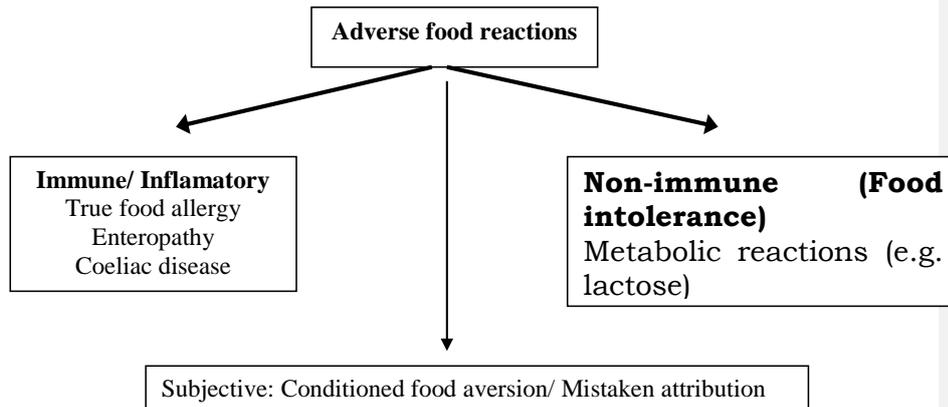


Figure 2.1 Classification of adverse food reactions  
(Partly adapted from Taylor & Hefle, 2001; Gut Foundation, 2000)

Non-immune reactions are varied in nature. They include metabolic disorders, such as phenylketonuria, lactase deficiency and food intolerances.

The latter includes a variety of symptoms and food substances and their physiological mechanism is unclear.

Conditioned food aversions are psychological reactions to foods. “Mistaken attribution” refers to situations where unrelated symptoms are mistakenly attributed to foods; or where the symptoms are food-related but the wrong food/ingredient is incriminated.

The general population refers to all adverse food reactions loosely as “food allergies”. However, this term should be reserved for true (Immunoglobulin E (IgE) mediated) food allergies, which are uncommon in adults (<1%) (Altman & Chiramonte, 1996; Ortolani *et al*, 2000). The distinction is important, as true food allergies can cause potentially fatal anaphylactic reactions. Food intolerance, on the other hand, is believed to be far more common (Young, 1997), although its exact prevalence is uncertain. MSG intolerance is a type of food intolerance which remains nowadays a source of scientific controversy.

## **2.2 FOOD INTOLERANCE**

### ***2.2.1 General Remarks***

Food intolerances are not food allergies. Contrary to public perception, food intolerances do not involve the immune system nor are they caused by proteins in foods.

### ***2.2.2 Food Intolerance***

#### ***2.2.2.1 Definition***

Food intolerances can be defined as idiosyncratic adverse food reactions mediated by non-immunological mechanisms.

They can be triggered by a range of food constituents including additives (such as sulphites) and certain natural food substances (such as glutamates). Food intolerance reactions are usually dose-related. Although the symptoms caused by food intolerance are rarely fatal, they can be very limiting and are often unforeseeable.

#### 2.2.2.2 Symptoms

Food intolerances have been reported to cause a wide range of symptoms, including:

- Cutaneous manifestations: urticaria and angioedema.
- Gastrointestinal symptoms: Nausea, vomiting, diarrhoea, abdominal pain, cramping and irritable bowel syndrome.
- Respiratory symptoms: rhinitis, asthma, and laryngeal edema.
- Neurological symptoms: headaches, migraine, fatigue and leg cramps (Bolin *et al*, 2000).

The type, intensity and frequency of symptoms varies from person to person, and one individual may suffer from multiple symptoms. For example, a person suffering from MSG intolerance might have both gastrointestinal and respiratory symptoms upon the consumption of MSG.

When carrying out DBPCFC on subjects suffering from these symptoms, an objective system of scoring is hard to establish as the subjective nature of the symptoms impedes their quantification.

### 2.2.2.3 Diagnosis

The causes, treatment and methods of diagnosis of food intolerances are under active investigation. There are no generally accepted *in vitro* tests available for the diagnosis of food intolerance. At present, therefore, diagnosis depends on an empirical process involving:

- (1) **Exclusion** of suspected foods or food ingredients, to determine whether symptoms diminish significantly or resolve completely as a result.
- (2) **Challenge** with suspected foods or food substances to determine which, if any, can provoke symptoms in those individuals who respond to dietary exclusion. Challenges can be conducted openly by ingestion of suspected foods, or in a blinded fashion using disguised or encapsulated dried foods, food substances or food additives. The generally accepted “gold standard” method is double-blind, placebo-controlled food challenge (DBPCFC) (Bock *et al*, 1988). However, there are many variables within DBPCFC which are not yet standardised. For example, the amount and type of substances used for testing are still different from study to study.

In a clinical setting, patients usually present after experiencing adverse reactions to food, or with a suspicion that chronic or recurrent symptoms are caused by certain foods. The steps followed for the diagnosis of food intolerance involve:

- Step 1. A medical evaluation (clinical history and examination) is carried out to ensure that symptoms are not due to some other identifiable cause or disease process. It has been found that a minority of the population has adverse food reactions as a consequence of psychological beliefs, such as food aversion.

This has been observed in subjects with unusual clinical manifestations and excessive complaints about multiple allergies (Patterson *et al*, 1997).

- Step 2. *In vitro* investigations, if necessary. Skin prick tests (or RAST) are the standard means of detecting allergen-specific IgE in patients where true food allergy is suspected. In the case of food intolerance no detectable immune response is expected. Although the mechanism behind food intolerances is unknown it has been suggested that they occur only in people with underlying atopic diseases (Altman & Chiamonte, 1996).
- Step 3. Subjects are placed on an elimination diet. The nature and duration of this diet varies from clinic to clinic and study to study. Most studies exclude allergens from the diet, as well as preservatives and other additives. Some very rigorous studies place their subjects on liquid nutritional formulas. At the RPAHAU, a standardized elimination diet is used, excluding natural salicylates, amines and glutamate, as well as additives such as preservatives, colourings, antioxidants and MSG. Depending on their response and symptom resolution, patients are encouraged to stay on the diet for 2-6 weeks. If, during this time, the symptoms resolve, it is presumed that they may be diet-related, and challenges are commenced. If symptoms do not subside after six weeks, patients are encouraged to return to their normal diet.
- Step 4. Challenges are conducted with a standard range of foods and food substances. Appropriate precautions are taken in high-risk patients (e.g. those with a history of laryngeal oedema, anaphylactoid reactions or moderate/severe asthma).

The most objective way of conducting challenges are carried out “double blind” with neither the therapist nor the subject being aware of the identity or sequence of the challenges. This aspect attenuates the psychological factors implicated in food intolerance (Young, 1997). Currently at the RPAH, the substances included in the standard challenge set are aspirin, sodium benzoate, sorbic acid, sodium metabisulphite, tartrazine colour, brilliant blue colour, monosodium glutamate, tyramine, phenylethylamine and lactose, with sucrose and starch as placebos. (In patients without gastrointestinal symptoms, lactose is considered a placebo). These substances were initially chosen either because they had already been reported to provoke adverse reactions in susceptible patients, or from clinical observation. Similarly, doses chosen were standardized according to published literature or clinical experience. Optimizing their diagnostic utility requires balancing their sensitivity (higher dose) against the need to minimise distress or risk from a severe reaction (lower dose). The doses employed for diagnostic purposes do not necessarily reflect the amounts eaten in a single meal or the population average daily consumption. From a regulatory point of view, this dosage system fails to take into consideration the actual food content levels and the intake of the general population. This last point is significant in terms of regulation and validation of procedures in the general population.

#### *2.2.2.4 Prevalence*

The prevalence of food intolerance is not known. Attempts have been made to estimate prevalence using questionnaires, followed by challenges in selected respondents, but these studies have major design flaws.

In particular, the questionnaires have not been validated, subject selection criteria for challenge studies have generally been too narrowly defined, and no challenge study has been carried out using an adequately defined baseline elimination diet.

Bearing these limitations in mind, a community survey in the U.K. found that 7.4% of the population believes itself to be food intolerant. However, using a DBPCFC protocol, Young (1997) reported that the real prevalence does not exceed 2%. In the U.S., more than 29% of households were found to have modified their eating habits because of “food allergies” (Yeung *et al*, 2000). In a recent study (Woods *et al*, 2001), the prevalence of reported food allergies and intolerances was examined worldwide using a questionnaire, and blood, lung function and skin prick tests. Of the 15 countries studied, Australia had the highest proportion of reported food allergies and intolerances (19.1%), Spain had the lowest (4.6%), and there was an overall average of twelve percent. Although this study did not differentiate between food allergies and food intolerances, it provided an interesting insight into Australian perceptions about food sensitivities. The reasons for these differences were not explored in the study. There has been some speculation that food intolerances may be increasing, but there are no published prospective studies which can confirm this. Most of this perception is anecdotal, though there are clinical reports which seem to confirm this position.

### **2.3 SUBSTANCES CAUSING FOOD INTOLERANCE**

Food is composed of many elements, many of which are necessary for life and growth. Some of these components are capable of generating intolerance and/or allergic reactions.

All food components can be reduced to certain chemical elements; such as nitrogen, carbon, oxygen, sulphur, sodium, potassium and others. It is rather the molecular structure of these elements which triggers a reaction within the body.

Besides the natural components of foods, there are a number of substances which are “intentionally added to a food to achieve one or more of the technological functions”. These are food additives, “not normally consumed as a food in itself and not normally used as an ingredient of food” (ANZFA, 2001).

In the last twenty years, food additives have been suggested as the culpable agents of adverse food reactions, despite the fact that there are a number of natural food chemicals which can elicit the same reactions and are often overlooked. Food additives are usually denounced because they are perceived as unnatural and unhealthy.

The substances capable of generating food intolerant reactions are varied in nature and include both food additives, such as MSG, propionic acid, tartrazine and sulphites, and natural substances, such as glutamate and salicylates.

A remarkable aspect surrounding food intolerances is the fact that substances like MSG and tartrazine, which are chemically and biochemically totally unrelated (Table 2.2) are nevertheless capable of inducing the same symptoms in sensitive individuals.

This phenomenon is one of the enigmas of modern medicine and is still undergoing further research (Allen *et al*, 1984; Bock & Atkins, 1990; Loblay *et al*, 1991; Mygind *et al*, 1996, Taylor & Hefle, 2000).

Of the hundreds of substances which have been suggested as elicitors of food intolerance this review will only mention the ones which are of direct relevance to the research carried out.

They include: salicylic acid, benzoic acid, sodium benzoate, sorbic acid, sodium metabisulphite, tartrazine colour, brilliant blue colour, tyramine, phenylethylamine and monosodium glutamate (MSG).

Salicylates are a group of chemicals found naturally in plants. They are not food additives, although they were used at one time as preservatives until the high incidence of associated adverse reactions was recognised. Salicylates are found naturally in many foods: fruits, vegetables, nuts, herbs and spices, jams, honey, yeast extracts, tea and coffee, juices, beer and wine (Swain, Dutton & Truswell, 1986). Salicylates, together with alcohol, are the only substances absorbed directly from the stomach during the digestion process. All other substances are absorbed in the intestine (Sherwood, 1997).

Benzoic acid and sodium benzoate are preservatives added to most processed foods. Their mode of action is based on “various interventions in the enzymatic structure of the microbial cell” (Lueck, 1980). Both compounds are well absorbed from the intestine and are excreted in the urine through a well-known mechanism. Intolerance reactions to these substances have been described in association with other additives.

Sodium metabisulphite has been regarded as a GRAS substance since 1959. However, levels of application are permitted in wines, if limited to 0.035%. At higher concentrations, sulphites affect the flavour of foods. Sulphites inactivate the activity of thiamin (vitamin B1). Idiosyncratic reactions can occur with low doses in sensitive asthmatic patients. Australia and New Zealand have the highest levels of sulphite consumption (JEFCA, 1995).

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Tartrazine and brilliant blue are both food colourings which have been accepted for use by the American FDA since 1939 (although brilliant blue was temporarily excluded in 1959). In humans, clinical symptoms such as asthma, hyperactivity and urticaria (hives) have been attributed to tartrazine (Vries, 1996) and as little as 0.15 mg has been shown to elicit asthma in sensitive patients. Tartrazine has also been linked to aspirin-sensitive asthma. Brilliant blue, usually used in beverages, confectionery and ice creams, has also been associated with food intolerance reactions. Normally, only about 5% of this dye is absorbed through the gastrointestinal tract, the remainder 95% being excreted in the faeces. There appears to be cross-reactivity between food colourings (Loblay & Swain, 1985); however, further studies need to be carried out in this area.

Tyramine and phenylethylamine are biogenic amines which have been reported to cause adverse reactions, especially in the pharmacological field.

MSG, a flavour enhancer, is the last substance included in this list and will be dealt with in detail in section 2.4.

Table 2.1. General features of substances causing food intolerance reactions

Name	Classification	Formula	MW	Properties	ADI (mg/Kg)	Toxicology (LD50 mg/Kg)
Salicylic Acid	Aromatic acid	$\text{HOC}_6\text{H}_4\text{COOH}$	138.12	Crystal powd. Sol. in water, alcohol & ether. Acrid taste	N/A	LD50 (oral, rat)- 891
Benzoic Acid	Aromatic acid	$\text{C}_6\text{H}_5\text{COOH}$	122.13	White powd. Benzoin odour. Slightly sol. in water.	0-5	LD50 (oral, rat)- 2530
Sodium Benzoate	Sodium salt of benzoic acid	$\text{C}_6\text{H}_5\text{COONa}$	144.11	Crystal powd. Odourless. Sol. in water & alcohol	0-5	LD50 (oral, rat)- 4070
Sorbic Acid	Propenylacrylic acid	$\text{C}_6\text{H}_8\text{O}_2$	112.14	Colourless needles or white powd. Sol. in hot water.	0-25	LD50 (oral, rat)- 7360
Sodium Metabisulphite	Inorganic salt	$\text{Na}_2\text{S}_2\text{O}_5$	190.10	Colourless crystal. Sulphurous odour. Sol. in water	0-0.7	LD50 (intravenous, rat) 115 mg/Kg
Tartrazine (FD&C No 5)	Pyrazole colour	$\text{C}_{16}\text{H}_9\text{N}_4\text{O}_9\text{S}_2\text{Na}_3$	534.36	Lemon yellow powder. Sol. in water	0-7.5	LD50 (oral, mouse)- 12.75
Brilliant Blue (FD&C No1)	Triphenylmethane colour	$\text{C}_{37}\text{H}_{36}\text{N}_2\text{O}_9 \cdot 2\text{Na}$	794.91	Greenish-blue powd. Sol. in ether	0-12.5	Experimental (tumour inducing)
Tyramine	Biogenic amine	$\text{C}_8\text{H}_{11}\text{NO} \cdot \text{C}_1\text{H}$	150	4-(2-Aminoethyl)phenol hydrochloride	N/A	N/A
Phenylethyl-amine	Biogenic amine	$\text{C}_{16}\text{H}_{19}\text{N}$	225	(-)-Bis[(S)-1-phenylethyl]amine	N/A	N/A
Monosodium Glutamate	Sodium salt of L-glutamic acid	$\text{HOOCCH}_2\text{CH}_2\text{C}(\text{NH}_2)\text{COONa}$	170.14	White powd. Meal-like taste. V.sol. in water	0-120 (FAO/WHO)	LD50 (oral, rat) 17000

ADI- Acceptable daily intake (established by the American Food and Drug Administration)

LD50 (Lethal Dose50) is the amount of a substance that, when administered by a defined route of entry (e.g. oral or dermal) over a specified period of time, is expected to cause the death of 50 per cent of a defined animal population (<http://siri.uvm.edu/ftp/ppt/whmis2/tsld031.htm>)

## 2.4 MSG INTOLERANCE

### 2.4.1 What is MSG?

Monosodium glutamate is the sodium salt of glutamic acid, an amino acid abundant in nature and present in most protein-containing foods. The term MSG technically only describes the sodium salt of glutamic acid which is manufactured and added to foods. However, most consumers designate as MSG any form of glutamic acid in the natural or manufactured state. Manufactured MSG is added to most processed foods for its flavour-enhancing properties. In nature MSG is present in the D-amino acid chemical configuration (Figure 2.2). Manufactured MSG can also contain minimum amounts of the L-form.

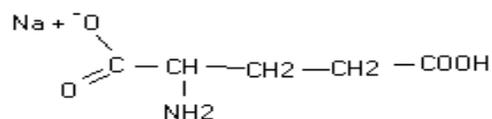


Figure 2.2. Chemical structure of MSG

Contaminants such as pyroglutamic acid, heterocyclic amines, peptides and dichloro propanols can also be present.

#### **2.4.2 History**

Glutamic acid was first isolated in 1866 by a German chemist. Forty years later, a Japanese chemist at the University of Tokyo, Dr Kikunae Ikeda, discovered the flavour enhancing properties of MSG, by researching the flavour-enhancing properties of the traditionally used seaweed *Laminaria Japonica*. After isolating MSG, Dr Ikeda developed a process for its extraction from flour and in 1909 the commercial production of MSG began. Commercial production of MSG in the United States did not begin until the 1940's. In 1995, the annual production of MSG worldwide was 400,000 tons, and by 1997 this amount had increased to more than 650 thousand tons (Yamaguchi & Ninomiya, 1998).

#### **2.4.3 MSG in food**

Glutamate is the most abundant amino acid present in nature (Young & Ajami, 2000). It is part of the intermediary metabolism of most living organisms and is found in large amounts in tissues and organs (Ninomiya, 1998). It has been estimated that a 70Kg man has a daily intake of ~28 g of glutamic acid, both derived from his diet and from the breakdown of gut proteins (Garattini, 2000).

Glutamate is present in nature both in its free form and bound to peptides and proteins. The free form is responsible for the flavour enhancing properties of MSG, while the bound form does not have any effect on taste (Ninomiya, 1998).

Free glutamic acid is present in most foods (Table 2.2 & Figure 2.3), although not all foods contain detectable levels of MSG.

Table 2.2 Bound and free glutamate levels in foods

Food	Bound glutamate (g/100g)	Free glutamate (g/100g)
Parmesan cheese	9.847	1200
Camembert cheese	4.787	390
Chicken meat	3.700	44
Tomatoes	0.260	246
Sweet corn	0.500	100

(Source: Sugita, 1990)

Generally, foods rich in protein have high levels of bound glutamate, while some vegetables can have large amounts of free glutamate. The glutamate content of foods has been said to affect the selection and acceptance of food worldwide. A recent study (Yoshida, 1998) suggested that most types of traditional seasonings around the world had a high content of glutamate (for example, Vegemite in Australia). This, they suggested, responded to the consumers' need for the umami taste.

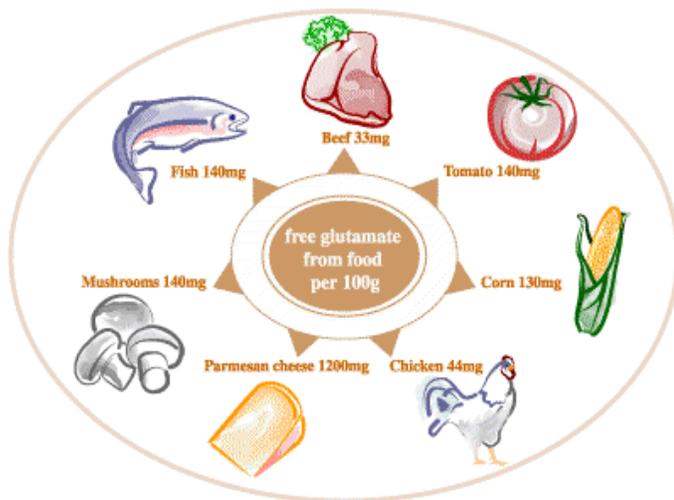


Figure 2.3 Free glutamate content per 100g /food (<http://www.glutamate.org/media/ginfoods.htm>)

Umami is “the characteristic taste imparted by monosodium L-glutamate” (Yamaguchi & Ninomiya, 1998). Although the MSG molecule contains both sodium and glutamate, the flavour imparting properties have only been attributed to the amino acid component of the molecule; thus the “the MSG taste cannot be attributed to the sodium moiety of MSG” (Garattini, 2000).

Umami is not palatable in itself; nevertheless, it makes a variety of foods delectable (Yamaguchi, 1998). In fact, the addition of MSG to foods for the elderly has been suggested as a means to provide sensory enhancement and assistance for adequate dietary intake and nutritional status (Schiffman, 1998).

MSG has been used as a flavour enhancer for more than forty years, and although it is added to many types of foods, in the western world it is normally associated with salty foods. In fact, MSG has been known to enhance both the sweet and salty flavour, as well as diminishing that of sourness and bitterness (Garattini, 2000).

The use of MSG in foods has been favoured by the increasing popularity of fast and manufactured foods. MSG is added to foods with the purpose of increasing the intensity of their flavour. However, its action is dependent upon the type and quantity of the food matrix. A list of foods and the suggested levels of MSG has been published by the Glutamate Manufactures Technical Committee to provide an indication of the uses of MSG (Yamaguchi, 1998). MSG is usually added within the range of 0.1% and 0.8 %.

Some applications include: meat and fish (by potentiating their protein flavour), vegetables (increasing freshness and intensity of flavour) and cereals, where undesirable flavours such as sourness, graininess and starchiness are masked by MSG.

MSG has been associated with certain adverse health effects in specific populations. Although the actual prevalence of MSG intolerance is not known, it has been suggested to be as high as 40% in the general population, although this value was given without accompanying documentation (Vegetarian Times, May 1996). In any case, the relationship between the flavour imparted by MSG and adverse health reactions has never been considered. Such a study could cast light on the subjective aspects of MSG intolerance.

**Comment [RHL2]:** MOVE DOWN TO 2.4.7 ????????

Since manufactured MSG entered the market more than fifty years ago, the levels of consumption have increased considerably. These levels vary from country to country (Table 2.5). This is expected, as both MSG and the umami taste were first discovered in Asian countries and therefore are more linked to the cultures of these countries. This explains the fact that Taiwan consumes almost ten times more MSG than the United States.

Table 2.3 MSG per capita consumption\*

Country	MSG consumed (g/d)
Taiwan	3.0
Korea	2.3
Japan	1.6
Italy	0.4
United States	0.35

\* Adapted from Giacometti, 1979

Levels of consumption in Australia have not been estimated. However, they would be expected to be quite high, due to the multicultural aspect of Australian society. The International Glutamate Information Service (2001) estimates that the average added intake of glutamate from MSG amounts to just 0.5 - 1.5 grams per day.

This amounts to very little when compared to the amounts of natural glutamate consumed from the normal diet.

#### ***2.4.4 Stability and chemical properties***

MSG is sold as a white crystalline material, readily soluble in water. The product is quite stable at room temperature. During processing, MSG remains stable, however, as any other amino acid with nitrogen content, MSG can undergo Maillard reaction.

The ionic form of MSG is dependent upon pH, its action being most effective at pH range of 5.5 to 8.0. The only degradation product of MSG identified to date is pyroglutamic acid, which is extremely stable at pH 2.5 to 11.0.

In summary, MSG seems to be a very stable compound. It should be noted that stability studies were done using water, so the reactivity of MSG in other food systems remains unknown. There has been no study investigating the stability of MSG in relation to MSG intolerance (it has been done in toxicological studies) and food systems. This study could shed some light on the complex issue of MSG reactivity.

#### ***2.4.5 Metabolism of MSG***

The mechanism of absorption and metabolism of both free and bound glutamate is well understood. The outline of processes has been collated in Figure 2.4. Glutamate plays an important role in nutrition and energy metabolism.

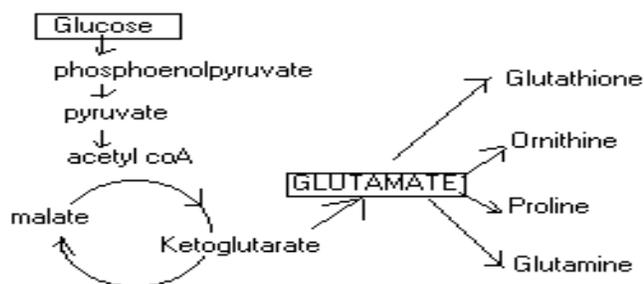


Figure 2. 4 Glutamate metabolic pathways

Glutamate metabolism involves oxidative deamination, transamination, decarboxylation and amination. In a recent review (Young & Ajami, 2000), the metabolism of MSG was concluded to be “highly compartmented”. This allows the molecule to participate in “a number of distinct and possibly competitive roles, including that of a nutrient, energy-yielding substrate, structural determinant, enzyme regulator and excitatory molecule” (Table 2.4). Such biochemical versatility does not facilitate the study of MSG as a possible cause of adverse food reactions.

Table 2.4 Functions of glutamate

Functions of glutamate
Substrate for protein synthesis
Precursor of glutamine
Neurotransmitter
Polyglutamate and cell signalling
Active sites of enzymes
Energy Source for some tissues

(Adapted from Young & Ajami, 2000)

Although the metabolism of glutamate is beyond the scope of this study, there are certain aspects which are relevant in terms of their possible role in the safety of MSG.

These include MSG as a neurotransmitter and MSG as the possible cause of intolerant reactions. With the latter, animal plasma glutamate levels were observed to increase after the oral ingestion of MSG. However, in humans “no circadian variations in plasma and whole blood glutamic acid” were observed (Garattini, 2000). In terms of metabolism and under normal conditions, humans are able to handle large external doses of MSG (Maga & Tu, 1995). Under test conditions, the plasma concentration of glutamate is dependent upon the size of the dose, the nature of the challenge vehicle (carbohydrates tend to lower blood plasma levels), the nutrient status of the subject and the macronutrient composition of the meal (food matrix interactions). These facts make the correct diagnosis of MSG intolerance even more complex.

In the central nervous system (CNS), glutamate acts as a precursor of the inhibitory neurotransmitter, gamma-aminobutyric acid (GABA), and it is also the major excitatory neurotransmitter of the CNS. In this context, the metabolism of glutamate is intrinsically related to the availability of Vitamin B6. As a neurotransmitter, MSG has been a source of controversy for the last fifty years. Neurotoxicity trials in newborn rats and mice have shown permanent lesions in their hypothalamus (Vries, 1996). This phenomenon has not been observed in higher primates and it is presumably not applicable to humans (Garattini, 2000).

Although there is little conflict about the toxicity of high levels of MSG in animals, particularly in rodents, there is “substantial disagreement about the significance of this observation for human nutrition and health” (Garattini, 2000).

In some animal species, high levels of MSG were known to cause irreversible cell injury such as “necrotizing brain damage in the hypothalamus” (FASEB, 1995) and other disorders such as convulsions, abnormal lipid metabolism and obesity. It is important to note that most of these animals studies were parenteral (i.e. injection rather than consumption) and that MSG was provided at very high levels within a very short period of time. For these reasons, it is highly doubtful that at the current levels of MSG intake (see Appendix 15 for levels of MSG in Australian foods) permanent damage of any kind could occur in humans.

#### ***2.4 6 History of use and regulation***

MSG was first allowed as a food additive in 1959 (the FDA recognised it as a “generally regarded as safe” or GRAS substance) and since then, worldwide MSG intake has been progressively increasing in adult populations. Since 1970, numerous studies and reviews have been carried out looking at the safety of MSG, so much so that MSG is considered the additive in which most research has been done. The last governmental study was carried out by FASEB in 1995. This study admitted the possibility of MSG as a causing agent of food intolerance. Furthermore certain labelling objectives were suggested. For example, manufactures of foods containing glutamate, such as protein hydrolysate, were encouraged to include these ingredients in their labels.

The issue of labelling has been a source of controversy between food manufacturers, governmental institutions and consumers who self-report MSG intolerance.

On the one hand, labelling requirements increase costs and can affect productivity; on the other, consumers claim to have the right to know the nature and type of food ingredients. Glutamate has been said to be present in food ingredients such as sodium and calcium caseinate, yeast extract, gelatin, autolysed yeast and hydrolysed protein. As the D-form of glutamate is extremely rare and minimum, it is assumed that the glutamate found in these ingredients is the L-form. This form is also found in tomatoes, mushrooms and Camembert cheese. In these natural foods, there has not been any push for further labelling, therefore it could be said that these labelling requirements respond to an unnecessary campaign.

Glutamic acid can be used as a food additive in five different forms: L-glutamic acid (620), monosodium glutamate (621), monopotassium glutamate (622), calcium dihydrogen di-L-glutamate (623), monoammonium glutamate (624) and magnesium di-L-glutamate; all of them having the same ADI of 0-120 mg/Kg. b/w. This ADI is not applicable for infants under 12 weeks of age, as in Australia MSG is not permitted for use in food manufactured specially for infants and young children.

#### ***2.4 7 MSG Intolerance***

As mentioned above, when referring to the safety of MSG there are two issues that need to be addressed. The first, its neurotoxicity, has already been mentioned in previous sections. The second, MSG intolerance, will be dealt in this section.

MSG intolerance was first reported in 1968 by Kwok who coined the term “Chinese restaurant syndrome” (CRS). Since then numerous studies have attempted to replicate Kwok’s findings without much success.

Consequently, there is no clear understanding of the epidemiology, clinical spectrum, range of cross-reactivity and mechanism of MSG intolerance.

When first described, CRS was characterized by headache, facial flushing, numbness of the upper body, head and neck, general weakness and palpitations. This list was later expanded in 1995 (FASEB) and the symptoms unstable asthma, atopic dermatitis, headaches, facial burning and abdominal pain were added.

**Comment [RHL3]:** CHECK ON THIS

In terms of epidemiology, there is no reliable data on the prevalence of MSG intolerance in the general population. In clinical studies, it has been found to be quite common, as might be expected in such populations. Interestingly, it has been found that food intolerance is three times more common in women than in men (Loblay & Swain, 1991).

Cross-reactivity has not yet being studied in large populations although there are indications that seem to suggest that MSG intolerance is rarely an isolated problem (Loblay & Swain, 1991).

The mechanism(s) underlying MSG intolerance have not yet been determined. However, the clinical characteristics do not support an IgE mediated mechanism (Yang *et al*, 1997).

MSG has been associated with acute attacks in susceptible asthmatic subjects (Allen *et al*, 1984), although further recent studies contradict these findings (Woods *et al*, 1998). Thus, the role of MSG in provoking asthma remains unsolved. This is partly due to the methodological differences of the DBPCFC protocols of the different studies. The definition, role and protocol of this method will be discussed in Section 2.5.

**Comment [RHL4]:** Is this really what you want to say?? Or: "the results have not been widely replicated, and the role of MSG in provoking asthma remains unresolved".

## **2.5 DOUBLE BLIND PLACEBO CONTROLLED FOOD CHALLENGE (DBPCFC): A METHOD TO DIAGNOSE FOOD INTOLERANCE**

### **2.5.1 An overview**

As outlined above, double blind placebo controlled food challenge (DBPCFC) is considered the “gold standard” for the evaluation of food sensitivities (Bock *et al*, 1988). It is important for scientific as well as clinical purposes that MSG challenge methodology be standardised. For this to occur the following issues need to be considered: patient-related parameters, challenge-related parameters, therapist-related parameters and procedure-related parameters (Table 2.5).

Table 2.5 Parameters influencing the standardisation of DBPCFC

Patient-related	Challenge-related	Therapist-related	Procedure-related
Subject selection	Challenge amount (fixed or amount p.b.w*)	Decoding protocol	Use of food versus capsules
Diet compliance	Substance and status	purity Interpretation and confirmation of results	Placebos
Nutritional status		Challenge administration	Statistical analysis
Attitude/ beliefs (preconceived ideas)		Symptom suggestion	Elimination diet protocol
Method compliance			Medical avoidance Reactions to placebo (its significance) Time elapsed between challenges Challenge administration (time, place) Double blind methodology

\* Per body weight

### 2.5.2 Patient-related parameters

In clinical studies where challenges are not conducted under highly controlled conditions, confounding variables may need to be taken into account (free-living subjects who are subjected to an innumerable amount of variables).

Firstly, subjects need to be selected to participate in the trial according to specific criteria. In many studies, subjects are selected as a consequence of a self-perceived disorder (Woods *et al*, 1998; Thacker, 2000). This selection procedure can be deceiving, as the community's knowledge about food sensitivities is both incomplete and unclear. A subject may claim to be sensitive to sulphites and yet not know what sulphites are and in which food products they are present.

Diet parameters also affect the patient insofar as subjects are expected to comply with a defined elimination diet. Once subjects start the trial, they are normally placed on an elimination diet which can last up to two weeks before starting the challenges. The stringency of the diet in relation to exclusion of naturally occurring free glutamate has not been previously considered. Nor has the duration been standardized (Yang *et al*, 1997). Compliance is another important variable, since food intake can affect the diagnostic reliability of the challenges.

Volunteers are ordinarily placed on a diet which excludes all those substances for which they will be tested. This avoids the presence of false negatives during the trial. One aspect that is not considered very often is the effect that the subject's nutritional status would have on the intake of challenge substances. In addition, the attitudes and beliefs of the subject could affect the outcome of the study.

Finally, subjects are expected to maintain compliance with the protocol of the study for periods as long as 3-4 months.

### ***2.5.3 Challenge-related parameters***

The main issues surrounding challenge standardization are composition, form and purity; dose used; interval between challenges; pause time after challenges reactions (to allow for a possible refractory period).

In most clinical studies, challenge substances are provided in fixed amounts which represent either the normal dietary consumption of a person in a day, or the cumulative dose for a person during one week. Other studies (Tarasoff & Kelly, 1990; 1993) provide challenge amounts according to the body weight and mass index of the subject (say 0.1g of MSG per kilogram body weight). The latter has been proposed as a more accurate measurement. However, it lacks practicality and does not add anything to a method which is in itself diagnostic.

There are a number of methodological hurdles with regards to the purity of the challenge material. Challenge substances are normally embedded within a complex biochemical and chemical food matrix. It is relatively complex to replicate these parameters in a blinded protocol. Freeze dried food has been suggested as the possible solution, together with pure chemical substances in gelatin capsules. The latter can provide a further complication because there are certain chemicals which, when manufactured, can contain impurities. For example, manufactured MSG has been said to contain minimum amounts of the R-form glutamic acid which is not naturally found in nature and which could cause sensitivity reactions.

#### ***2.5.4 Therapist-related parameters***

Factors associated with the person carrying out the clinical study are not normally considered. However, therapists play an essential role in the development and evaluation of results. Therapists are responsible for the decoding of the challenges as well as the interpretation and confirmation of results.

The decoding process consists of the interpretation of the diet and symptoms during and after the trial. This process can be a complex one as many of the symptoms elicited can be subjective in nature. Therapists should establish a set number of symptoms and their intensities before decoding the challenges. This will ensure that unnecessary unknowns be introduced during the trial. In order to keep the process as objective as possible, it would be advisable that symptoms and their causes are not suggested to the subjects so that they may not have preconceived ideas about their state of health. Therapists should be aware of this fact.

#### ***2.5.5 Procedure-related parameters***

Lastly, those factors related to the challenge protocol which may have an effect on the outcome of the trial need to be considered. Challenges can be conducted with ingested foods/ingredients or with purified food substances in encapsulated form.

Both methods have their inherent faults and their use depends on the aim of the study. From a diagnostic perspective and for scientific internationalisation standardization purposes, it would be more appropriate to use capsules. This is because capsules are of uniform appearance, and taste can be eliminated as a confounding factor.

The use of placebos can also be another source of disagreement. Even though the substances tested worldwide are not always the same, it could be possible to establish a common substance for the placebo. For instance, sucrose, common sugar has not been known to produce any adverse effects and it is inexpensive and easy to pack and preserve. There are many other substances which hold similar characteristics and which could be used worldwide as placebo substances.

Another aspect, which has received numerous criticisms, is the fact that the DBPCFC method does not have a standard statistical method of analysis. This makes the comparison of results across studies significantly complicated. Non-parametric tests are said to have more applications and they allow for the comparison of reactions between placebos and active substances.

## CHAPTER 3. MATERIALS AND METHODS

### 3.1 ETHICS REVIEW COMMITTEE APPROVAL

Approval was sought and granted by the Ethics Review Committee of the Central Sydney Area Health Service (RPAH Zone) for particular parts of this study. The relevant sections are included in Appendix 1.

### 3.2 INTRODUCTION

This research project is divided into four parts, which correspond to the outlined aims of this study (Chapter 1). The methodology used for each section is different and is described separately. An overview of the methodology is shown in Table 3.1.

Table 3.1. Methodology overview

Section Title	Overview of methodology
Part 1. Database Study	This section was carried out by analysis of existing data. A number of patients were selected from the RPAH Allergy Unit's database. Their prevalence of food intolerance and association with MSG intolerance was considered.
Part 2. Re-challenge Clinical Study	Subjects who had been previously challenged ( $\geq 1$ year) at the Allergy Clinic (RPAH) were retested by DBPCFC. Certain patients were excluded (those with asthma or a history of laryngeal/ tongue oedema or anaphylactoid reactions).
Part 3. Diet Clinical Study	A small group of new patients presenting to RPAH Allergy Unit underwent two sets of food challenges, one before (on their usual diet) and one after being on a defined elimination diet. This study was carried to facilitate further research projects at RPAHAU. No results were expected at the time of completion.
Part 4. MSG Questionnaire	A brief (5-10 min) anonymous questionnaire about MSG (self-administered) was offered to: (a) patients presenting to the Allergy Clinic, (b) adult volunteers in suburban shopping centres, (c) adult volunteers undergoing clinical study and (d) adult volunteers at The University of New South Wales. Results from the four communities were compared.

### **3.3 PART 1. DATABASE STUDY**

#### ***3.3.1 Subject selection and study protocol***

No subject consent was necessary for this study because no human subjects were involved. A large database (~8,000 patients) held at the Allergy Unit (RPAH) was searched and certain information was retrieved from the patients' files. This included their past and present medical history, as well as their food sensitivity and diet records. The information was gathered into worksheets (Appendix 2) collated by Dr Loblay, Dr Swain and the author at the Allergy Unit. Once information was gathered into the worksheets, the retrieved data was integrated into the Unit's database (Novell system) for further analysis.

#### ***3.3.2 Data analysis***

For each patient undergoing dietary investigation, a file was created comprising personal and clinical details, dietary history and challenge reactions. All the data was tabulated in summary form spreadsheets, which were used as the basis for subsequent statistical analysis. The database management system *Structured Query Language* (SQL, Microsoft 2000) was used for the extraction of data from the files created. All other statistical analysis was carried out using Microsoft Excel (1998). Unless otherwise stated, these two programs were used for all other statistical analysis.

The proportion (p) of patients that reacted to each challenge was tabulated and 95% confidence intervals was calculated as follows:

---

$$1.96 \sqrt{p(1-p) / n}$$

As the number of patients was sufficiently large (n=222), it is reasonable to assume a normally distributed proportion of patients (Central Limit Theorem, 1984). Since each patient was tested with multiple challenge substances, and there may be an association between these reactions, the overall results were analysed using McNemar's test (1947). The null hypothesis being that the frequencies differ no more than expected by chance:

		MSG	
		+	-
Active challenge	+	A*	B*
	-	C*	D*

\* A,B,C,D- Frequency values expected for each category

The significant difference between these values was determined by calculating Chi-square by McNemar's formula and consulting a chi-square table. One degree of freedom was assumed for this test:

$$\text{Chi-Square} = \frac{(B-C)^2}{B+C+1}$$

### 3.4 PART 2. RE-CHALLENGE CLINICAL STUDY

#### 3.4.1 Subject Selection

Patients were selected from the RPAHAU database based on certain inclusion and exclusion criteria. Inclusion criteria included age (18 to 65 years) and having being previously assessed via DBPCFC at the Allergy Unit. Exclusion guidelines included a

past history of asthma, laryngeal/tongue oedema or anaphylactoid reaction (see Appendix 15- Glossary for definitions).

Patients with these conditions were excluded as their safety could have been compromised in the home-test conditions of this research. Subjects with mental disorders or undergoing intense drug treatment were also excluded from the study as this could affect the objectivity of the results. Of 222 patients contacted, twenty-six agreed to participate in the study (12%).

The protocol followed is outlined in Figure 3.1.

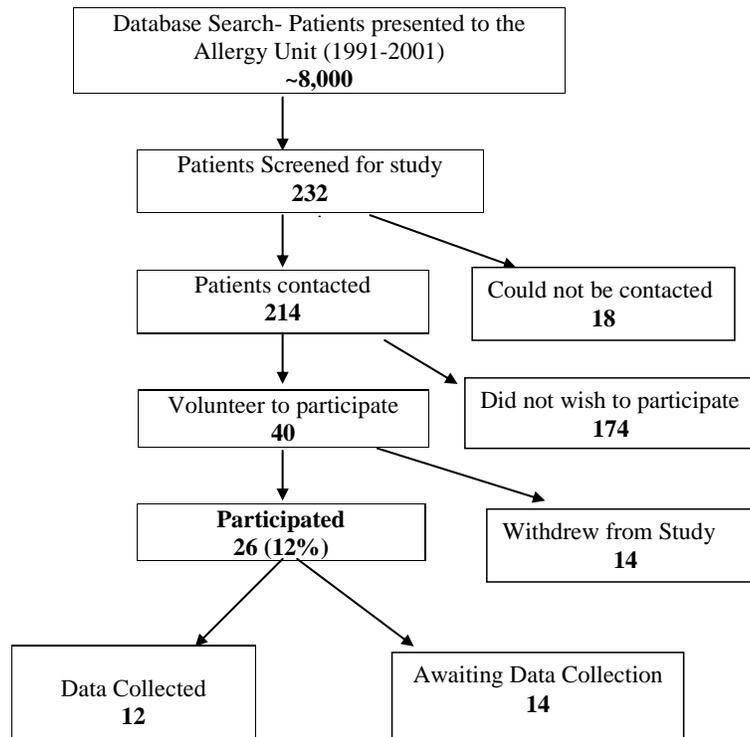


Figure 3.1. Patient recruitment sequence

### **3.4.2 Study protocol**

#### *3.4.2.1 General Procedures*

All selected subjects were first contacted via an introductory letter (Appendix 3) in which they were offered the possibility of participating in the study. The procedures were outlined and the exclusion criteria clearly stated.

The benefits from participating in the study were outlined. These included free doctor and dietitian appointments and dietary follow up. No monetary contribution was promised. Subjects were asked to contact the Allergy Unit if interested in participating. This could be done by phone, fax, email or by reply paid post (an envelope was enclosed).

An information package was sent to those subjects who volunteered to participate. After two weeks, subjects were sent the battery of challenge capsules (Section 3.4.2.5) and a questionnaire (Section 3.6). As challenges were to be performed at home, subjects were provided with all the necessary information to ensure safe practices. Patient follow-up was done by telephone or mail by dietitians at the Allergy Unit or by the author. A flow diagram of the study protocol is collated in Figure 3.2.

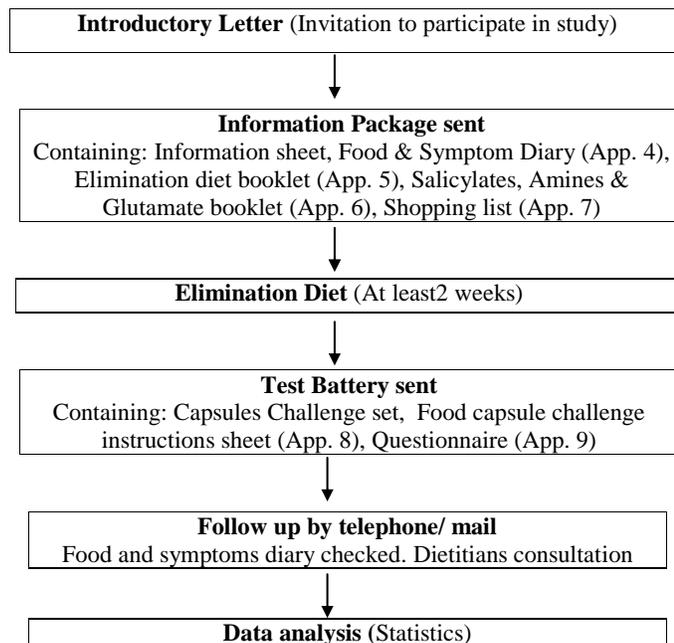


Figure 3.2. Flow diagram of study protocol

#### 3.4.2.2 Food & Symptom Diary

Patients were sent a diary and instructed to keep a detailed record of (a) all food and beverages consumed, (b) the type and duration of any symptoms experienced, (c)

details of all food and capsule challenges taken, and (d) the dose and type of medication taken when necessary.

#### *3.4.2.3 Information booklets*

The elimination diet booklet contained a detailed explanation about the nature of the elimination diet and its necessity. Instructions about which foods to eat and which foods to avoid were also outlined, as well as their reasons for inclusion and exclusion.

The importance of compliance was stressed, as dietary infractions could lead to the recurrence of symptoms and false positive or confusing challenge results. Practical advice on shopping, food preparation and how to vary the diet was provided via the “shopping list” and the “Salicylates, amines and glutamate” booklet.

#### *3.4.2.4 Elimination diet*

A diet excluding natural amines (such as tyramine and phenylethylamine), salicylates and glutamate as well as added preservatives, colourings, antioxidants and MSG was chosen as subjects undergoing re-challenge had been previously tested under these conditions. This diet was developed by Dr Loblay and Dr Swain at the RPAH Allergy Unit based on experimental clinical data and research studies (Loblay & Swain 1985, Swain, Soutter & Loblay 1996) done in the last twenty years.

Patients were instructed to comply with this diet for at least two weeks before starting the challenges. Gluten and dairy products were also excluded from the diet if they were known to cause adverse effects.

#### *3.4.2.5 Challenge dosage instructions*

Challenges commenced after at least two weeks on the elimination diet. Test substances were taken at home (subjects who had a past history of asthma, laryngeal/tongue oedema or anaphylactoid reactions were not allowed to participate). Patients were instructed to consume the numbered capsules half an hour before or two hours after breakfast.

This ensured that the test substances were consumed on an empty stomach. Challenges were spaced by at least three days to allow for delayed reactions. Any response to a challenge was followed by a pause of a further three symptom-free days before proceeding to the next challenge.

Challenges were carried out in a double blind mode, with neither the researcher nor the patients aware of the order of the substances tested. Challenges were numbered in one of ten different sequences, thus minimising observer bias when assessing the challenge reactions.

The challenge set included two sets of placebos (two different sets of sucrose) in order that the results obtained would be as objective as possible. Sucrose was chosen as the placebo as there are no known gastrointestinal symptoms associated with its consumption.

Two types of containers were used (child proof and translucent orange containers) to ensure objectivity. Some challenges were divided into an “A” dose and a “B” dose, representing a small dose and a large dose of the same or related compounds. These were taken on the same day, the small dose (“A”) first and if there was no reaction within two hours the second dose (“B”) was taken. Patients were told not to

consume dose “B” if any noticeable reaction occurred after consuming the small dose (“A”). The type and amount of substance in a sample sequence is shown in Table 3.2.

Table 3.2 Challenge substances and capsule arrangement

Set number (sample)	Test Substance	Amount tested	Number of capsules
1 A	Aspirin (acetyl salicylic acid)	600 mg	2
1 B	Aspirin (acetyl salicylic acid)	600 mg	2
2 A	Sodium benzoate	500 mg	1
2 A	Sodium benzoate	500 mg	1
2 A	4-OH benzoic acid/sorbic acid	200mg/200mg	1
2 B	Sodium metabisulphite	500 mg	1
3	Tartrazine	30 mg	1
3	Brilliant blue	10 mg	1
4	Phenylethylamine/Tyramine HCl	4 mg/150 mg	1
5 A	MSG	2.5 g	5
5 B	MSG	2.5 mg	5
6 A	Sucrose	1 g	2
6 B	Sucrose	1 g	2
7	Sucrose	1 g	2

All capsules were packed into a square cardboard box (11x11cm) and all substances contained were indicated on the outside of the box (Figure 3.9).

### 3.4.3 Sample preparation

The battery of test substances comprised those compounds which had been previously tested in the Allergy Unit. These substances were chosen as they have been reported as major precipitants of gastrointestinal, cutaneous, respiratory and/or systemic disorders. The amounts used are equivalent to the average amounts present in the standard diet of a person. Tartrazine and brilliant blue were assessed together as they usually appear together in foods containing colour. Benzoic acid, sodium benzoate, sorbic acid and sodium metabisulphite, which are used as preservative agents in many foods, were also part of one challenge.

Challenge sets were prepared by the author under the supervision of a pharmacist in the Pharmacy Department at RPAH. This Department provided all chemical test substances. All substances were encapsulated in opaque (whitened with titanium dioxide- an inert substance) gelatine capsules (size 0). The expiry date of the capsules was estimated to be one year after production. Filled capsules were packed separately into numbered plastic bottles of two kinds. Acetyl salicylic acid (aspirin) and one set of placebos were packed in childproof containers, all other substances were packed in translucent orange vials (Figure 3.3).

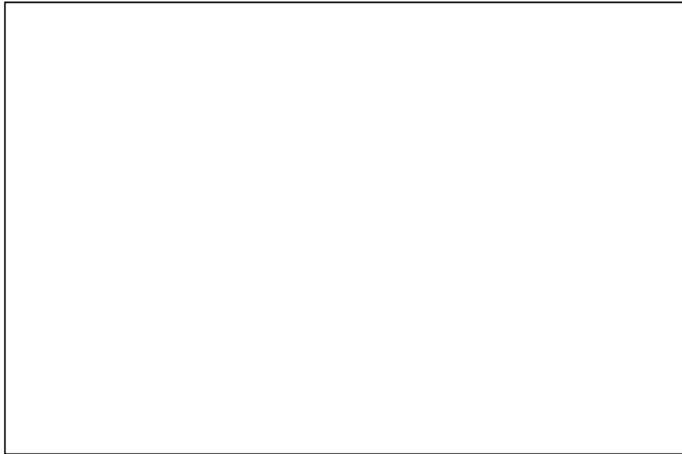


Figure 3.3 Translucent Orange vials used for capsule packing

The method for capsule preparation was provided by the Pharmacy Department at RPAH (Appendix 10). Deviations to this method, introduced to increase the efficiency and speed of production, are outlined as follows:

**1.** Formulation was checked (as in Table 3.2) and the required substances were weighed to make up 100 capsules (plus two for loss).

Note: Each capsule can contain 500 mg of sucrose or similar density powder. Grinding was conducted when the crystal size of the powders was too large. Sucrose was added to make up for the volume whenever the volume of substance needed was less than 500-mg, Manual compression was used for very fine powders.

**2.** The substances were mixed well using pestle and mortar.

3. The capsule filling machine (Figures 3.4 and 3.5) was then loaded with 100 capsules and the lids were removed.

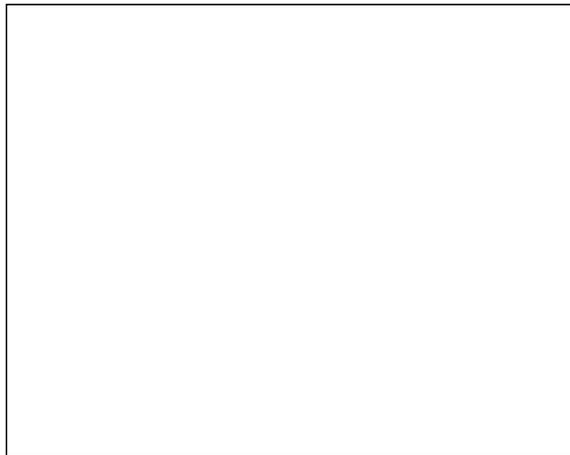


Figure 3.4 Capsule filling machine

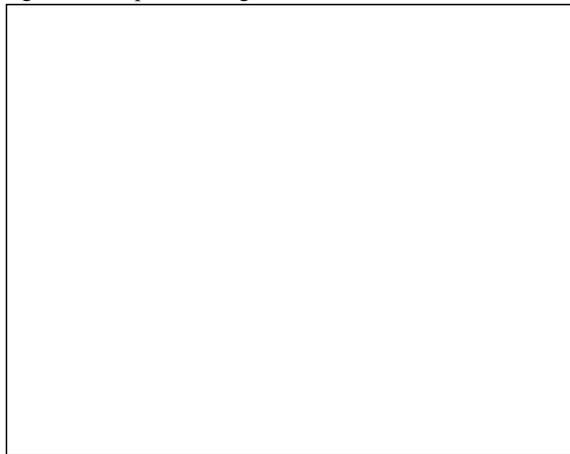


Figure 3.5 Loaded capsule filling machine

4. After leveling all capsules the powder mixture was poured and the powder distributed evenly on the surface (Figure 3.6).

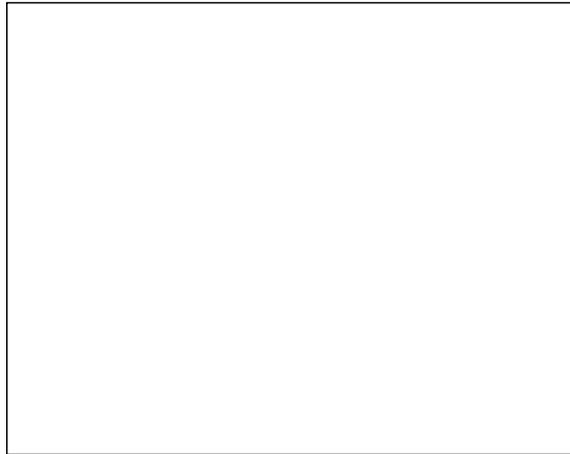


Figure 3.6 Capsule-filling machine with powder substance

5. The lid of the capsule-filling machine was closed and capsules were removed for individual weighing. The capsules' surface was cleaned by dusting off extra powder that may have been attached to the outer surface of the capsule.
6. An electronic balance was tared with an empty capsule. Each capsule's weight was checked and discarded if the weight differed by more than 10%.
7. Capsules were then packed into the appropriate vials and labeled with a batch number (Figures 3.7 and 3.8).

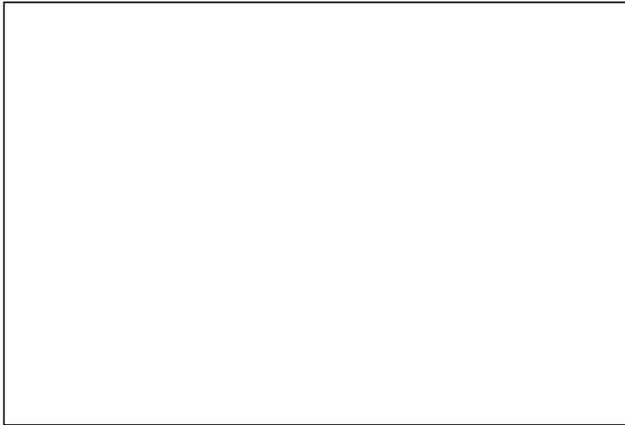


Figure 3.7 Sample (MSG) capsules

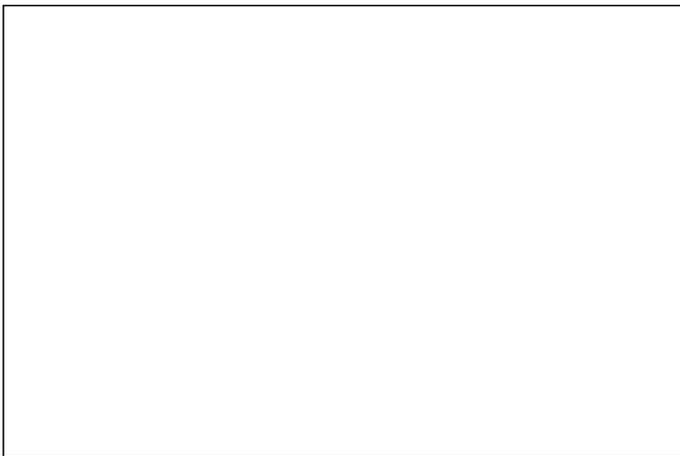
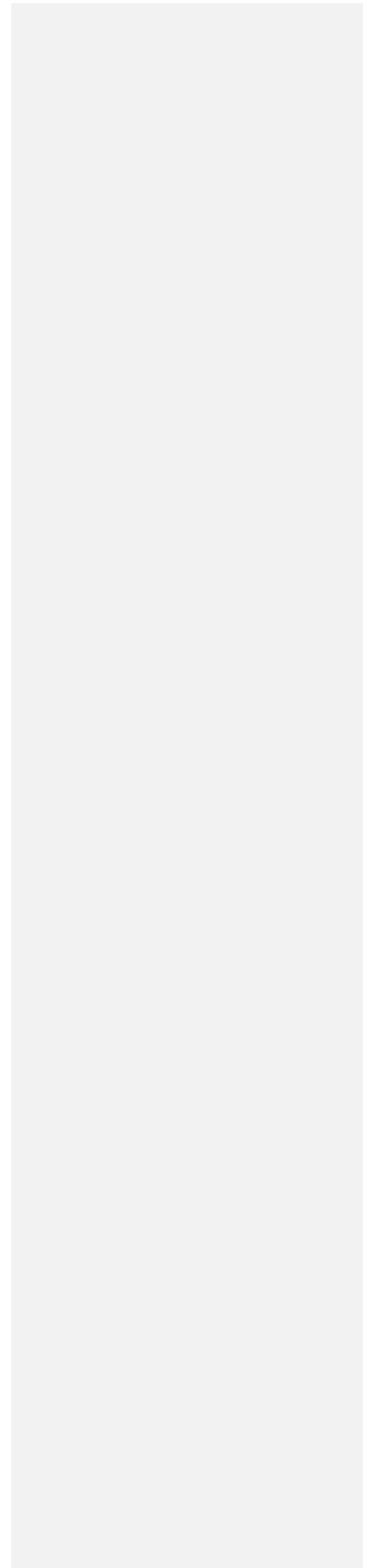


Figure 3.8 Capsule filled vials

**8.** Once vials were completed, challenge sets were assembled in ten different combinations and stored at the Allergy Unit (Figure 3.9).



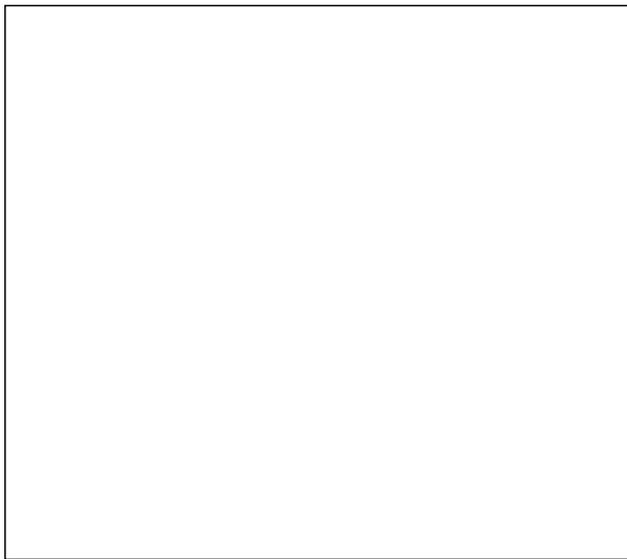


Figure 3.9 Complete challenge set ready for delivery

### **3.4.4 Data Analysis**

#### *3.4.4.1 Patient information analysis*

Upon completion of the challenges, subjects were encouraged to send their diaries by mail or bring them to their next doctor/ dietitian consultation. Their diet and symptoms were analysed according to their existing baseline symptoms. Once a clear conclusion was achieved the code was broken. The results obtained were then integrated into the Unit's database for further analysis.

Patients' symptoms were classified into five different categories: headache, skin, respiratory, gastrointestinal tract (GIT) and other CNS (central nervous system) reactions. The symptoms included under each category were as follows:

- Headaches - migraine, other headaches

- Skin - eczema, hives, other skin, other tissue swelling, tongue/ throat swelling
- Respiratory - asthma/ wheeze/ cough, blocked nose/ sinuses, hay fever/ sneezing, other respiratory
- Gastrointestinal - bloating/ wind/ gas, burning mouth/ tongue, constipation, diarrhoea/ loose stools, discharge/ irritation, indigestion/ reflux, mouth ulcers, nausea, other GIT, pain/cramps/colic, vomiting
- Other CNS - aches/pains, anxiety/panic attacks, blurred vision, depression/moody, dizziness, excessive sweating, fatigue, hyperactive/restless, irritable, other CNS, PMT, poor concentration, sleep disturbance

#### 3.4.4.2 Statistical analysis

The results for this section were tabulated according to whether the patient's response upon rechallenge was the same or different. To test if there were significant changes in the two challenges, a McNemar test for significant difference was used, the null hypothesis being that there are significant differences between the first and the second test. The results were summarised according to the following table:

		AFTER	
		+ve	-ve
BEFORE	+ve	A	B
	-ve	C	D

The Chi-square goodness-of-fit statistic was determined as follows :

$$\text{Chi-square} = \frac{([A - D] - 0.5)^2}{A + D}$$

One degree of freedom was estimated (at  $\alpha = 0.05$ ) and p-values were derived from tables of the distribution of Chi-square statistics.

For each patient, the results were tabulated in four categories according to their response to the challenges on both occasions: ++ (when both responses were positive), +/- (when the first response was positive while the second was negative), -/+ (when upon rechallenge a substance gave a positive reaction) and -- (when no reaction was recorded on both occasions). The null hypothesis was that the challenge findings in each case were due to chance alone. Expected proportions were calculated from the known figures in the group as a whole, assuming the same frequency of positive and negative reactions to occur at random in both the first and second challenge series.

### **3.5 PART 3. DIET CLINICAL STUDY**

#### ***3.5.1 General remarks***

The procedures followed in this part are the same as those outlined in Section 3.4. Any modifications to this process are outlined below. As outlined in the Introduction section of this chapter (Section 3.2), no results were expected from this study. This study was designed and prepared for future research at the RPAHAU. However, the methods and protocols of this study have been included in this paper because they constitute part of the designing work of the author.

#### ***3.5.2 Subject selection and study protocol***

Patients coming to the Allergy Unit for the first time were selected for this study. Their medical history was taken by one of the doctors on duty at the Allergy

Unit. Certain exclusion and inclusion criteria were established and passed on to the doctors for pre-screening.

Exclusion criteria included a past history of asthma, laryngeal/tongue oedema or anaphylatoid reaction (see Appendix 15 Glossary for definitions). Inclusion criteria included age (18 to 65 years), willingness to remain in their normal diet for the duration of the first set of challenges and to modify their diet for the second part of the study.

After an appointment with the doctor, patients were met by one of the dietitians at the Allergy Unit and introduced to the possibility of participating in this research study. An introductory letter and a consent form (Appendix 11) were provided.

Subjects were provided a set of challenge capsules and information regarding their consumption (as in Section 3.4.2.5). They were encouraged to continue in their normal diet while these were consumed.

Hardly any information about diet, sensitivities and symptoms was provided at this point. This was done in order to avoid subject's bias in their diet and perceptions. Once subjects had completed the challenges, results were recorded in the same manner as in the previous section (Section 3.4.4.1).

After at least two weeks on the elimination diet subjects were provided with another set of challenge capsules. This time, information regarding diet, compliance and sensitivities was provided. An outline of this protocol is shown in Figure 3.10.

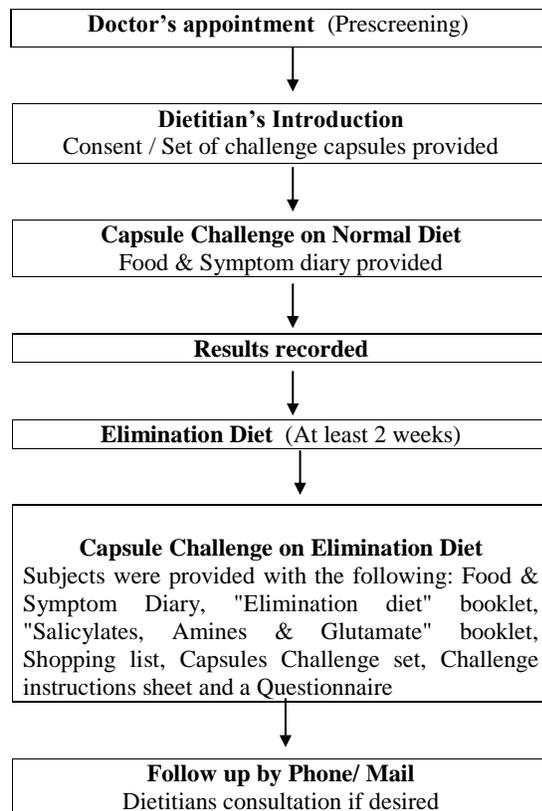


Figure 3.10 Protocol used in diet clinical study

### 3.6 PART 4. MSG QUESTIONNAIRE

#### 3.6.1 General remarks

The procedures followed involved the design and administration of a short questionnaire. No subject selection was necessary; however, children under 18 and

adults above 65 were excluded. The questionnaire was anonymous and no further commitment was required from those answering the questionnaire.

### ***3.6.2 Questionnaire Design***

The questionnaire was designed and formatted to provide an overview of consumer's knowledge about MSG. Self-reported MSG intolerance and perceived symptomatology were also considered. The questionnaire consisted of seven questions. Question 6, "Do you know what MSG is?" was included in order to be able to assess the kind of knowledge that the population has about MSG. Question 7, "Which of the following foods do you believe contain MSG?" provided further information about natural and added glutamate. A number of "distracters" (foods that do not contain MSG) were included in the list. Questionnaires took between five to ten minutes to be completed.

### ***3.6.3 Data analysis***

#### ***3.6.3.1 Data classification***

Five different subject groups were identified: patients presenting to the Allergy Clinic, patients at the Allergy Unit undergoing research studies, adult volunteers in suburban shopping centres, adult volunteers studying any degree at the University of New South Wales, adult volunteers studying Food Science and Technology at the University of New South Wales

For all groups, random sampling was carried out, although it was noted that more females were willing to volunteer than males. For all five groups, the results were incorporated into the Allergy Unit's database (Novell system) for further analysis.

Patient's answers about "What is MSG?" were also classified into ten different categories: (1) miscellaneous (incorrect), (2) flavour enhancer, (3) food additive (unspecified), (4) a salt, (5) monosodium glutamate (know only the name), (6) meat tenderiser, (7) artificial food colouring, (8) food preservative, (9) artificial flavour and (10) correct answer (including both natural and manufactured glutamate)

#### *3.6.3.2 Statistical analysis*

All results were tabulated as percentages and the relevant sections graphed. Mean values between the different groups were compared.

## **CHAPTER 4. RESULTS AND DISCUSSION**

### **4.1 PART 1. DATABASE STUDY**

For the selected population, the proportion of patients reacting to each challenge was tabulated (Figure 4.1). As expected, the proportion of patients reacting to MSG was the largest when compared with all other challenge substances. This is not surprising, as these patients were selected from the RPAHAU on account of their having being challenged with MSG.

Figure 4.1 Proportion of patients reacting to challenge substances

However, this does not indicate that these patients presented with symptom complaints about MSG; rather, they presented to the Clinic with diverse symptoms presumably associated to the consumption of food. Generally, of those who seek treatment at the RPAHAU, 40% to 50% do not recognise any specific chemical trigger before food challenge.

The “colours” capsule challenge had the second largest proportion of positive challenge responses.

This result cannot be counted as completely valid because it includes challenges from the last ten years and the substances tested have changed since then. In the current set of challenges tartrazine and brilliant blue are used while erythrosine (green) and sunset yellow were utilized in previous years. This proportion, though high, could represent an uneven distribution of responses. It is expected that the different colours would have a different response rate. Further research could confirm this expectation. In a previous study (Loblay & Swain, 1985) it was noted that the reactivity of selected clinical patients to food colourings was very similar. In this study it was noted that those

who reacted to tartrazine also reacted to erythrosine and sunset yellow. This result, however, represents the outcome of a very specific subset of the population and needs further confirmation.

The response rate for the placebo (sucrose) was 36%, which represents one third of the patients assessed. Though the reasons underlying this high response rate are diverse, they can be partially attributed to the selection parameters of the inclusion criteria. Some of the reasons for this outcome have been listed as follows:

- None of the patients had asthma, or a history of anaphylaxis or angioedema. Thus GIT/ CNS symptom subjectivity may have clouded the outcomes,
- An incomplete resolution of symptoms on the baseline elimination diet could have affected the amount of “background noise” during capsule challenge; this fact would increase the rate of placebo reactivity,
- The existence of subjective confounders could affect the outcome of the challenge. Although subjects were chosen keeping in mind their ability to be objective, it is hard to expect complete adherence to the protocol. For example, subjects who do not comply with the diet will have a higher rate of reactions.

Those patients who had a positive reaction to MSG also had a positive reaction to at least one other challenge compound (Figure 4.2). No one reacted only to MSG. This finding is of major importance in terms of dietary and medical management. Patients presenting food sensitivities are prone to react to more than one chemical substance, and they therefore need to avoid a wide range of foods and medicines.

Figure 4.2 Response rate of patients who reacted to MSG and other substances

A chi-square test was carried out on the reactivity rates of these substances and MSG. It was noted that a correlation exists between these substances and MSG (Appendix 12).

Of all those subjects that reacted to MSG, 43% also reacted to colours, 40% also reacted to salicylates and preservatives and 37% also reacted to propionates. It is interesting to note that artificial colours were the substances responsible for the most adverse reactions after MSG. This phenomenon, although identified in clinical observations, has not been linked to any toxicological and/or biochemical study. In fact, the chemical, physical and biological nature of these two compounds has previously been believed to be totally unrelated.

In terms of symptoms, those involving the gastrointestinal system were the most common (Figure 4.3), followed by headaches and other CNS manifestations. Skin disorders were the least common, although MSG seemed to exhibit a higher proportion of skin reactions than other substances. Respiratory manifestations were mostly reported after the consumption of propionates and preservatives.

Figure 4.3. Symptom response rate of the different challenge substances

The consumption of MSG was observed to elicit more than one type of symptom. When MSG intolerance was first described (Kwok, 1948), certain symptoms (numbness of the back, general weakness and palpitations) were associated with this additive. Later, in 1995, FASEB expanded this list of symptoms to include unstable asthma, atopic dermatitis, headaches, facial burning and abdominal pain. In the present study, it has been observed that besides the already mentioned manifestations, there are other symptoms associated with MSG intolerance.

These include blocked nose/ sinus problems, constipation/ diarrhoea, indigestion/ reflux, nausea, mouth ulcers and vaginal irritation. For these symptoms to be included under the current “MSG symptom complex” (FASEB, 1995) further confirmatory tests need to be carried out. As with other food intolerances, the association between symptoms remains unsolved. The nervous system has been suggested as a possible link between these symptoms. Although only a hypothesis, it is possible that these substances might trigger a reaction in the finer nerve endings of the different systems and thus provoke a multifactorial response (Loblay, personal communication, 2001).

#### **4.2. PART 2. RECHALLENGE CLINICAL STUDY**

At the time of writing, the results of 14 patients had been collected. The proportion of patients who had the same response before and after challenge was larger (83%) than that of patients who did not (17%). These results were collated in Figure 4.4.

Figure 4.4. Overview of results from those patients who underwent capsule rechallenge.

As can be observed, in the majority of cases the results were reproduced. This was further verified using McNemar's test for significant changes. By calculating the chi-square value (Appendix 13), it was confirmed that there were no significant changes between the first and the second set of results. Thus it can be concluded that the DBPCFC procedure followed at the RPAH Allergy Unit gives reproducible results.

A significant proportion of subjects (12%) reacted to the challenges the first but not the second time. This could be due to experimental errors or to the fact that food intolerances (like true food allergies) can subside with time.

Only 4% of those rechallenged experienced reactions in the second trial after having had no response in the first one. This situation was only encountered in the "colours" and "amines" challenges. As mentioned before, the "colours" challenge has experienced changes in composition in the last ten years.

Thus it is possible that two subjects have been challenged with different substances than those used ten years ago. Reactivity to amines could reflect changes in food sensitivity or, as with the placebos, false negatives.

#### **4.4. PART 4. MSG QUESTIONNAIRE**

##### ***4.4.1 Survey Data of the population as a whole (n= 224)***

A total of 224 volunteers were examined, 73% of which were females. The average age of the volunteers was 26 years. The observation that a greater proportion of females offered to complete the questionnaire could be associated with the fact that, as published in the literature, food intolerances are approximately twice as common in women (Loblay et al, 1991). Furthermore, both the Allergy Unit and the UNSW

Department of Food Science and Technology has more female staff and students respectively.

In the present study, the proportion of volunteers who self-reported any kind of food sensitivity (Figure 4.5) was larger than that reported in the literature (Metcalf, 1997; Vatn 1997; Young, 1997). According to these authors, the real prevalence of food intolerance does not exceed 3%. However, the perceived prevalence of food sensitivity has been estimated to be larger than 27% (Yeung et al, 2000).

Figure 4.5. Self-reported reactivity (%) to food substances

The most common self-reported food sensitivities were in the category of “other foods”. More than fifty foods were reported as causing food sensitivity: alcohol, amines, salicylates, chocolate, coffee, avocado and eggs being the most common. Others included banana, onion, seafood, mushrooms, nuts, kiwifruit, butter and chili.

Of the single items listed in the questionnaire, MSG had the highest rate of responses. Overall, MSG was the second most common self-reported food sensitivity (26%), followed by milk and preservatives (25% each). Such a high rate of self-reported MSG intolerance has not previously been recorded in the literature. However, it is

important to note that a large portion of the population assessed (41%) had had some contact with the Allergy Unit at RPAH, introducing a possible bias into the figures. A similar point can be made with regard to the self-reported prevalence of sensitivity to milk and preservatives. Interestingly self-reported sugar sensitivity was the least common.

With respect to symptoms, wind and bloating was reported to be the most common symptoms associated with food consumption (42%) followed by diarrhoea/constipation (38%).

Fatigue was often identified (39%), but was not associated with food. Of the symptoms which were reported to occur “rarely and/or never”, eczema was the symptom most frequently not associated with food (77%), while “nausea/vomiting” had the largest proportion of food associated symptoms (7%).

When asked if they knew what MSG was, 71% responded affirmatively while the remaining 29% had no knowledge about this substance. This figure is quite remarkable, as it means that more than one in four subjects do not know anything about this food additive. Of those who claimed to know what MSG is, only 6% knew how to define correctly the substance (Figure 4.6).

Figure 4.6. Classification of MSG definitions as seen by the surveyed population

MSG is the sodium salt of glutamic acid, and is probably the most common amino acid in nature. While the lay population could not be expected to know the exact nature of this compound, it is important that its natural occurrence is not overlooked.

Thus, a correct answer was scored when a subject was able to mention both MSG as an added flavour enhancer and as the natural component of some foods.

Of the total population 11% gave a “miscellaneous” answer. This category was used to indicate those answers which expressed unclear or incomplete concepts. Some of these included “an amine”, “found in Chinese foods”, “found in tomatoes”, “only healthy in moderation”, “a white powder”, “made from plants”, “a poison” and “a yeast”.

The majority of subjects believed MSG to be an additive or a flavour- enhancer (70%). This suggests that MSG is best known as a “manufactured” ingredient rather than as a natural substance. From this questionnaire it can also be deduced that the general population has an unclear view about MSG, although it would be advisable to confirm these results with a similar study on a larger scale.

Furthermore, for the benefit of the food industry and health authorities, it would be advisable to conduct a promotional campaign about MSG. This campaign could emphasize two aspects; firstly, the definition of MSG as a natural substance, and secondly to outline the food substances in which MSG is present. By doing this, consumer perception about the safety of MSG will be significantly increased.

The presence of natural glutamate in different foods was also assessed; however, certain subjects did not complete the whole inventory, which seems to indicate that the list provided was too large. In these cases, it was assumed that no answers were given because the subjects did not know the response.

At least 15% of the population seemed unclear about the presence of MSG in foods, although this ignorance could have been compounded by the length of the

questionnaire. The largest proportion of unknown responses was observed in the “Camembert and Brie cheeses” category (49%), followed by the “spearmint chewing gum” option (48%). No evident relationship can be observed between these substances in terms of flavour, manufacture or aspect. Camembert and Brie cheeses have high levels of natural glutamate, but spearmint chewing gum does not contain natural glutamate or added MSG.

Rice was the food most often identified as non-natural glutamate containing (67%). Other foods, which were reported as having no “natural MSG”, include milk (61%), corn (59%), broccoli (57%) and grapes (54%). The latter two are rich in natural glutamate. It is noteworthy that most of the answers recorded account for “added MSG”, “no MSG” or “unknown answers”. The notion of natural glutamate seems foreign for most of the population. In terms of added MSG, “Chinese take-away” was the food most often identified as having added MSG (Figure 4.7). This may reflect the public’s awareness as a consequence of past publicity.

Figure 4.7 MSG content of foods as seen by the general population

Meat pies, canned soft drinks and pizza were perceived as containing added MSG, which is rarely the case. Kelp seaweed had a high proportion of “no MSG” answers, however MSG was first identified from this plant and its natural glutamate content is high. This food also had the highest recorded number of unknown responses. This can be attributed to the fact that seaweed is not a common ingredient in Australian cooking.

In conclusion, the population’s perception about MSG seems to be incomplete and unclear. The reason for this is yet to be determined, although it is likely that the cultural and social backgrounds of the subjects influenced their knowledge.

In the design of future studies, the following suggestions can be made:

- Introduce a question about cultural background. It would be interesting to observe differences between those of Asian origin and those who are not.
- With regards to the definition of MSG, it might be better to provide a list of concepts (including all those recorded in this study), so that subjects may be allowed to tick an answer rather than having to write something which may be incoherent.
- For those who claim to be MSG sensitive, it would be rather useful to determine which foods are avoided and to what degree are they excluded from the diet.
- Information about the frequency of symptoms, as well as their nature, could provide useful insights about “real” MSG intolerance.

- With regards to the symptom list provided, it would be advisable to format it in a different manner, as it was found that many of the subjects did not understand its structure fully.
- Finally, the list of foods provided appeared to be too long for some subjects. It was noted that many subjects selected those foods which had MSG while the rest was left as “unknown”. Most people knew that MSG could be added to Chinese take-away but many of the other foods were left blank or marked as “unknown”.

For further studies, it would be advisable to restrict the number of foods by restricting them into some groups such as manufactured foods, fresh foods and foods of Asian origin. This division would make it possible to detect trends over time in the understanding of MSG.

- Another issue that could affect people’s definition of MSG is its flavour. It would therefore be advisable to include a question about the perceived “flavour” of MSG. This would make it possible to consider the relationship between food “tastiness” and MSG content.

#### ***4.4.2 Data comparison amongst the different population groups***

The number of subjects interviewed in each group was different (Table 4.1). The groups differed in age and knowledge about food and food sensitivities.

Table 4.1 Group population characteristics

Group name	Number	of	Proportion (%)
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	subjects assessed	with perceived MSG sensitivity
Clinic Patients	72	22
Food Science Students	34	7
Rechallenge clinical study	20	14
Shopping centre	59	11
University Students	39	10

As expected the group with the highest proportion of self-reported MSG intolerance was the clinic patients. This group was interviewed in the waiting room before or after their appointment with the doctor and/or dietitian.

In terms of symptoms, the most common manifestation associated to food was observed to be wind and bloating. This was the case in all the groups interviewed, except for the Food Science students, where diarrhoea was noted to be the most common symptom (Table 4.2).

Table 4.2 Characteristic symptoms associated to the different groups interviewed

Group Name	Sometimes/ often is food related	Sometimes/ often not food related
Clinic Patients	Wind/ Bloating (44%)	Nose/sinus problems (47%)
Food Science	Diarrhoea/constipation (47%)	Headaches/ migraine (50%)
Rechallenge	Wind/ Bloating (65%)	Nose/sinus problems (35%)
Shopping Centre	Wind/ Bloating (37%)	Fatigue (46%)
University	Wind/ Bloating (31%)	Muscle joint/ aches (44%)

With regards to common symptoms not associated with food, it was noted that, with the exception of the groups associated with the Allergy Unit (clinic and

rechallenge patients), all other groups had symptoms related to the central nervous system.

Not unexpectedly, those who underwent rechallenge had the highest proportion of subjects who knew what MSG was. However, of this population, 5% did not know what MSG was. This result could have an effect on the DBPCFC, especially in terms of diet compliance.

Figure 4.8 Proportion of MSG knowledge in population subgroups

It was also noted that a high proportion (23%) of subjects presenting to the Allergy Clinic did not know what MSG was. This was surprising, as this particular sub-population would be expected to have a better understanding of the triggers for food sensitivity. University students doing courses other than Food Science and Technology had the lowest knowledge about MSG. This could be due to their younger age and the nature of their field of study (mostly Arts students). Subjects assessed at shopping centres had a better understanding about MSG than university students did. At first glance, this seems surprising, but this difference could be explained by the publicity about MSG that was released several years ago. The student generation would not have

been exposed to this information to the same extent as older people surveyed in the shopping centres. In terms of understanding the nature of MSG, those who underwent rechallenge had the highest proportion (35%) of correct answers (Figure 4.9)

Figure 4.9 Definition of MSG as seen by the different population groups

No individual in the university sub-group gave a correct definition of MSG. Furthermore, this group was the one with the highest score for the definition of MSG as “a salt”. All groups gave high scores for MSG as a “flavour enhancer”, but the Food Science and Technology students had the highest proportion of this option as their answer. Unlike other university students, Food Science and Technology students have a training which should facilitate their identification of MSG. However, for some unknown reason, these students were unable to recognise the biochemical nature of MSG (that is, glutamic acid). Either these students were at the beginning of their university training (and thus did not know about MSG at the time of the survey) or their education has been incomplete in some way.

Lastly, the presence or absence of MSG in the listed foods was compared across groups. The proportion of correct answers per group is collated in Table 4.3.

Table 4.3 Proportion (%) of correct answers as recorded from the different groups

Group name	Proportion of correct answers (%)
Clinic patients	26
Food Science	46

Rechallenge	49
Shopping Centre	32
University students	31

As expected, the highest proportion of correct answers was observed in the group that underwent capsule rechallenge. However, clinic patients showed the lowest proportion of correct answers. This result seems contradictory, as this group is expected to know more than the general population and university students. One factor that could account for this result is that the questionnaires were handed out in the waiting rooms at the Allergy Unit, and many of those assessed did not have time to complete them.

#### ***4.4.3 MSG knowledge from those who perceive themselves MSG sensitive***

Of those who perceived themselves to be sensitive to MSG, 83% were female and more than half (62%) had some connection with the Allergy Unit. Such a high proportion of females was expected, as almost three quarters of those surveyed were female.

The most common symptom associated to food present in this sub-population was diarrhoea and constipation (34%), followed by wind/bloating (32%), and indigestion/reflux (27%).

Sinus problems (21%) and fatigue (20%) were also common symptoms in this population, but they were not associated with the consumption of foods. It is interesting to consider that all the symptoms associated with the consumption of food are connected to the gastrointestinal tract.

Surprisingly, not all subjects in this group knew what MSG was; 20% indicated that they did not know. This fact gives a useful insight into the perceived prevalence of

MSG, as numerous studies have based their findings on subjects who perceived themselves to be MSG intolerant. Of those who claim to know the definition of MSG, only 13% gave a correct answer (Figure 4.10). This is also significant, since avoidance is the only effective means of symptom relief in patients with food intolerance.

Figure 4.10. Classification of MSG as described by those who self-report MSG sensitivity

Those who self-report MSG sensitivity would tend to avoid foods containing MSG (or rather that they think contains MSG). These foods were reported to be Chinese take-away, chicken noodle soups, stock cubes, Thai restaurant meals, seasonings, sweet and sour sauce and flavoured potato crisps. All of these foods share the fact that they are processed foods and have a high flavour profile. Other foods which may contain natural glutamate are not normally excluded from the diet (e.g. spinach, miso, mushrooms and fresh tomato).

In conclusion, natural glutamate is not normally associated with the traditional “Chinese restaurant syndrome” and it is not taken into account in research studies. This fact may account for discrepancies in the literature with regards to MSG intolerance.

## CHAPTER 5. CONCLUSION

MSG has been suggested as the causative agent of food intolerant reactions; however, confirmatory methods for these adverse reactions are contradictory in many aspects. This study aimed at clarifying some of these issues and the outcomes are as follows:

From the database study, it was concluded that in the patient population at RPAHAU, MSG intolerance is a common disorder. In this population it was also found that isolated MSG intolerance was rare. All of the assessed had intolerance to more than one food substance, “colours” being the highest source of adverse reactions after MSG. These results, although significant for the management and diagnosis of patients, do not represent the actual prevalence of MSG intolerance in the general population. It would therefore be advisable to conduct a MSG challenge study in the general Australian population.

The rechallenge DBPCFC study undertaken at RPAHAU gave reproducible results. The protocol used has been described in previous sections (Sections 2.5 and 3.4) and could provide the basis for a standardisation process in the future. This study provided fixed doses of food substances and a defined baseline, based on a defined elimination diet. Although the rechallenge study provided positive and reproducible results, it should be noted that these results are preliminary, due to the small number of patients involved in this particular study. Further research in this area would confirm the results of the rechallenge study and strengthen the case for an international standardisation of DBPCFC procedures.

The MSG questionnaire provided useful insights into the population's knowledge about MSG. It was found that the proportion of the population surveyed which accurately understood the definition of MSG was less than expected. In general, popular knowledge about MSG is incomplete and in certain instances, wholly inaccurate. Many of the previous studies that assessed the presence of MSG intolerance were carried out on subjects who perceived themselves to be MSG sensitive, but these studies failed to identify the accuracy of these perceptions. The results of this study serve to indicate the need for an education of the public regarding the definition, role and presence of MSG in foods. This recommendation is of particular value to food manufacturers, as one of the most significant findings of the questionnaire was that a majority of those surveyed could not accurately identify which foods contained MSG. In addition, the fact that almost all those surveyed failed to recognise that MSG was naturally present in foods, would also be of significance to food regulatory authorities. Future questionnaires need to be designed with the following in mind;

- 1) MSG definition questions need to provide further definition, for example options to be chosen, so as to reduce the number of incoherent responses
- 2) The length of the questionnaire needs to be reduced in order to allow those surveyed more time to complete it
- 3) The following aspects could be positively considered in a survey: the cultural background of the participant, the relationship between MSG and taste perception, the relationship between MSG, those who claim to be MSG

intolerant, and which foods those people avoid (for MSG intolerant respondents only)

In conclusion, an internationally standardised DBPCFC method needs be developed in order for a scientific and medical consensus of the nature of MSG intolerance to be reached. In this sense, the rechallenge study and database study from RPAHAU firmly endorse the need for international standardisation to eventually occur. With regard to lay understanding of MSG intolerance, the MSG questionnaire strongly indicated the need for public education about MSG and its presence in foods.

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## APPENDIX 15. GLOSSARY OF TERMS

- **Adverse food reactions (food sensitivity)**- any unpleasant bodily reaction caused upon the consumption of a food product. They include the following disorders: toxic reactions, food sensitivities (which includes food allergy and food intolerance) and psychological reactions (strongly held beliefs) (Fireman and Slavin, 1996).
- **Anaphylactoid reaction**- An adverse reaction which resembles anaphylaxis in its gravity and symptoms but which is not mediated by the immune system.
- **Anaphylaxis (anaphylactic reaction)**- A severe, rapidly progressing allergic reaction mediated by the immune system. “A hypersensitive state of the body to a foreign protein” (Churchill Livingstone Pocket Medical Dictionary). Symptoms include: progressive swelling of the lips, face and eyes, breathing difficulty, tongue or throat swelling, wheezing, asthma, light headedness, collapse...etc (RPAH Allergy Unit).
- **Angioedema**- A severe form of urticaria which may involve the skin of the face, hands or genitals and the mucous membranes of the mouth and throat.
- **ANZFA- Australia and New Zealand Food Authority**
- **Arthritis**- “Inflammation of one or more joints which swell, become warm to touch, are painful and are restricted to movement” (Churchill Livingstone Pocket Medical Dictionary).
- **Asthma**- Sudden difficulty in breathing characterised by wheezing caused by muscular spasm of the bronchi (lung). This reaction is triggered by the immune system.

- **Atopic Dermatitis**- A variety of infantile eczema which may be associated with asthma or hay fever.
- **Attention deficit hyperactivity syndrome (ADHS)**- Attention deficit hyperactivity disorder (ADHD) is a disorder characterized by impulsiveness, poor attention span and extreme restlessness.
- **Bronchospasm**- “Sudden constriction of the bronchial tubes due to contraction of involuntary plain muscle in their walls” (Churchill Livingstone Pocket Medical Dictionary).
- **Colic**- “Severe pain resulting from periodic spasm in an abdominal organ. Intestinal colic abnormal peristaltic movement of an irritated gut” (Churchill Livingstone Pocket Medical Dictionary).
- **CRS (Chinese Restaurant syndrome)**- A group of symptoms traditionally associated with the consumption of Chinese restaurant food and linked to MSG levels in these foods. Symptoms traditionally recorded include muscle tightness, dizziness and face flushes.
- **Dermatitis**- Inflammation of the skin.
- **Double blind-placebo controlled food challenge (DBPCFC)**- A diagnostic tool used for the assessment of food allergy and food intolerance. The investigation protocol involves a preliminary period (2-6 weeks) on a defined elimination diet. Upon improvement patients are given a battery of blind challenges which are expected to elicit symptoms if a sensitivity is present. Specific food intolerances are identified and dietary modifications introduced based on the individual’s circumstances.

- **Eczema**- Skin adverse reaction which begins with reddening of the skin, then vesicles appear. These rupture, forming crusts or leaving pits which exude serum. In the process of healing the area becomes scaly.
- **Elimination diet**- A type of diet which restricts the subject's range of intake by eliminating certain foods or substances from their normal diet. At Royal Prince Alfred Hospital Allergy Unit patients undergoing food sensitivity assessment follow a defined elimination diet. The substances omitted from the diet include salicylates, amines, preservatives and glutamates.
- **Erythema**- Reddening of the skin. "*Erythema multiforme* a form of toxic or allergic skin eruption which breaks out suddenly and last for days" (Churchill Livingstone Pocket Medical Dictionary).
- **FASEB**- Federation of American Societies for experimental biology
- **Food allergy**- "A term which has come to be used to cover all adverse reactions to food whether or not the underlying mechanism has been identified" (Churchill Livingstone Pocket Medical Dictionary). True food allergy is defined as any adverse reaction mediated by the immune system and caused, almost always, by the ingestion of food proteins (Yeung et al, 2000, Hefle and Taylor, 1999).
- **Food intolerance**- Any adverse food reaction of unknown mechanism affecting only certain parts of the population on an individual basis. Food intolerance is caused by the ingestion of certain food substances of non protein nature. Food intolerance includes metabolic food disorders, anaphylactoid reactions and idiosyncratic disorders (Taylor, 1999).
- **FSC**- Food standards Code (published by ANZFA, Commonwealth of Australia)

- **GABA** - Gamma-aminobutyric acid. An excitatory neurotransmitter, precursor of glutamate.
- **Hives**- See urticaria.
- **Idiosyncratic reaction**- This term is used to describe a variety of individual food reactions of an unknown nature. The causal relationship between consumption and consecutive physiological reaction remains unproven in some cases. Sulfite-induced asthma is a proven food idiosyncrasy. MSG sensitivity, on the other hand, remains unproven.
- **Immunity**- Is the “ability of the body to resist or eliminate potentially harmful foreign materials or abnormal cells” (Sherwood L, 1997). The body is able to defend itself from invading pathogens as well as identify and destroy abnormal cells.
- **Immunoglobulin (syn- antibodies)**- High molecular weigh proteins produced by lymphocytes which combine with antigens producing immunity.
- **Irritable bowel syndrome (IBS)**- “Unusual motility of both the small and large bowel which produces discomfort and intermittent pain, for which no organic cause can be found” (Churchill Livingstone Pocket Medical Dictionary).
- **Maillard reaction** – Browning oxidative reaction that causes protein degeneration.
- **Metabolic food disorder**- A food intolerant reaction occurring in subjects who have a metabolic disorder, which inhibits them from processing their food properly. Lactose intolerance and favism are examples of this disorder.

- **Migraine**- Recurrent localised headaches that are often associated with vomiting and visual sensory disturbances. It is thought to be caused by intracranial vasoconstriction.
- **MSG (Monosodium glutamate)** – The sodium salt of glutamic acid which main function is as a food additive. Glutamic acid, an amino acid, is also found naturally present in many foods including tomato, cheese and mushroom.
- **Neurotransmitter** – The chemical messenger that is released from a neuron in response to an action potential and influences another neuron with which it is anatomically linked.
- **Nutrients**- “Those substances needed for growth, metabolism and maintaining life. These must be supplied by the external environment as the human body is unable to synthesize them” (British Society for Nutritional Medicine).
- **Nutrition**- As defined by the British Society for Nutritional Medicine, nutrition is “the sum of processes involved in taking nutrients, assimilating and utilizing them”.
- **Oedema (edema)**- “Abnormal infiltration of tissues with fluid” (Churchill Livingstone Pocket Medical Dictionary).
- **Pruritus**- Itching (ocular pruritus- in the eye, palatal pruritus- in the roof of the mouth).
- **RAST (Radio-allergosorbent)**- Allergy testing method in which a patient's blood serum is combined with an allergen in a test tube to determine if serum antibodies react with the allergen.
- **Renal**- Regarding the liver.

- **Rheumatoid arthritis**- “A disease of unknown aetiology, characterised by a chronic poly-arthritis mainly affecting smaller peripheral joints, accompanied by general ill health and resulting eventually in varying degrees of crippling joint deformities and associated muscle wasting” (Churchill Livingstone Pocket Medical Dictionary).
- **Rhinorrhea**- Nasal discharge.
- **Urticaria** (*syn* **nettle rash, hives**)- “An allergic skin eruption characterised by multiple, circumscribed, smooth, raised, pinkish, itchy weals, developing very suddenly, usually lasting a few days and leaving no visible trait” (Churchill Livingstone Pocket Medical Dictionary).