Histamine Intolerance

Histamine and Seasickness

Reinhart Jarisch
Editor

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Editor
Reinhart Jarisch, MD
Floridsdorf Allergy Center
Vienna
Austria

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Preface 1

An incredible fact: 12 years have elapsed since the first German edition. The second edition had to be reprinted eight times.

It is an opportune moment to present the third edition with the most recent results of our research.

The investigation of seasickness in the German navy has been concluded, and has confirmed the efficacy of vitamin C chewable tablets.

A study concerning the significant condition of the irritable bowel has been completed.

Wine enthusiasts will be glad to read about the most recent results of our investigations in regard of red wine, sparkling wine and champagne. Particularly our analyses on red wine in respect of other biogenic amines have yielded exciting data. Some wines are marked by a typical distribution pattern, similar to the fingerprint in the study of crime. Some biogenic amines are responsible for the poor quality of wine, which makes it possible to identify certain poor-quality wines in the laboratory.

Wasp venom allergy is gaining increasing importance in recent times, especially because of rising death rates in recent years. These deaths are caused by anaphylactic shock.

Death rates are even higher among drug addicts, and probably also caused by anaphylaxis. In Austria alone, more than 200 persons died last year of drug abuse. The major significance of histamine research is illustrated by the fact that opiates like heroin release histamine.

By performing investigations in drug addicts we showed that the risk of anaphylaxis can be determined in advance. Thus, these investigations benefit other persons as well.

Last but not least, studies in patients who received specific allergy vaccination have proven the value of antihistamine premedication, which we have been using for several years now. It enhances the safety of treatment.

Antihistamine premedication was specifically included in the list of measures to prevent anaphylactic shock at the 2012 annual meeting of the American Academy of Allergy Asthma and Immunology (AAAAI) in Orlando.

The contents of the individual chapters have been updated and significant new results of research have been incorporated in this edition.

We have come another step closer to the aim of good health by expanding our knowledge and improving therapies.

Vienna, Austria
February 2014

Reinhart Jarisch, MD

Preface 2

… on Chapter 10 *by Wolfgang Hausner*

Sometime in the distant past, Man first ventured upon the sea and started to sail. When this occurred is rather uncertain, but we may assume with certainty that seasickness became apparent at this point in time.

Not all persons are affected by seasickness. In fact, the term itself is flexible. It is not as clearly defined as pregnancy, for instance. One is either pregnant or one is not.

Thus, two persons may assert, with good reason, that they are seasick: one experiences nausea for a short period of time, vomits a little, and feels much better afterwards, whereas the other vomits the living daylights out of his body and the stomach feels like an open wound tortured by regular and painful seizures. The person's regurgitations consist largely of gastric acid, the throat feels burned, and tears well up in the eyes.

A proverb sums up this pathetic condition quite aptly: One first fears one will die, and then fears one will not.

Over the years, several substances to counteract this condition have been tested and introduced in the market. Some alleviate the condition and are frequently associated with side effects, but a universal remedy does not exist.

Prof. Dr. Reinhart Jarisch has achieved a genuine breakthrough in this field. He has shown that the primary cause of seasickness is histamine – a fact that was not recognized until now. This information alone will not make a seasick person healthy, but Dr. Jarisch does not merely tell us why we become seasick. He also has a formula at hand which is simply astounding. I hope it will be utilized by as many persons as possible.

Austrian World Circum Navigator — Wolfgang Hausner

Contents

Contributors

Knut Brockow, MD Department of Dermatology and Allergology Biederstein, Technische Universität München, Munich, Germany

Manfred Götz, MD Department of Pediatric and Adolescent Medicine, Pulmonary and Infectious Diseases, Wilhelminenspital der Stadt Wien, Academic Teaching Hospital, Medical University of Vienna, Vienna, Austria

Wolfgang Hemmer, PhD Floridsdorf Allergy Center, Vienna, Austria

Reinhart Jarisch, MD Floridsdorf Allergy Center, Vienna, Austria

Christian Layritz, MD Department of Medicine 2, University Hospital of Erlangen, Erlangen, Germany

Verena Niederberger, MD Department of Otolaryngology (ENT), Medical University of Vienna, Vienna, Austria

Martin Raithel, MD Department of Medicine 1, University Hospital of Erlangen, Erlangen, Germany

Felix Wantke, MD Floridsdorf Allergy Center, Vienna, Austria

The Johns Hopkins Asthma and Allergy Center, Baltimore, MD, USA

Introduction

1

Reinhart Jarisch

Headache is usually assigned to the cervical spine or the weather. Laborious investigations such as X-rays of the cervical spine, computed tomography, or magnetic resonance tomography are used to determine the cause of the condition. In other words, we still live in a static rather than a dynamic age: pathophysiological changes are simply ignored. Consequently, patients are issued a normal report although they are ill and in turmoil.

A blocked nose is believed to be related to a deformation of the nasal septum, although 40 % of the population have this anatomical variant and many of them have no symptoms. A running nose is assigned to allergy even when allergy tests are negative. This occurs although we are well aware of the fact that some persons experience a "blocked nose" when they consume wine.

Bronchial asthma may be caused by so-called exogenous factors. In other words, it may be caused by environmental factors such as the house dust mite, pollen, epithelial tissues of animals, and mildew. It may also be caused by endogenous factors (arising from within) – also known as intrinsic factors – of unknown origin. Many patients have been long aware of the fact that red wine and even Emmental cheese or pizza with tuna fish may cause shortness of breath.

Furthermore, some drugs are inhibitors of diamine oxidase, which is the enzyme that degrades histamine and is specifically used for the treatment of asthma. This approach is used although we are well aware of the fact that histamine provocation is employed to obtain evidence of bronchial asthma and a positive test result helps to diagnose bronchial asthma.

When faced with gastric symptoms, the clinician performs gastroscopy in order to demonstrate the Helicobacter pylori bacterium, although a histamine-free diet would clarify the situation much more rapidly and economically.

R. Jarisch, MD
Floridsdorf Allergy Center, Franz-Jonas-Platz 8, Vienna A-1210, Austria
e-mail: jarisch@faz.at

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Cardiac arrhythmia in young adults gives rise to extensive cardiological investigations, usually with a negative outcome, followed by a statement to the effect that the patient is fine. However, the patient knows this is not the case.

Diarrhea and soft stools are a reason to perform an X-ray investigation of the bowel and laborious examinations of the bowel, many of which can be quite embarrassing and usually yield a negative result. One does not consider the fact that food intolerance might be a part of the problem. Even patients with Crohn's disease are simply given drugs, without taking the option of a histamine-free diet into account.

Low blood pressure is a typical symptom of histamine intolerance but is still accepted as "the will of God" in most cases. Besides, some drug allergies are actually an expression of histamine intolerance. Even patients with neurodermitis may suffer from it and may benefit from a histamine-free diet.

This book does not intend to invent a new type of medicine. Rather, it intends to fill a gap in medicine which has been pervaded by alternative medicine. The latter has been a clinical failure but a financial success in this sector. This book will help to explain medical processes in the style of Hugo Portisch (a very successful Austrian journalist who is able to explain complex matters of foreign policy in a way that any person would understand them) and to demonstrate a simple way of implementing those facts which patients are frequently aware of unconsciously.

Histamine and Biogenic Amines

2

Reinhart Jarisch, Felix Wantke, Martin Raithel,
and Wolfgang Hemmer

2.1 Histamine

Reinhart Jarisch

Histamine is a simple chemical substance with a molecular weight of 111 Da. It was discovered in the ergot in 1911. Many great discoveries in medicine are based on coincidences, errors, or sheer carelessness. This is true of histamine as well. Several years later it was discovered that the ergot investigated at the time was contaminated with histamine-producing bacteria and the ergot itself does not contain histamine.

This discovery is important in that it can be immediately extrapolated to foodstuffs. In other words, those types of food that undergo a process of maturation involving bacteria naturally contain high levels of histamine. In order to minimize the production of histamine in red wine while it is undergoing fermentation, one has now started to use cooled vats because bacteria grow faster at high temperatures and more slowly at low temperatures.

Histamine is the principal mediator (inflammatory substance) in allergic diseases such as allergic rhinitis (hay fever) or bronchial asthma. Besides, histamine is the classic triggering substance for urticaria (hives) and plays an important role in drug allergy and drug intolerance.

R. Jarisch, MD (✉) • F. Wantke, MD • W. Hemmer, PhD
Floridsdorf Allergy Center, Franz-Jonas-Platz 8, A-1210 Vienna, Austria
e-mail: jarisch@faz.at; wantke@faz.at; hemmer@faz.at

M. Raithel, MD
Department of Medicine, University Hospital of Erlangen,
Ulmenweg 18, D-91054 Erlangen, Germany
e-mail: martin.raithel@uk-erlangen.de

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2.1.1 Physiological (Natural) Effects

The human body produces histamine, which stimulates the secretion of gastric juices. Histamine has a vasodilating and therefore antihypertensive effect and acts as a neurotransmitter in the circadian rhythm and in controlling appetite, learning abilities, memory, emotions, neuroendocrine regulation, and immunomodulation.

Undesirable effects include headache, a blocked or runny nose, respiratory obstruction leading to bronchial asthma, tachycardia (rapid pulse), extrasystole (additional heart beats), even massive cardiac problems, gastrointestinal symptoms that may lead to soft stools or diarrhea, and low blood pressure (hypotension). Swelling below the eyelids is quite common. Urticarial exanthema (nettle rash) may occur occasionally. Histamine is produced by the human organism, is deposited in blood and tissue cells (basophilic granulocytes and mast cells), and is always available for immediate release. Besides, histamine may also enter the body from the outside. This occurs on the one hand through inhalation, such as during histamine provocation for the investigation of bronchial asthma, or orally by the ingestion of food or beverages containing histamine. After intestinal absorption, histamine reaches the bloodstream.

Histamine may also be injected into the skin during a so-called prick or intradermal test. It is known to cause wheals or erythema (reddening of the skin), similar to a mosquito bite.

Intravenous administration of histamine may trigger any of the above-mentioned symptoms. The most dreaded of these are splitting headaches, perceived by patients as a tearing sensation in the head.

While the reactions of histamine on the skin are rather harmless, such as itching or wheals, the entry of histamine into the bloodstream may have fatal effects.

A scientific investigation performed by Sattler and Lorenz (1990) elucidates this phenomenon. The authors investigated two groups of 15 pigs each, who were given a small quantity of alcohol and Emmental cheese through a gastric tube. One group of pigs was given an inhibitor of diamine oxide (a histamine-degrading enzyme, abbreviated to DAO) prior to this step. The group of pigs that received no previous treatment tolerated alcohol and cheese without difficulties. All pigs in whom the histamine-degrading enzyme had been blocked by medication experienced anaphylactic shock after the ingestion of alcohol and Emmental cheese; three pigs died. The experiment was then repeated. The pigs were again given an inhibitor of DAO, but additionally received an antidote in the form of drugs that could block the histamine receptor (H1 and H2 receptor blockers were administered). A small quantity of alcohol and Emmental cheese were then given, and the food containing histamine was tolerated without difficulty. Thus, it becomes obvious that histamine alone is not hazardous. Rather, it is the absence of appropriate degradation mechanisms that is responsible for the symptoms.

Stale meat contains large quantities of histamine. Very stale meat is known as carrion. It is tolerated without difficulties by animals like lions and even pigs. If humans were to eat such food, they would most certainly die. Lions tolerate such intake of histamine easily because their bodies have sufficient quantities of the histamine-degrading enzyme. The question that arises here is: Would it be possible

to increase the quantity of DAO in the human body and thus protect it specifically from allergic or allergy-like diseases?

There is a natural model for this phenomenon: pregnancy. During pregnancy a large quantity of DAO is produced in the placenta from the third month of gestation onward. The physiological purpose of this measure would be to protect the uterus (which is sensitive to histamine) from frequent exposure to histamine due to the ingestion of food. To ensure that the fetus is not passed out prematurely, the maternal body produces about 100–300 times more than the normal quantity of DAO. This protects the uterus from the effects of histamine and premature termination of pregnancy. It is also the reason why many allergic pregnant women report complete resolution of allergic diseases such as hay fever or asthma from the third month of pregnancy onward, which then return after delivery of the infant and expulsion of the afterbirth (also see chapter on Pregnancy and Allergy).

2.2 Diamine Oxidase

Felix Wantke

Almost every foodstuff contains histamine. The body has to protect itself effectively from histamine, which is a highly potent biological substance. Therefore, the first barrier to histamine exists in the intestine. The cells of the intestinal mucosa, known as enterocytes, produce and contain an enzyme which is able to degrade histamine (Baenzinger et al. 1994; Maslinski and Fogel 1991). The enzyme is known as diamine oxidase, has a molecular weight of 90,000 Dalton (Da), and contains copper. Diamine oxidase is mainly found in the small intestines, the liver, the kidneys, and white blood cells. In pregnant women, diamine oxidase is additionally formed in the placenta. Interestingly, pregnant women have about 100- to 300-fold higher diamine oxidase levels in the blood than nonpregnant women. Diamine oxidase is continuously produced and sectreted into the intestinal lumen. Therefore, in a healthy person, histamine-rich food is largely eradicated of histamine in the intestine. The remaining quantity of histamine is degraded by diamine oxidase when it passes through the intestinal mucosa. Histamine is degraded into imidazole acetaldehyde and then into imidazole acetic acid. The cofactor of diamine oxidase is 2,4,-trihydroxyphenylalanine quinone (McGrath et al. 2010).

Diamine oxidase is a sensitive enzyme. It can be inhibited by various substances, such as other amines, alcohol, its degradation product acetaldehyde, and various medications (Sattler et al. 1988, 1989). Several studies have shown that diamine oxidase is reduced in the presence of inflammatory bowel diseases. As mentioned earlier, diamine oxidase in the intestine is the first protective mechanism to shield the body from histamine in food. Diamine oxidase also protects the body from histamine formed physiologically by intestinal bacteria in the intestine (Sattler et al. 1988, 1989).

When histamine is absorbed despite these mechanisms, it is transported into the liver through the bloodstream. There, histamine is further degraded by N-methyltransferase, which is the second important histamine-degrading enzyme in the body. N-methyltransferase cleaves histamine into N-methylimidazole acetic

acid via N-methylhistamine and N-methylimidazole acetaldehyde. The main function of N-methyltransferase is to degrade histamine formed in the body (Maslinski and Fogel 1991). In patients who experience symptoms after consuming histamine-rich food, i.e., in patients with "histamine intolerance," the degradation of histamine in the bowel through the enzyme known as diamine oxidase is most likely disrupted (Sattler et al. 1988, 1989; Wantke et al. 1994, 1996, 1999). Two theories exist with regard to this phenomenon: on the one hand, these patients may have a diamine oxidase deficiency; the cells in their intestinal mucosa simply contain or produce far less diamine oxidase than the healthy intestinal mucosa cells of control subjects with no complaints. The second explanation is that diamine oxidase may be present in an inactive form and is therefore unable to fulfill its function of histamine degradation, thus causing a degradation deficit. A typical example of deficient activity of diamine oxidase is the inhibition of diamine oxidase by a drug. There are at least three types of histamine intolerance based on reduced diamine oxidase activity. Apparently, a very small number of people have a congenital diamine oxidase deficiency and do not lose it in the course of their lives. Secondly, in the course of an infection of the bowel mucosa, a person may experience a transient deficiency of diamine oxidase. Once the infection has subsided, the individual's levels of diamine oxidase return to normal. Thirdly, a person's diamine oxidase activity may be reduced exogenously (i.e., from the outside) after the administration of various substances that inhibit diamine oxidase. These primarily include alcohol (Sessa et al. 1984; Sessa and Perin 1994) and its degradation product acetaldehyde, certain foodstuffs with high levels of amines, and – especially important – a very large number of drugs (Sattler et al. 1988, 1989; Wantke et al. 1994, 1996, 1998, 1999). It should be noted that the second histamine-degrading enzyme – N-methyltransferase – is also adversely affected in the presence of insufficient histamine degradation by diamine oxidase. In this situation, degradation products of histamine inhibit N-methyltransferase (in other words, the intestinal barrier to histamine collapses) (Sattler et al. 1988, 1989). This explains why the inhibition of diamine oxidase in the bowel may disrupt a person's histamine metabolism, especially when the person consumes several foodstuffs containing histamine. No medication known at the present time is able to markedly increase a person's diamine oxidase activity. Injection of heparin increases diamine oxidase levels in serum transiently because diamine oxidase is released from the intestine (Daniele and Quaroni 1990). However, such treatment is neither realistic nor meaningful. In the in vitro setting, the antihistamine diphenhydramine was shown to increase diamine oxidase activity by 20 %.

2.3 Determination of Histamine, Diamine Oxidase, and Tryptase

Reinhart Jarisch

Histamine in plasma is determined by a radioimmunoassay manufactured by Immunotech Company in Marseille, France. After withdrawal of blood the test tube should be immediately immersed in ice-cold water and processed

(a refrigerated centrifuge is required), or it should be frozen. Normal values are below 0.3 ng/ml.

Diamine oxidase in plasma is determined by a radioimmunoassay (Tufvesson and Tryding 1969) of Sciotech Company in Tulln, Austria. A beta counter is used for measurement. Values below 11 are considered pathological. However, nonallergic and histamine-intolerant persons with no symptoms have values above 20.

Tryptase levels are determined by a radioimmunoassay of Phadia Company in Uppsala, Sweden. Values above 11.4 µg/ml are considered pathological by allergy specialists. Internists suspect mastocytosis from a level of 20 µg/ml onward.

2.4 Histamine Intolerance

Reinhart Jarisch

Histamine intolerance is defined as the intolerance of histamine ingested with food, caused by a deficiency of the histamine-degrading enzyme diamine oxidase (DAO) or an imbalance between histamine and DAO.

Based on our clinical experience, histamine intolerance is not a congenital condition. In other words, it is not caused by genetic factors but is probably an acquired disease. According to the data of a French study for which 33,000 persons with food intolerance were surveyed, about 1 % of the general population suffers from histamine intolerance. As 80 % of persons with the disease are women and around the age of 40 years, it appears to be related to a reduction of female sexual hormones. Moreover, certain drugs inhibit DAO and may, as our experience has shown, block the histamine-degrading enzyme for several weeks.

2.4.1 What Are the Actual Symptoms?

To start anatomically from the top and proceed downward, the patients have frequent headaches, even migraine, a blocked or runny nose, respiratory complaints or even bronchial asthma, cardiac arrhythmia in the form of tachycardia or extrasystole (rapid pulse or irregular pulse), gastrointestinal complaints which may lead to soft stools or diarrhea, chronic low blood pressure, and itching and wheals on the skin. Besides, some data indicate that dysmenorrhea (pain at the start of the menstrual cycle) may be caused by histamine. The above-mentioned facts show that histamine intolerance becomes clinically significant when the organism is burdened with more histamine than it is able to degrade at a certain point in time. As histamine is just a single substance, its source is of no importance for the organism. It may arise in the body itself, i.e., from blood or tissue cells (basophilic granulocytes and mast cells), or may be ingested with food. Besides, allergic diseases like hay fever or asthma supply the body with excessive quantities of histamine. As histamine is also able to multiply, a person may develop allergic or allergy-like symptoms when his/her histamine levels exceed the individual tolerance limit.

Case Report

One patient with hay fever was unable to tolerate a specific type of white wine during the pollen season, but did tolerate it very well after the pollen season. This explains the problem of histamine intolerance and why it is occasionally difficult to comprehend for the patient. A patient may well be able to tolerate cheese or wine alone, but not a combination of the two. The problem is compounded by the fact that organic or non-standardized foods contain different quantities of histamine.

Histamine is one of several so-called biogenic amines. The latter include putrescine, tyramine, tryptamine, cadaverine, spermine, and spermidine. Different quantities of these are present in food. All of the substances can be degraded by the histamine-degrading enzyme DAO. The consumption of a specific dish with relatively small quantities of histamine but a larger quantity of other biogenic amines may deplete a person's DAO reserves. Thus, no DAO is available for the degradation of histamine. Apart from the above-mentioned risk groups, some patients have a so-called pollen-associated food allergy, such as those with a birch pollen allergy do not tolerate apples, nuts, and carrots as well. In terms of statistics these patients are also subject to a higher risk of histamine intolerance (Jarisch et al. 1999). Besides, some types of food are so-called histamine liberators, i.e., they independently release histamine in an unspecific manner. Examples of these are strawberries or citrus fruits, which release large quantities of histamine. Some patients with mastocytosis release large quantities of histamine spontaneously from blood and tissue cells containing histamine and consequently demonstrate symptoms of allergy. These include persons with a history of contrast medium allergy. Fish poisoning (scombroid poisoning) may also be caused by these mechanisms (Morrow et al. 1991; Russell and Maretic 1986).

In other words, triggered by a hitherto unknown stimulus, some persons who ingest stale or partly stale fish (which contains a large quantity of histamine) tend to release greater quantities of histamine than those actually introduced into their bodies. This causes an enormously high concentration of histamine in the body, which may have life-threatening sequelae or even fatal consequences. The individual patient cares little as to whether his/her allergic disease is a genuine allergy or is caused by the unspecific release of histamine or a histamine degradation disorder. What does make a difference to the patient is the rapid establishment of an unequivocal diagnosis in order to find a suitable therapy. As the diagnosis of this condition may be quite complex and may involve the interaction of several mechanisms, the investigator must be very well informed about allergic and histamine-related reactions. Thus, the investigator must be a medical specialist working in the field of allergy.

2.5 Diagnosis of Histamine Intolerance

Reinhart Jarisch and Martin Raithel

2.5.1 Differential Diagnosis

An increasing number of patients have been complaining of food intolerance in recent times. The patient reports to the doctor with gastrointestinal symptoms, i.e., pain in the upper abdomen, flatulence and bloating, spasms, and diarrhea.

A *genuine food allergy* occurs in early childhood and resolves when the child enters primary school. In rare cases, genuine food allergies are found in adults as well.

Cross-reactions between pollen and food occur in adults.

Nonallergic reactions are known as intolerance.

Histamine intolerance is defined as an imbalance of the ratio between histamine and the histamine-degrading enzyme diamine oxidase in favor of histamine. The enzyme histamine N-methyltransferase is present in very many organs (Klocker et al. 2005), but is of lesser significance. It is dependent on proper functioning of DAO. Histamine N-methyltransferase may be inhibited by biogenic amines (Fuhr and Kownatzki 1986).

The frequency of intolerance in our patients (Floridsdorf Allergy Center in Vienna) may be divided into the following types:

1. Fructose malabsorption (FIT)
2. Sorbitol malabsorption
3. Histamine intolerance (HIT)
4. Lactose intolerance (LIT) (usually suspected to be a reflexive reaction)

FIT and LIT are diagnosed by the established procedure of hydrogen breath testing when the patient has a hydrogen gas-forming intestinal flora.

By performing an allergy test for food (prick test and prick-prick test with fresh food), including a test for inhaled cross-reacting pollen and tests for FIT, HIT, and LIT, we are able to clarify the condition in 87 % of our patients at the allergy center in Floridsdorf in Vienna.

2.5.2 Diagnosis

The diagnosis is established by medical history taking and the determination of histamine and diamine oxidase before and after a 14-day histamine-free diet.

2.5.2.1 Medical History

Patients report intolerance to histamine-containing food, such as red wine, hard cheese, salami, tuna fish, tomatoes, or sauerkraut.

One of the causes of the China restaurant syndrome is excessive histamine.

Red wine intolerance may be regarded as the “opinion leader” of HIT. However, red wine intolerance does not rule out HIT because some types of red wine, optimized by appropriate cellar technology, contain very little histamine.

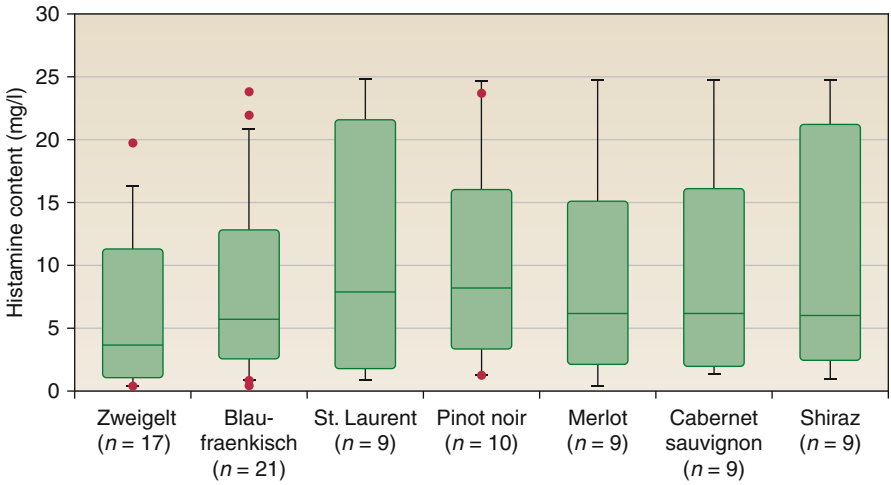

Fig. 2.1 Histamine content in Austrian red wines of different varieties ($n = 84$, all wines were of vintage 2004)

Histamine tests conducted on 100 types of Austrian red wine revealed markedly different levels ranging from high to low (Fig. 2.1). Basically, wine produced under favorable hygienic conditions is less prone to the development of undesirable bacteria and contains less histamine.

Histamine tests are already available for domestic use. These are employed to determine histamine levels of red wine at home (HistaSure TM Wine, Labor Diagnostika Nord GmbH & Co. KG).

Symptoms that may indicate histamine intolerance (from the cranial to the caudal aspect) are the following:

- Migraine
- Lower lid swelling without consuming alcohol
- A runny and/or blocked nose postprandially
- Bronchial asthma
- Postprandial tachycardia
- Diarrhea
- Hypotension (This is a typical symptom because histamine dilates the majority of vessels. As one would expect, the blockade of histidine decarboxylase in animal experiments leads to hypertension (Campos et al. 1996).)
- Further isolated or more rare symptoms (see the following chapters)

However, as the above-mentioned symptoms may have other causes, the latter should also be investigated and ruled out.

In 80 % of cases the typical histamine-intolerant patient is female and 40 ± 5 years old.

Table 2.1 Data registered before and after a histamine-free diet ($n=99$)

	Responders ($n=41$) before the diet	Responders ($n=41$) after the diet	Nonresponders ($n=58$) before the diet	Nonresponders ($n=58$) after the diet
Histamine (ng/ml)	0.22	0.18 ($p<0.02$)	0.25	0.22 ($p=0.1$ n.s.)
DAO U/l	8.2	13.9 ($p<0.0001$)	12.8	14 ($p<0.1$ n.s.)

DAO diamine oxidase

2.5.2.2 Negative Histamine Provocation

After medical history taking and initial blood sampling for histamine and DAO, the patient is asked to maintain a histamine-free diet for 14 days. A second blood sample is then taken to determine histamine and DAO levels, and the patient is asked about his/her symptoms.

In a patient with HIT, histamine levels are increased and/or DAO levels reduced at the first blood test.

After a 14-day diet, the patient's histamine levels – if high at primary testing – will have returned to one half of the initial levels, and his/her DAO level will have increased. Simultaneously, the patient's symptoms will have reduced by a half, or he/she will have no symptoms at all (Table 2.1). If the patient has no HIT, his/her blood levels remain the same and the symptoms will be unchanged (Jarisch 2012).

2.5.2.3 Determination of Histamine and Methylhistamine in Urine

Determination of methylhistamine and histamine in urine is another method of identifying persons with HIT. The advantage of urinalysis is that it first shows whether large quantities of histamine are formed, released, and metabolized in the body. This may be the case in patients with various allergies, inflammations, mastocytosis, histamine intolerance, bone marrow changes, etc. (Raithel et al. 2002; Schwab et al. 2002). Owing to its large mucosal surface of about 250 m^2, the gastrointestinal tract is responsible for the greatest part of the excretion of methylhistamine in the human body. The excretion of methylhistamine in healthy persons is largely stable in various age groups; it is below 6.5 µg/mmol creatinine × m^2 body surface area (Fig. 2.2). The ratio between the excretion of methylhistamine and histamine in 12-h urine collection is on average 5:1 (range, 3–8: 1). Methylhistamine is regarded as a stable product of histamine degradation and can be reliably measured in the urine sample by tandem mass spectroscopy (Labor Buchwald/Schultis, Weiden/Opf., Germany) (Raithel et al. 2002; Winterkamp et al. 2002).

In case of a suspected histamine-mediated reaction, one determines methylhistamine and histamine in urine during a two-day balanced diet and a two-day potato-rice diet (negative control). Although this standardized function test is not specific for HIT, food allergy, or mastocytosis, it is very useful to prove the presence of increased histamine resorption, production, metabolization, and excretion under a specific diet (Raithel et al. 2002; Weidenhiller et al. 2002). As HIT is very

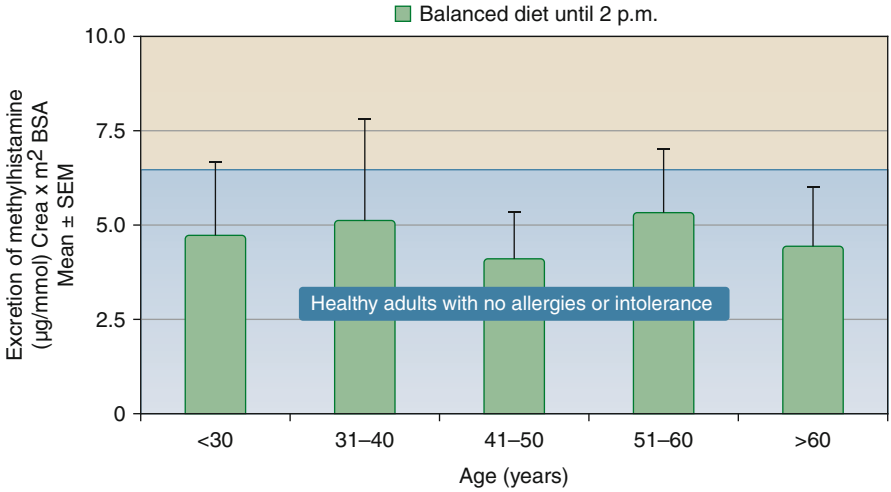

Fig. 2.2 Methylhistamine levels in 12-h urine in various age groups of healthy persons. Normal levels <6.5; women: 4.3 ± 1.6 ($n = 32$); men: 5.2 ± 2.3 ($n = 22$); Gaussian normal distribution. The methylhistamine/histamine ratio is 3–8:1. *BSA* body surface area, *SEM* standard error of the mean

frequently associated with (in part clinically non-apparent) disorders of GIT, and the formed or absorbed quantity of histamine in GIT can be very clearly registered by methylhistamine in urine, this urine test may be used as a method of detection (Weidenhiller et al. 2002; Winterkamp et al. 2002, 2003). Histamine in the intestines reaches the liver through the portal vein. After being methylated in the liver, it is eliminated in large quantities by persons with histamine intolerance. Simultaneously, depending on the person's hepatic function, absorbed or secreted quantities of histamine, plasma volume, and other factors, one finds a greater or lesser elevation of histamine levels in plasma and urine. The ratio between methylhistamine and histamine changes. Free histamine levels increase. Given a ratio <3 between methylhistamine and histamine, one suspects HIT.

In more than 90 % of cases, persons with evident food allergy (FA) or HIT eliminate more than 6.5 µg methylhistamine/mmol creatinine × m^2 body surface area (Raithel et al. 2002; Weidenhiller et al. 2002). Switching to a hypoallergenic elimination diet (low-histamine potato and/or rice diet) is commonly followed by lesser excretion of methylhistamine, normalization of the patient's methylhistamine/histamine ratio, and resolution of his/her clinical symptoms. Although this test demonstrates the presence of HIT or FA with high probability, the physician must rule out other significant differential diagnoses as well (also refer to Table 2.9, Differential diagnoses) (Befus et al. 1999; Raithel et al. 2002; Schwab et al. 2002; Winterkamp et al. 2002).

2.5.2.4 Histamine in Stool

The same is true for the determination of histamine in stool, which has not been evaluated thoroughly thus far and mainly reflects a person's level of active luminal

histamine. In contrast to the urine or plasma test, histamine levels in stool do not reflect a person's systemic burden, but merely show local levels of histamine in the bowel lumen. The normal quantity of histamine in stool is reported to be about 60 µg per gram of stool. Persons who ingest large quantities of histamine-containing food may achieve high levels of histamine in stool. Therefore, HIT can be suspected only in the presence of clinical symptoms as well. As shown in the table on differential diagnosis and as described in Sect. 3.6 titled *Diarrhea and Allergic Gastrointestinal Diseases*, one must perform further investigations in this setting as well because any of several diseases with local effects on the gastrointestinal tract (such as small intestinal bacterial overgrowth or infection) (Befus et al. 1999), chronic diseases, or diseases located outside the intestines (e.g., mastocytosis) may be present. Thus, HIT cannot be diagnosed by the determination of histamine in stool or DAO in plasma alone.

Rather, the above-mentioned function tests and modification of the patient's diet (a histamine-free or a potato-rice diet) are useful for a more detailed evaluation. In persons who clearly respond to a histamine-free diet in terms of resolution of their symptoms, normalization of plasma histamine levels, an increase in plasma DAO levels (Jarisch 2012), and/or normalization of their methylhistamine/histamine ratio in urine after a potato-rice diet (Raithel et al. 2002), one need not perform oral provocation with histamine in the majority of cases. In ambiguous cases, when the symptoms do not resolve or when histamine levels are partly resolved, one has to use the diagnostic gold standard of double-blind placebo-controlled histamine provocation.

2.6 Origin of Histamine

Wolfgang Hemmer and Felix Wantke

Histamine, a small nitrogenous substance with a molecular weight of 111 Da, is one of several so-called biogenic amines. The latter constitute a class of chemical compounds which exert manifold biological effects in animal as well as plant tissues. Histamine is actively formed in the human body and is involved in the regulation of various body functions, such as the secretion of gastric juices, cell growth, cell differentiation, and wound healing. In specific regions of the brain, histamine serves as an important neurotransmitter that regulates the circadian rhythm (it makes a person more alert) and promotes learning and memory. The most well-known aspect of histamine is its central role in allergic reactions. It binds to histamine receptors and causes contraction of smooth muscles (intestines, lung, uterus) and dilatation of blood vessels and causes blood plasma to diffuse into surrounding tissue (skin, mucous membranes). Clinical sequelae of these phenomena include flush, itching, hives (urticaria), swelling, dyspnea, and a drop in blood pressure.

Sometimes, histamine may also trigger "allergy-like" symptoms after ingestion. Many types of food contain histamine, although in physiologically insignificant quantities. However, a small number of foodstuffs have very high concentrations of

histamine. Thus, depending on a person's tolerance level, even the ingestion of small quantities of these foods may be associated with intolerance reactions. The following is a list of foodstuffs containing especially large quantities of histamine.

- Fish: e.g., tuna fish, mackerel, and anchovy
- Cheese: e.g., Emmental, Camembert, and Roquefort
- Hard cured sausage: e.g., salami and raw ham
- Vegetables: e.g., sauerkraut
- Alcoholic beverages: e.g., red wine

A well-known and vivid example of histamine production in plants is stinging nettle. The itching and painful skin reactions that occur when a person touches the plant are triggered by small hair which contains serotonin, acetylcholine, formic acid, and also histamine. The number of vegetable-based foods with high histamine levels is limited. In Central Europe, tomatoes and their processed products (such as ketchup) are prime among these, followed by spinach, eggplant, and avocado. However, the large majority of foodstuffs containing high amounts of histamine do not primarily or "naturally" contain histamine. Fresh foods such as fresh meat, fresh fish, eggs, or milk contain insignificant quantities of histamine.

Why do some foods contain so much histamine? The reason is that histamine is synthesized in these foodstuffs in the course of processing, preservation, and ripening, as well as natural aging processes (autolysis). Various microorganisms (usually bacteria) are involved in these processes. These microorganisms produce histamine and other biogenic amines in the course of their own metabolism, which then accumulate in food.

The basic product for histamine is the amino acid histidine, which is a part of all animal and plant proteins. Through a single chemical step of conversion (decarboxylation), histamine develops from histidine. Analogously, other biogenic amines develop from other amino acids. These amines may also, in part, unfold their pharmacological effects in the human body, such as tyramine from tyrosine, putrescine from ornithine, or phenylethylamine from phenylalanine. Obviously, histamine is no food additive, but all types of food whose production or ripening involves microorganisms in a direct or indirect way are usually rich in histamine and other biogenic amines. Such food includes all fermented foodstuffs such as milk products (cheese!), sauerkraut, wine and beer, vinegar or soy sauce, and meat products manufactured by drying, salting, or smoking, such as raw sausages like salami or raw ham. In the latter instance, microorganisms (especially lactobacilli) are significantly involved in the aromatization and preservation of food intended for human consumption.

Any increase in the period of ripening or shelf life naturally leads to higher histamine levels in these foods and also gives rise to the rule that products stored for a very long time tend to contain large quantities of histamine. A further important factor involved in the emergence of histamine is the type of bacteria or bacterial strains specifically involved in the process of ripening, because not all types or strains are able to develop histamine. During the production of wine, for instance, raw wines are now "inoculated" to an increasing extent with bacterial strains that were proven to form no, or very little, histamine. Thus, the final product contains much lower levels of histamine.

Table 2.2 Histamine levels in various samples of Emmental, Gouda, Cheddar, and Tilsit cheese. The wide range of histamine levels within a single type of cheese is worthy of note

	Emmental	Gouda	Cheddar	Tilsit
	Histamine content in mg/kg	Histamine content in mg/kg	Histamine content in mg/kg	Histamine content in mg/kg
Sample 1	<0.1	29.5	15.3	37.2
Sample 2	25.0	41.0	21.8	50.0
Sample 3	66.0	54.0	1,300.0	60.2
Sample 4	110.0	180.0		
Sample 5	215.0			
Sample 6	235.0			
Sample 7	307.0			
Sample 8	438.6			
Sample 9	555.0			
Sample 10	2,500.0			

Source: Häberle (1987), Lembke (1978), Pechanek et al. (1980), Pechanek et al. (1983)

These facts explain why histamine levels of a specific food may vary considerably. The histamine content of Emmental cheese from a supermarket may range between <0.1 mg/kg and 2,500 mg/kg (Table 2.2). One may find cheese with very low quantities of histamine placed next to histamine "bombs" containing 2,500 mg/kg, which certainly cannot be recommended for consumption. Flagrantly high histamine levels are a reliable indicator of complete spoilage of food. Poor hygiene in food processing from the outset may favor this phenomenon.

The freshness of the basic product and its germ content are also worthy of note. One aspect is the germ content of milk during the production of cheese. Owing to the natural microflora of raw milk, cheese made from raw milk usually contains more histamine than cheese produced from pasteurized milk. Extremely high histamine levels are probably caused by inappropriate storage or excessive ripening after controlled ripening of the product during its production, regardless of whether this occurs in a shop or one's personal household.

Fish and seafood (mussels, crabs, squid) are especially prone to rapid spoilage due to the excessive formation of histamine. Very high histamine levels have been reported in some species of fish, especially those of the mackerel family (Scombroidei). These include tuna fish, mackerel, and swordfish, whose meat spoils very easily (scombroid intoxication). In many cases, typical fish poisoning is probably, at least in part, histamine poisoning. Fish meat is very rich in histidine, the amino acid from which histamine is formed. In addition, fish is a very perishable product. Fish caught from warm waters, such as tuna fish, is a special problem. Tuna fish weighs more than 100 kg and lives in warm water. If not cooled or processed immediately, it may achieve a body temperature of 35–40 °C after being hauled out of the water. Such temperatures are ideal conditions for the growth of bacteria in the intestines of the fish (bacteria naturally live in the intestines of every fish). As tuna fish meat is especially rich in histidine, enormous quantities of histamine may accumulate due to bacterial activity. Table 2.3 shows the rapid spoilage of fish at room temperature.

Table 2.3 Increase of histamine levels during spoilage. Storage of hake at 4 and 30 °C (based on Pechanek et al. 1980). Data given in mg/kg

	Storage temperature	
Time point	4 °C	30 °C
Start of test	2.4	<0.1
Day 1	2.7	0.6
Day 2	3.6	1.3
Day 3	4.0	23.5

The continuity of the cold chain and rapid processing of the catch are absolute prerequisites for achieving low histamine levels. Immediate freezing at temperatures below −20 °C is the best way of protecting fish meat from the new formation of histamine. It is more effective than preservation. It should be noted that histamine is a thermostable substance. It cannot be destroyed by freezing or heating (baking, frying, boiling, microwave). Basically, the histamine levels of food produced by an "organic" process are not lower than those of food produced on an industrial scale. In fact, controlled hygienic conditions and the use of purebred yeast or bacteria in large enterprises may reduce the risk of undesirable microbial growth and the associated intensive production of histamine.

Even in the case of wine and other alcoholic beverages, histamine develops in the process of fermentation and subsequent ripening. Grapes, freshly squeezed grape juice, and young wine contain no or very little histamine, although histamine is occasionally reported to be the cause of a person's complaints. The exact time point when histamine levels increase during the development of wine has not been fully clarified yet. We have partly contradictory data in this regard. The largest quantities of histamine appear to be formed by specific bacteria during the so-called process of malolactic fermentation and not during the actual process of alcoholic fermentation itself. This process, during which the existing malic acid is transformed into the less acidic lactic acid and carbon dioxide, is a typical feature of red wine. For this reason red wine usually has much higher histamine levels than white wine. Histamine-forming bacteria involved in malolactic fermentation (*Pediococcus*, *Lactobacillus*) thrive best when wine contains a relatively small quantity of acids or when its acid content is low from the outset. Less histamine develops in very acidic wine because degradation mainly occurs by the action of *Leuconostoc oenos* – a bacterium which, depending on the strain, forms little or almost no histamine. Histamine levels can be kept low even in red wine by the application of appropriate technology in the wine making process. Controlled malolactic fermentation achieved by active addition of suitable *Leuconostoc oenos* strains has been usually associated with significantly lower histamine levels in wine than found in wine which underwent a "spontaneous," i.e., uncontrolled malolactic fermentation (Fig. 2.3). However, even controlled malolactic fermentation may be associated with high amine levels, and not all wines that underwent a spontaneous malolactic fermentation have high histamine levels. Recently, attempts have been made to use specific strains of *Lactobacillus plantarum* for malolactic fermentation. These strains have the ability to oxidatively degrade the existing biogenic amines (Capozzi et al. 2012).

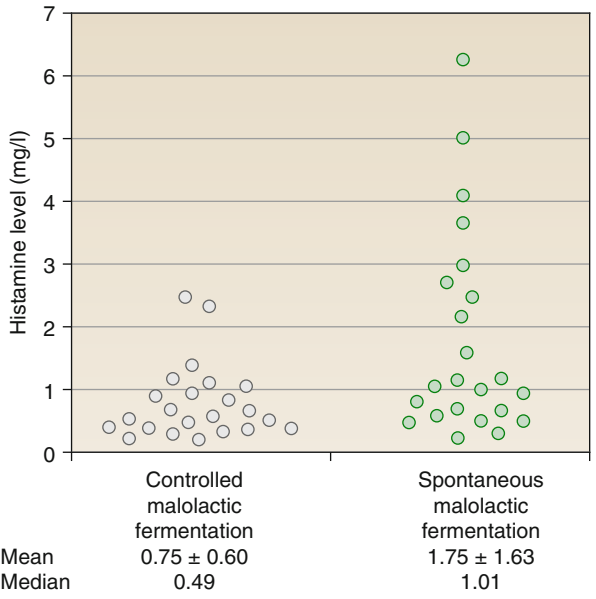

Fig. 2.3 Histamine levels in Austrian red wine after controlled ($n=23$) or spontaneous malolactic fermentation ($n=23$) (according to Gappmaier 2000). Controlled degradation: mean 0.75 ± 0.60, median 0.419; spontaneous malolactic fermentation: mean 1.75 ± 1.63, median 1.01

In addition to histamine, other biogenic amines are found in wine. In fact, some of these are present in larger quantities than histamine. Several examinations have proven that some of these other biogenic amines are closely correlated with histamine. In other words, they occur in high concentrations when histamine is also present in large quantities and occur in low concentrations when histamine levels are low. Therefore, all of these amines seem to be derived from the same source and are formed jointly. Specifically, a close correlation was observed between histamine, putrescine, tyramine, and cadaverine (Konakovsky et al. 2011). On the other hand, phenylethylamine, an amine also held responsible for intolerance reactions, occurs entirely independent of histamine, but is closely related to isoamylamine.

Both occur in high concentrations, especially in red wine of poor quality and even in white wine (Eder et al. 2002). Similar mechanisms appear to exist for other foodstuffs like cheese and raw sausages. As a result, food rich in histamine usually contains other biogenic amines as well. The practical implications are quite important because the two monoamines tyramine and phenylethylamine may, per se, trigger intolerance reactions, especially after drinking wine (Lüthy and Schlatter 1983). Intolerance to "histamine-rich" food does not necessarily mean that the person experiences adverse reactions to histamine alone. Thus, the diagnosis of histamine intolerance may be rendered difficult from the clinical point of view. In cases of adverse reactions to tyramine or phenylethylamine, one should always consider the fact that these amines bind to receptors other than histamine and are metabolized differently. Therefore, many diagnostic and therapeutic measures oriented to histamine are of limited use with regard to these amines.

2.7 Histamine Levels in Food

Felix Wantke

2.7.1 Cheese

While fresh milk and fresh milk products such as buttermilk, yogurt, cream, or cream cheese preparations only contain small quantities of histamine, cheese that takes several weeks to ripen nearly always contains a substantial amount of histamine. Therefore, next in rank after alcoholic beverages, cheese is the most common trigger of symptoms. Depending on the mode of manufacture and storage, histamine levels may vary markedly in one and the same type of cheese. Therefore, it is difficult to make a clear division between "harmless" types of cheese and "questionable" ones (Tables 2.4 and 2.5) (Pechanek et al. 1983; Souci et al. 1994; Wantke et al. 1993). However, one may basically formulate guidelines as to how the intake of histamine can be kept within limits without having to forgo cheese altogether:

Table 2.4 Guidelines for histamine levels of milk products

	Histamine mg/kg	Maximum value
Milk, yogurt		
Pasteurized milk	0.3–0.7	
Extended shelf life milk	0.8	
Condensed milk	1.2	
Yogurt	2,1	
Hard cheese		
Emmental cheese	<10–500	2,500
Bergkäse (Alpine type of cheese)	<10–1,200	
Parmesan	<10–580	
Cheddar	<10–60	1,300
Blue mold and blue-green mold cheese		
Austrian blue and blue-green mold cheese	<10–80	
Stilton	150[a]	
Roquefort	2,000[a]	
Semihard cheese		
Gouda cheese	<10–200	500
Edam cheese	<10–150	500
Raclette cheese	<10–150	
Stangenkäse (a type of semihard cheese)	<10–150	
Fontina cheese	<10–100	
Bierkäse cheese	<10–80	
Tilsit cheese	<10–60	
Dutch-type cheese	<10–60	
Mondsee cheese	<10–30	
Monte Nero	19.2[a]	
Trappist cheese	<10	
Geheimratskäse (a Dutch-type cheese)	<10	
Mild full-fat cheese	<10	

Table 2.4 (continued)

	Histamine mg/kg	Maximum value
Soft cheese		
Camembert, Brie	<10–300	600
Schlosskäse cheese	<10–100	
Romadur, Limburger	<10–70	
Harz cheese	390[a]	
Acid curd cheese		
Harz cheese	<10–50	390
Sheep's milk cheese	17.4[a]	

[a]Individual measurements

Table 2.5 Frequency and percentage of histamine loads in various types of cheese

Histamine load				
Histamine mg/kg	Moderate <20	High 20–100	Very high 100–500	Extremely high >500
Hard cheese	10 %	25 %	35 %	30 %
Semi-chard cheese	70 %	20 %	7 %	3 %
Mild full-fat cheese	100 %			
White mold cheese	40 %	20 %	20 %	20 %
Blue and blue-green mold cheese	70 %	30 %		
Red-smear cheese	50 %	40 %	10 %	
Quargel (similar to Harz cheese)	75 %	25 %		

Source: Pechanek et al. (1983)
How frequently should one anticipate high levels of histamine? 220 random samples of Austrian cheese were examined

- As a rule, avoid all those types of cheese that take a long time to ripen. These are primarily hard cheeses like Emmental, Bergkäse (a group of cheeses produced in the Alps), Alpine cheese, Parmesan, and in part even Cheddar cheese.
- Avoid those types of cheese that have ripened over a long period of time (such as "old" Gouda cheese) and opt for semihard cheese that ripens in a short period of time.
- With regard to mold-ripened cheeses, avoid extremely ripe or overripe pieces, such as semiliquid Camembert.
- Cheese made from raw milk (i.e., non-pasteurized mild) tends to contain a larger quantity of histamine due to the flora of raw milk. Cheese made from raw milk must be labeled as such. This includes many types of hard cheese and nearly all farm-gate cheeses.
- Mild full-fat cheese, Dutch-type cheese, and *Geheimratskäse* (another Dutch-type cheese) contain less histamine. These types of cheese also have lower levels of other biogenic amines.
- We lack data for processed cheese. However, as it is largely produced from Emmental cheese, its histamine content is probably quite high.
- Curd cheese, cottage cheese, and other cream cheese products are largely free of histamine.

2.7.2 Chocolate

Chocolate does not contain histamine, but does contain other biogenic amines, such as tyramine and phenylethylamine. These amines are derived from cocoa and mainly develop during fermentation and subsequent roasting. Therefore, to minimize one's intake of histamine through food, one must take cocoa drinks and of course chocolate in various desserts (pastries, biscuits, ice cream, etc.) into account. Tyramine and phenylethylamine, which are partly present in cheese, raw sausages, and spoiled meat as well, are discussed as specific causes of migraine.

2.7.3 Meat and Meat Products

Fresh meat contains no or very little histamine. Raw sausages and raw ham are produced by drying raw meat, usually with the aid of salt (dry curing) and fire curing. Microorganisms, primarily lactobacilli, play an important role in the aromatization and preservation of these products. Raw sausages and raw ham should be marketed after a minimum statutory period of ripening. During the period of ripening, biogenic amines develop to various extents (Table 2.6) (Pechanek et al. 1983; Souci et al. 1994; Wantke et al. 1993). This group of food products includes raw sausages such as salami, Kantwurst, Cervelat, Knappseer, Landjäger, and Mettwurst sausage and raw hams such as Westphalian ham, Bündner meat, Parma ham, Tyrol bacon, Hamburg bacon, and Osso Collo. Even fresh meat and meat products intended for early consumption, if stored inappropriately or for too long, may spoil and develop histamine.

Table 2.6 Guidelines for histamine levels in meat and sausage products

Food	Age	Histamine mg/kg
Beef	Fresh	<2.5
Chicken	Fresh	<1
Minced meat	Fresh	<1
	3–4 days old	<1–8
Fried sausage	Fresh	<1
	5 days old	1–6
Raw sausages/raw ham		
Salami		<10–280
Cervelat sausage		<10–100
Knappseer sausage		<10–100
Kantwurst		<10–50
Mettwurst	First week	<1
	Second week	<1–10
	Third to fourth weeks	<1–80
Osso Collo		20–300
Westphalian ham		40–270
Graubünden meat		6.6

Table 2.7 Guidelines for histamine levels in fish and fish products

Type of food	Histamine in mg/kg	Maximum value
Fish		
Fish, freshly caught	0	
Fish, spoiled		to 13,000
Frozen food	0–5	1,500
Frozen fish, breaded	0–7	?
Fish products		
Full preserves (sardines, anchovy, tuna fish)	0–35	1,500
Mackerel, smoked	0–300	?
Young salted herring, Bismarck herring	0–10	?

2.7.4 Fish and Fish Products

Like fresh meat, fresh fish contains a very small quantity of biogenic amines. However, it is prone to very rapid microbial spoilage when histamine develops in large quantities. When processed properly, frozen foods and canned fish hardly develop histamine. However, measurements have shown that at least in some instances one may anticipate significant quantities of histamine. This may be a sign of delayed processing or, in frozen fish, due to interruption of the cold chain. Owing to the chemical structure of their muscles, fish related to the mackerel (mackerel, tuna fish, bonito) are subject to very marked and rapid formation of histamine (Table 2.7).

Histamine is also formed in fish products preserved with salt (such as young salted herring) and/or fire curing (kippers, smoked rock salmon). Marinated fish is indirectly loaded with histamine because of the histamine contained in many marinades (vinegar!); these include Bismarck herrings and rollmops. Seafood (mussels, crabs, shrimps, squid) is subject to the same phenomena as fish. For practical purposes it might be useful to know that even in cases of mild and barely perceptible changes in the taste of fish or seafood, one may anticipate high levels of histamine and other biogenic amines (especially putrescine and cadaverine).

2.7.5 Vegetables, Fruit, and Nuts

Very few vegetables have naturally high histamine levels, but histamine may be a component of fermented vegetable foods (such as sauerkraut) or when food is pickled in vinegar-based marinade for preservation (e.g., pickled cucumbers, mixed pickles) (Table 2.8) (Jarisch and Wantke 1996; Pechanek et al. 1983; Souci et al. 1994; Wantke et al. 1993).

Table 2.8 Histamine levels in vegetables and vinegar

Type of food	Histamine in mg/l
Vinegar	
Cider vinegar	0.02
Distilled vinegar	0.5
Red wine vinegar	4.0
Vegetables	
Tomato (ketchup)	22
Spinach	30–60
Eggplant	26
Avocado	23
Sauerkraut	10–200

2.7.6 Other Biogenic Amines in Food, Histamine Liberators

Many foodstuffs contain other substances similar to histamine (so-called biogenic amines), which may also cause undesirable effects. These include tyramine, putrescine, phenylethylamine, cadaverine, spermine, and spermidine. These substances are commonly found in conjunction with histamine because, like histamine, they also result from microbial activity. However, some foodstuffs (e.g., chocolate, citrus fruits) contain other amines and no histamine but may still trigger symptoms. The reason is that some of these amines (tyramine, serotonin) resemble histamine in that they may exert a direct effect on blood vessels, while others (putrescine) possibly unfold their effect by hindering histamine degradation. In the laboratory (cell culture), cadaverine, spermine, and spermidine have been known to release histamine from specific cells that contain histamine. Thus, they act as histamine liberators. However, their practical significance is not clear yet. Several other foodstuffs are believed to release histamine in the body. The most well known of these are strawberries and citrus fruits. Experience has shown that patients with wine or cheese intolerance demonstrate intolerance to such histamine liberators remarkably often. This is possibly due to the additive effect of exogenous histamine in food and endogenous histamine released in the body. Thus, when testing a (hist)amine-free diet, it would be helpful to also delete potential histamine liberators from one's bill of fare.

2.8 Histamine in Alcoholic Beverages

Wolfgang Hemmer

Alcoholic beverages are the most common triggers of intolerance reactions in the general population. In a recent Danish study, as many as 9.9 % of 4,000 surveyed persons reported that they are unable to tolerate alcoholic beverages (Linneberg et al. 2007). Women (60 %) and persons with allergic rhinoconjunctivitis or asthma are affected remarkably often. The primary symptoms of alcohol intolerance,

which may occur just a few minutes after its consumption, include flush (redness of the face), a blocked or runny nose, a sensation of heat, itching, headache, and cardiovascular problems (tachycardia, hypotension).

Although any type of alcohol may cause symptoms and a very large number of patients report intolerance to several alcoholic beverages, red wine is undoubtedly by far the most common trigger (Linneberg et al. 2007; Nihlen et al. 2005). This concurs very well with the fact that, among all alcoholic beverages, red wine contains by far the greatest quantity of histamine. The main reason is that red wine is subject to malolactic fermentation after the alcoholic fermentation process. During this process, histamine and other biogenic amines are produced by bacteria. White wine, on the other hand, is usually separated from yeast quite early after fermentation. Further microbial activity in raw wine is arrested by sulfurization.

2.8.1 Red Wine

The highest levels of histamine in red wine have been 30 mg/l and more, but usual levels are well below this limit. In our own investigation of 100 Austrian red wines of high quality, the mean histamine level was 6–8 mg/l. The highest level was 27 mg/l and the lowest 0.5 mg/l (Konakovsky et al. 2011) (Fig. 2.4). Red wines produced from different varieties of grapes do not differ significantly in terms of their histamine levels. Rather, each variety demonstrates a wide range of values from low to very high; no specific variety can be referred to as a reliable low histamine one. Furthermore, "simple" or cheap wines do not by any means contain more histamine than expensive quality wines.

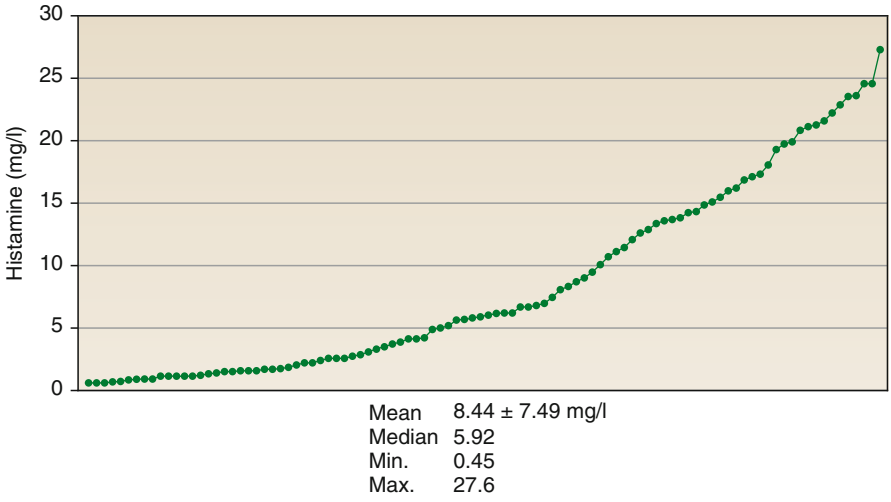

Fig. 2.4 Histamine levels in 100 Austrian red wines of high quality

The possibility to minimize the production of histamine by controlling malolactic fermentation has been referred to in Sect. 3.6. Recently some winegrowers have tried to further reduce the emergence of histamine during the maturation of wine by means of specific fining and filtering procedures or to remove histamine afterward from the final product. Thus, they were able to produce red wines whose histamine levels were similar to those of white wine (below 0.1 mg/l). However, one cannot rule out the fact that this might compromise the taste of wine because important flavor carriers might be partly removed in the process. The basic and interesting question that arises here is: Do high concentrations of histamine and other biogenic amines have a negative impact on the sensorial quality of wine? High histamine levels are frequently interpreted as a sign of incorrect pressing or poor cellar hygiene. Therefore, one may expect wines with very high values to be deficient in taste. However, this appears to be incorrect. Our own investigation of red wines evaluated earlier by professional wine experts showed that wines with high histamine levels (and simultaneously high tyramine and putrescine levels) tended to be rated better than those with low histamine levels. However, this does not mean that wines with low histamine levels have a poorer taste, but that a high production of histamine is not necessarily associated with deficient taste. It would not be justified to conclude, in all cases, that such wines were produced under poor hygienic conditions. Predictors of poor quality ratings are high concentrations of phenylethylamine and isoamylamine, which have also been observed in many defective musts and white wines and which develop at an early point in time, i.e., during the process of fermentation (Eder et al. 2002; Konakovsky et al. 2011).

2.8.2 White Wine

The Austrian white wines we investigated were all below the level of 0.1 mg/l. In dry white wines cultivated by the classical mode, e.g., Grüner Veltliner or Welschriesling, histamine values are usually below 10 µg/l (0.01 mg/l). These wines may be considered to be free of histamine. However, white wines subjected to malolactic fermentation like red wine may achieve histamine levels above 1 mg/l. Sweet wines (dessert wines, port wine, sherry, etc.) also tend to have higher histamine levels because of the longer period of ripening for grapes and the manufacturing process.

2.8.3 Sparkling Wines and Champagne

The sparkling wines we investigated revealed remarkable differences. We found consistently low histamine levels below 0.1 mg/l (in fact, usually below $\leq$0.01 mg/l) in Austrian brands, whereas French champagnes and German sparkling wines varied between 0.1 and 1 mg/l (and were partly higher). Thus, the levels were higher by a factor of 10–100 (Fig. 2.5). French Crémants were all uniformly around 0.05–0.1 mg/l. Although histamine levels may vary in the various vintages, these differences were quite reproducible. Obviously, red sparkling wines have high histamine levels as do red wines.

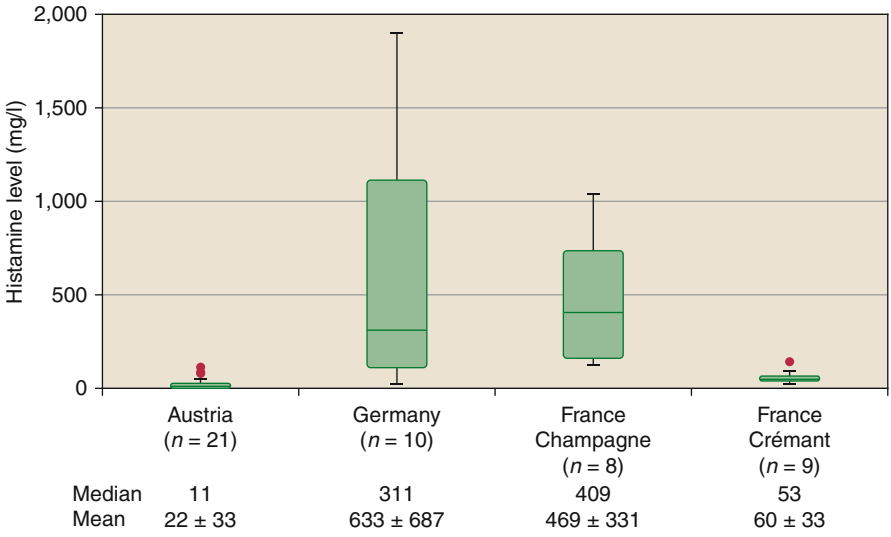

Fig. 2.5 Comparison of histamine levels in Austrian, German, and French sparkling wines. Data in µg/l (1,000 µg/l = 1 mg/l)

2.8.4 Beer

Top-fermented beer (wheat beer) tends to have higher histamine levels than bottom-fermented ones. This is especially true of the yeast-clouded type because it still contains the yeast sediment which contains a large amount of histamine. Even nonalcoholic beer contains histamine. Its histamine levels are similar to those of normal bottom-fermented beer because they are fermented in a similar manner and dealcoholized later.

2.8.5 Hard Liquor

Little is known about histamine levels in hard liquor. According to our clinical experience, hard liquor is rarely mentioned as a cause of intolerance reactions. This may be due to the fact that these beverages are consumed in small quantities or that they are rarely consumed by the patients, who are mainly women. Due to the small size of the histamine molecule – histamine is barely 2½ times heavier than ethyl alcohol – it may be assumed, in any case, that certain quantities of the histamine probably contained in the mash pass into the distillate.

2.8.6 Why Does Histamine in Alcoholic Beverages Have a Particularly Strong Effect?

Although alcoholic beverages contain small quantities of histamine compared to cheese, raw sausages, or spoiled fish, they are most frequently mentioned as the causes of symptoms. The possible reasons are manifold.

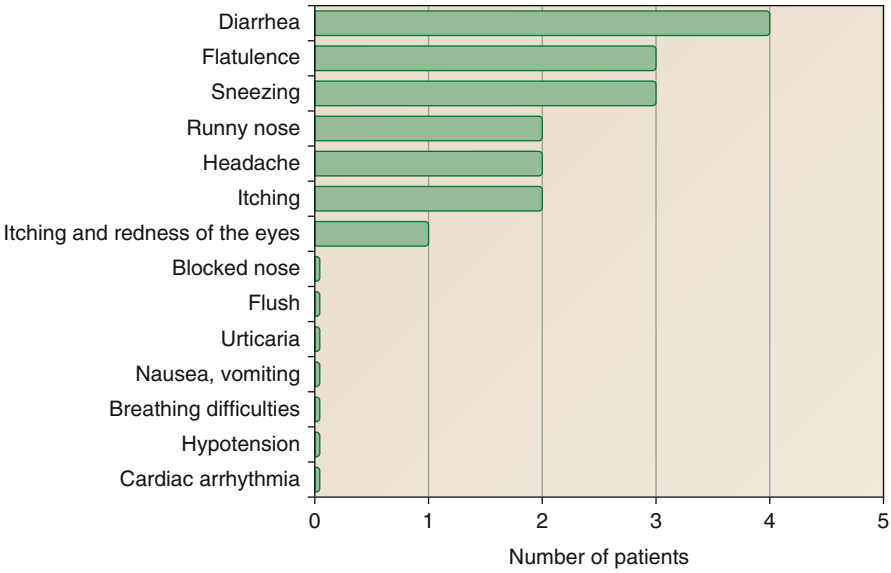

Fig. 2.6 Symptoms in ten healthy female controls after double-blind placebo-controlled oral provocation with 75 mg of histamine. Four of ten probands reacted 3–12 h after the administration of histamine in terms of spontaneous diarrhea and other symptoms. Only one test person developed sneezing attacks and a runny nose within 60 min (Source: Wöhrl et al. 2004)

First, histamine is absorbed in the gut from fluids much more easily than from solid food. This causes a brief but intensive local exposure to histamine in the intestinal mucosa. In provocation studies it was found that five of ten healthy test persons with no clinical intolerance of food containing histamine experienced symptoms after the intake of 75 mg of histamine – which corresponds to about 200 g of a hard cheese with a high histamine level – when histamine was administered to the person in fasting condition and in liquid form. Interestingly, the majority of reactions – prime among these were watery stools – occurred a few hours after administration of the test solution, possibly after non-absorbed and non-metabolized histamine had reached the large bowel (Fig. 2.6) (Wöhrl et al. 2004). Other investigations revealed that healthy controls show a three- to four-fold increase in diamine oxidase activity (DAO, a histamine-degrading enzyme) in the peripheral blood 15 min after they had consumed 125 ml of red wine which had been supplemented with 2.5 mg of histamine, although they experienced no subjective or objective symptoms (Wantke et al. 1999). This short-lived but measurable activation of histamine degradation mechanisms by relatively small quantities of histamine also underlines the potential significance of its intake in liquid form.

Besides, alcohol per se increases the permeability of the intestinal mucosa so that large quantities of histamine – whether from the alcoholic beverage itself or from simultaneously ingested food – could enter the bloodstream. This is in agreement with the observation that the simultaneous consumption of alcohol and food rich in histamine (such as cheese plus red wine) very frequently causes symptoms.

We do not know yet whether alcohol or its degradation products additionally cause specific inhibition of DAO (which is asserted quite often). This would imply that a large quantity of histamine may enter the body through the intestinal mucosa. In animal experiments it was found that, after feeding alcohol, DAO activity was reduced in gastric and duodenal tissue but remained the same in the remaining small intestines and, in fact, increased in the liver and kidney. As this was associated with a rapid increase of DAO levels in the bowel lumen, the activity drop observed in some portions of the intestines is due to alcohol-induced secretion of DAO rather than specific inhibition of the enzyme. Additionally, the intake of alcohol appears to stimulate the neogenesis/synthesis of DAO in the hours that follow (Sessa et al. 1984a, b), similar to the condition observed after the administration of large quantities of putrescine and spermidine (Perin et al. 1986).

2.8.7 Other Causes of Wine and Alcohol Intolerance

Intolerance of red wine is frequently considered a supreme example of histamine intolerance and the cardinal clinical symptom leading to the diagnosis. Regardless of histamine's significant role in alcoholic beverages, this simplification is not justified because wine and alcohol intolerance may be caused by other phenomena unrelated to histamine. Some of these are very rare, while others may be quite common. In general, *red wine and alcohol intolerance* is probably a heterogeneous condition caused by various pathomechanisms which lead to intolerance reactions either independent of each other or even in a synergistic manner.

Alcohol itself (ethyl alcohol, ethanol) might play an important causal role in intolerance reactions to alcoholic beverages. This phenomenon is well known in the Japanese, Chinese, and in other Asians, who are extremely prone to such hypersensitivity reactions. The cause is a mutation in the gene coding for aldehyde dehydrogenase 2 (ALDH2). This enzyme normally degrades a toxic substance, namely, *acetaldehyde*, which is formed before from ethanol by the action of alcohol dehydrogenase (ADH) (Goedde et al. 1983). However, the mutated enzyme (ALDH2-487lys allele) is unable to do so. This causes acetaldehyde levels in the body to rise very rapidly when the person consumes alcohol. In higher concentrations, acetaldehyde was found to release histamine from mast cells and basophils, leading to characteristic symptoms such as flush, cardiac arrhythmia, asthma, etc. (Matsuse et al. 2007). Approximately 50 % of all Asians are carriers of this genetic variant. Thus, the final reason for this type of alcohol intolerance is secondary release of histamine through degradation products of ethanol, caused by genetic factors. It is not because of the histamine contained in the alcoholic beverage itself. The crucial role of histamine as a mediator substance in this setting is demonstrated by the fact that the symptoms can be markedly alleviated by the administration of H1 and H2 receptor blockers (Miller et al. 1987). Interestingly, H2 receptor blockers (cimetidine) proved to be much more effective than H1 blockers for this purpose. One explanation for this phenomenon could be the fact that cimetidine is also a potent inhibitor of alcohol dehydrogenase and thus prevents excessively rapid accumulation of acetaldehyde.

This genetic variant, which is common in Asians, is extremely rare in Europe and therefore does not serve as a plausible explanation for the high prevalence of alcohol intolerance in the general population. Interestingly, however, recent investigations in alcohol-intolerant Europeans demonstrated other genetic variants of aldehyde dehydrogenase (ALDH1b1) which are significantly associated with alcohol intolerance (Linneberg et al. 2010). Additionally, polymorphisms of alcohol dehydrogenase could be involved; its first step is to convert ethanol into acetaldehyde. Some enzyme variants of alcohol dehydrogenase are able to do this very rapidly. This may lead to a temporary increase in acetaldehyde levels, associated with the above-mentioned consequences, because the accumulating acetaldehyde cannot be metabolized/detoxified fast enough. In fact, genetic analyses have confirmed that carriers of these genetic variants suffer from alcohol intolerance twice as often as do other individuals (Linneberg et al. 2010).

Taken together, these findings indicate that intolerance reactions to wine and other alcoholic beverages among Europeans may be more frequently caused by genetic differences in alcohol metabolism rather than by the histamine content of these beverages. This is supported by double-blind placebo-controlled provocation studies, in which more than one half of patients with a history of wine and/or beer intolerance also reacted to pure ethanol (Ehlers et al. 1996; Ehlers et al. 2002). Likewise, other studies in patients with red wine intolerance also showed that the probands developed symptoms to all tested red wines equally often, regardless of whether their histamine content was high or low (Kanny et al. 2001).

It should be added here that the treatment of alcoholics with disulfiram (tetraethylthiuram disulfide, Antabus®) is also based on the accumulation of acetaldehyde. Disulfiram is a strong inhibitor of ALDH2. The intentional five- to ten-fold increase in acetaldehyde after the intake of alcohol leads to intolerance reactions such as redness of the skin, nausea, headache, cardiac arrhythmia, and a drop in blood pressure. The toxicity of some types of mushrooms (such as crumble cap or inky cap) when ingested together with alcoholic beverages is caused by the fact that coprin, the toxin contained in the mushrooms, inhibits ALDH2.

A further, at least theoretical, cause of histamine release after the consumption of alcoholic beverages could be the specific effects of alcohol on the gastric mucosa. It was found that beer and especially red wine (but not hard liquor) stimulate the production of *gastrin* to a marked extent. Following intensive production of histamine in enterochromaffin-like cells (ECL) of the stomach, this not only raises the production of gastric acids but also measurably increases histamine levels in blood within efferent veins of the stomach (Chari et al. 1993, Intorre et al. 1996). To what extent these increases in histamine levels persist after passing the liver, and could be a factor involved in the known symptoms of wine intolerance, is not established yet. The gastrin-stimulating ingredients in wine and beer are probably specific organic acids originating from glucose degradation during the process of fermentation or bitter acids derived from hops. Biogenic amines and ethanol, which are always present in wine and beer, are not involved in this phenomenon. Only at very low concentrations (<4 %) in the stomach, ethanol causes a direct moderate activation of gastric acid production, but does not increase the production of gastrin (Chari et al. 1993).

Finally, it should be mentioned that alcohol itself has a vasodilating effect and may cause immediate symptoms such as redness of the skin, a sensation of heat, or headache.

In addition to histamine, other biogenic amines such as *tyramine or phenylethylamine* have been occasionally suspected to be causes of intolerance reactions (especially migraine) to wine and other alcoholic beverages. A small number of older experimental studies exist on this subject, which provide no, or no convincing, evidence of this association (Jansen et al. 2003).

Sulfite, which has been accused of being a significant cause of intolerance reactions after the consumption of wine (especially as a trigger of acute asthmatic attacks in asthma patients) also appears to be of limited relevance. The mechanism by which sulfite triggers hypersensitivity reactions in these persons has not been clarified yet. It has been attributed to the inhalation of gaseous sulfur dioxide (SO_2), formed out of sulfur salts, which may cause bronchial constriction through cholinergic reflexes. In a similar way, SO_2 formed in the stomach might trigger symptoms like abdominal pain or diarrhea by increasing intestinal motility. In rare cases the person may have true allergic reactions.

However, the few controlled provocation studies performed thus far in asthmatics with wine intolerance failed to show a consistent effect of sulfite or could demonstrate such effects in just a small percentage of subjects and when using very high sulfite concentrations (300 mg/l) (Vally u. Thompson 2001; Vally et al. 2007). Thus, hypersensitivity to sulfite appears to be of minor significance in the context of wine intolerance. According to the existing EU regulations, sulfite concentrations ≥300 mg/l are only permitted in dessert wines (*Auslese*, *Beerenauslese*, ice wine, etc.). The upper limit for dry white wines is 200 mg/l while that for red wines is just 150 mg/l.

In very rare cases, intolerance reactions to wine may be genuine *allergic reactions* (Schad et al. 2005; Sbornik et al. 2007). The allergens responsible for this condition are so-called lipid transfer proteins (LTP). The term refers to a group of food allergens which are proven causes of anaphylactic reactions to the most diverse vegetable foods. Due to their significant stability against enzymatic degradation, small quantities of LTP are apparently able to survive the manufacturing process of wine.

A person may also develop allergic reactions to animal proteins used as *fining agents* in the production of wine and beer, such as egg white/lysozyme, milk/casein, fish gelatin, or fish collagen. However, cases of this type have never been documented thus far and are generally very unlikely, because very slight traces of these proteins remain in the final product. Some authors believe such reactions may possibly occur in persons with a very severe egg allergy, who are usually children (Weber et al. 2007; Kirschner et al. 2009). The same is true for alternative vegetable protein-based fining agents, such as wheat gluten. Using sensitive methods, traces of these proteins can be found in some wines treated in this manner, but it is doubtful whether this residual allergenicity is sufficient to elicit hypersensitivity reactions in persons with a wheat allergy (such as those with IgE antibodies to omega-5 gliadin/Tri a 19) (Restani et al. 2002). Wines of this type are harmless for persons with celiac disease.

2.9 How It All Started: Wine Intolerance

Reinhart Jarisch

A lot of things in Vienna start with a visit to the *Heuriger* or a wine tavern. The same is true for histamine intolerance. Several years ago I observed visitors to the *Heuriger* who complained of "a blocked nose" after consuming just a small quantity of wine. At the time I had no explanation for this clinical phenomenon. Besides, there is always one person at a Heuriger table who only drinks mineral water although he is not the driver. As I see it, this person simply does not tolerate wine. In other words, he obviously suffers from histamine intolerance. The third observation was that some persons like to drink *Schilcher* wine. It is an extremely interesting wine, described as sour by those who have no knowledge of wine and dry by connoisseurs. Today I know that Schilcher wine contains very little histamine. That is apparently the reason why it is given preference by some wine enthusiasts or is almost the sole alternative for those who wish to enjoy wine despite histamine intolerance.

To summarize, some people complain of a blocked nose when they take wine. Some people do not drink wine at all because they say they dislike its taste. Yet others only drink "sour wine," apparently because they do not tolerate histamine. This observation has definitely been made by many others as well. However, to my knowledge, no appropriate conclusions have been drawn yet.

If one wishes to study histamine intolerance, one needs a catchy object of investigation – a kind of opinion leader (or key feature) – which we believe we have found in red wine. Therefore, as the first step we investigated various wines in respect of their histamine levels and found that particularly red wines, but also late harvest wines, dessert wines, and French champagne, contain a large quantity of histamine. Interestingly, differences were found in beer as well. In fact, even some brands of nonalcoholic beer are not free of histamine. The only exception that lives up to its name, contains no alcohol and almost no histamine, bears the apt name of *Null Komma Josef* (Austrian slang for "none at all") from the Viennese brewery known as Ottakringer. As man does not live from wine alone, the next logical step was to identify foodstuffs that also contain high levels of histamine. We then made a list of 20 most common luxury foods with high histamine levels and named it the "Top 20 list." It aroused a great deal of interest among colleagues, but naturally among patients as well, and became well known throughout Austria within a short period of time. This led to the conclusion that there is an actual need for a histamine-free diet list. This is interesting because we have a large number of diet lists for allergy patients, but they are by far not as widespread or popular as this "Top 20 list."

Owing to the clinical success of this histamine-free diet list, we published the preliminary data in "Hautarzt" (The Dermatologist), which is the best German-language scientific journal for dermatological diseases. We then published it in the English language in the second-best allergy journal of the world, namely, *Clinical and Experimental Allergy*. Surprisingly, this study was not merely accepted;

it also received an editorial which mainly stated that the editors of the journal regard the histamine-free diet as a hypothesis concerning histamine intolerance, to be regarded as a first step. The editors compared our work:

- To the use of acetylsalicylic acid in willow bark for combating fever and pain a long time before chemical knowledge about aspirin came into existence
- To the administration of morphine to combat pain a long time before morphine receptors were discovered in the brain
- To the diagnosis and treatment of immediate-type allergic reactions a long time before allergology was made socially acceptable in the scientific sense by the demonstration of IgE antibodies

Apart from being glad about this honor, it served as a challenge to undertake the next logical step, namely, to establish appropriate blood investigations which could help to diagnose histamine intolerance. Thus, it was necessary to introduce established assays for the determination of histamine levels in plasma and DAO levels in serum. However, our simple hypothetical diagnostic procedure could not be fully translated into the reality of medicine because all patients did not follow the conceived pattern of elevated histamine levels and reduced DAO levels. We learned to live with the fact that some parameters could be pathological, and we also learned to live with the fact – without understanding it – that some patients have only one or the other symptom despite an identical clinical constellation and despite the same exposure to biogenic amines. To put it plainly, it is still not clear why some patients react in terms of headache alone, whereas others develop cardiac arrhythmia, asthma, diarrhea, and hypotension.

Apparently, every person has a predestined weak organ which presents as the signal organ in the event of disorders.

In the meantime we have modified our list of histamine-free foodstuffs. A major and consistent contributing factor was the assistance of patients who sought our advice and noticed that the list was quite useful but deficient in some aspects. Therefore, we eventually landed with the now third improved version, which does not only include food with high histamine levels but also takes the fact into account that other biogenic amines may be of significance in causing histamine intolerance.

Besides, this list also takes into account the fact that one should avoid foodstuffs which may act as histamine liberators. Our most recent clinical experience indicates that this list is now "perfect" to the extent that anything can be perfect (Fig. 2.7).

Once histamine tolerance had been established and described, the next question obviously was the following: Why was this disease not discovered earlier? Why was no attention drawn to it previously? Why have we apparently overlooked this disease so far?

All that so-called conventional medicine overlooks immediately becomes the prey of alternative medicine-based attempts to offer therapy. Thus, it is no surprise that the symptoms listed in this book, which may be caused by histamine intolerance, constitute the daily bread of doctors working in the field of alternative medicine (Wantke et al. 1993).

However, in view of the fact that medical knowledge is doubled every 5 years, it was only a question of time until science would draw appropriate conclusions from

Histamine-free food:

In hypersensitive persons, the ingestion of food containing large quantities of histamine or histamine liberators may lead to allergy-like symptoms, such as a sensation of heat, redness of the face, headache, gastrointestinal symptoms (including diarrhea), nettle rash, fatigue, hypotension, cardiac arrhythmia, or asthma attacks. Therefore, persons sensitive to histamine should avoid food containing histamine.

The most common triggers of symptoms are the following:

1. Alcoholic beverages – especially red wine
2. Cheese – especially hard varieties like Emmental cheese
3. Chocolate – food containing cocoa
4. Salami – raw sausages, raw ham
5. Nuts
6. Fish
7. Tomatoes, sauerkraut, spinach
8. Citrus fruits, kiwi, strawberries

☐ You should *very strictly adhere to a histamine-free diet for at least 2 weeks!*

☐ After this time you may tentatively include food containing histamine in your diet.

Selected list of the most important types of food that contain histamine

Cheese	Histamine (mg/kg) from–to (max.)
Emmental, Cheddar	<10–500 (2500)
Bergksäe	<10–0210
Pamesanr	<10–085
Camembert, Brie	<10–300 (600)
Gouda, Edam, Stangenkäse	<10–200 (900)
Schlosskäse, Romadur	<10–100
Blue and blue-green mold cheese	<10–80
Tilsit cheese, "Geheimratskäse", mild full-fat cheese	<10–60
Quargel (similar to Harz cheese)	<10–50

Alcoholic beverages	Histamine (mg/kg) from–to (max.)
Austrian red wines	<0.5–20 (28)
Austrian white wines	0.005–0.1
Austrian sparkling wine	0.005–0.1
German sparkling wine	0.1–2
Champagne	0.1–1
Beer	0.02–0.25
Wheat beer	0.12–0.3
Non-alcoholic beer	0.015–0.04

Vinegar	Histamine (mg/kg) from–to (max.)
Red wine vinegar	4

Raw sausage/Raw ham	Histamine (mg/kg) from–to (max.)
Salami, Milan sausage, Landjäger (spicy) sausage, smoked sausage	<10–280
Cervelat sausage, Kantwurst	<10–100
Westphalian ham, Osso Collo, sausages with garlic, Mettwurst	<10–300

Fish/fish products	Histamine (mg/kg) from–to (max.)
Spoiled fish	to 13000
Full preserves (e.g. tuna fish, anchovy, sardines, herrings, smoked mackerel)	0–15 (300)
Fish sauces	3–8

Vegetables	Histamine (mg/kg) from–to (max.)
Tomatoes (ketchup)	22
Sauerkraut	10–200
Spinach	30–60
Avocado	23
Eggplant	26

Histamine liberators: Cocoa and chocolate (except white chocolate), citrus fruits (oranges, grapefruit), nuts (especially walnuts), strawberries

Histamine-free food:

- potatoes, rice, pasta, bread, bread rolls,
- all types of meat, fresh or deep-frozen: turkey, beef, pork, chicken, etc.; eggs,
- all types of vegetables not mentioned above, such as green salad, carrots, zucchini, etc.
- all types of ham that do not require a period of ripening: burgundy ham, pressed ham, turkey ham, etc.
- all types of sausages that do not require a period of ripening, pork sausage, meat loaf, wiener, fried sausages, etc.
- all milk products that do not require a period of ripening: yogurt, all types of milk, fresh cheese, curd

Fig. 2.7 Patient information sheet for a histamine-free diet

the existing results of investigations with the aim of helping patients effectively on the basis of well-founded scientific data.

The question that persists is: Why was this disease overlooked? Histamine intolerance is problematic because the symptoms are similar to those of allergy, but the appropriate allergy tests, especially those concerning food intolerance, are negative.

Three frustrated persons remain:

- The patient who knows that he has complaints but is given a negative allergy test
- The referring physician who knows that the patient has a disorder but is confronted with a condition he is unable to resolve
- The physician who tests for allergy and knows he has been unable to locate the cause of the patient's allergy-like symptoms

Now one should be aware of the fact that an allergen with IgE antibodies sensitized to the allergen is required for a typical so-called type I allergy. This is essential to cause the body to release histamine. In mathematical terms, it could be based on the following formula:

$$\text{allergen} + \text{IgE antibody} = \text{histamine}$$

This formula is very reminiscent of school. We all recall our mathematics class and the formula $A^2+B^2=C^2$. It was a time when we proved our brilliance by rote learning rather than by thinking. Possibly, learning by rote moved on to university, where a person is again mainly called upon to exercise his histrionic abilities of learning by rote rather than his/her thinking abilities.

If one were to replace the word *allergen* with *food containing histamine* in the above formula, and consider the fact that an antibody is interesting and important in terms of immunology but does not make a person ill, what remains is the simple equation that any foodstuff containing histamine exerts the effect of histamine. However, not all people react to food containing histamine. Therefore, there must be two different groups of persons: those who are able to degrade histamine by the corresponding enzyme and those who are unable to do this in adequate measure. In other words, the classical allergy formula needs to be modified in that histamine exerts an effect when a person ingests food or an alcoholic beverage containing histamine and also has a deficiency of the histamine-degrading enzyme. Immediately, this knowledge makes it clear why histamine exerts its effect in two ways, i.e., the allergy-based or immunological pathway and the second pathway based on an enzyme defect. For the patient, however, it makes no difference how he/she develops a surplus of histamine. In both cases the person suffers from the effect of histamine. The first step from the above data was, logically, to order the patient with clinical symptoms of a histamine effect to adhere to a histamine-free diet and to see whether one could achieve clinical improvement merely by avoiding these types of food. We investigated patients with food or wine intolerance, bronchial asthma, headache or migraine, urticaria, rhinopathy, and atopic dermatitis (in all 100 patients) and registered a statistically significant improvement of clinical symptoms by adherence to a histamine-free diet only in persons with food or wine intolerance and headache or migraine. This outcome was no surprise. On the other hand, the nonachievement of statistical significance in the other diseases is not discouraging because, in all instances, a few patients derived benefits. This was true of more than

50 % of cases in some instances. Considering the fact that histamine is one of the most important inflammatory mediators in many diseases, it was no surprise to note that reducing exogenous histamine led to clinical improvement.

Let us return to our "opinion leader," which is wine. Red wine is particularly suitable for such examination because of its high histamine content. In a few studies we investigated whether normal persons and histamine-intolerant persons react to wine (Wantke et al. 1994, 1996). In the so-called red wine provocation test, probands or patients were given a specific quantity of histamine, and their histamine levels were measured after 15 and 30 min. A normal person has a low baseline histamine level, a mild increase after 15 min, and a return to the baseline level after 30 min. Patients with histamine intolerance have a high baseline value compared to normal persons and show a continuous increase in blood histamine levels after being exposed to histamine in wine.

In a specific case, one glass of red wine led to audible shortness of breath within a few minutes in a patient with asthma.

However, the problem with regard to wine is that it contains other biogenic amines in addition to histamine, as well as sulfur dioxide. Thus, the actual cause of a person's wine intolerance could not be determined.

In one study we performed wine provocation tests, noted clinical symptoms, and performed the same provocation a few days later after administering premedication in the form of an antihistaminic agent (H1 receptor blocker). The premedication suppressed all symptoms except for drowsiness, which may well have been due to alcohol itself. The above mentioned makes it quite clear that patients with histamine intolerance who are unable to tolerate wine containing histamine may yet enjoy wine by taking premedication in the form of an H1 receptor blocker, without having to reckon with clinical symptoms in the following hours.

In a further study we investigated the driving fitness of healthy persons who had taken white wine or red wine. We used a low-histamine white wine and a histamine-rich red wine and performed the investigation on a driving simulator in cooperation with ÖAMTC (Österreichischer Automobil-, Motorrad- und Touring Club: a motor drivers' club in Austria) (Wantke et al. 1999).

The anticipated result was that those persons who had taken histamine-rich red wine had much poorer driving skills and performed more driving errors than did persons who had taken white wine.

In fact, all probands who had taken white wine said it felt as if they had taken mineral water. They felt absolutely fine, whereas those who had taken red wine said they felt dizzy and their driving fitness was impaired. Some even said they were unable to drive and would never steer a motor vehicle in their condition.

However, an interesting fact was that those who took red wine reacted just slightly poorer than they had before taking wine, whereas those who took white wine and felt clinically normal made much more driving errors.

This outcome was entirely contradictory to our expectations. Our interpretation was that a person who realizes he/she is unable to drive or who realizes that his/her driving fitness is impaired is able to compensate for the condition to the extent that

he/she makes very few driving errors, but persons who fail to perceive the effect of alcohol are misled easily and therefore much more prone to accidents. Although the outcome was very evident in numerical terms, it failed to achieve statistical significance – obviously because of the small number of cases. The study has not been published so far because a scientific journal usually publishes only those studies that eventually demonstrate a statistical difference.

However, I believe the results are still quite impressive for daily use. These data could also mean that taking a glass of wine mixed with soda is by no means entirely safe. Obviously, a person forfeits any personal control over his/her driving fitness because one hardly tastes wine in the wine plus mineral water mixture, which may result in greater unfitness to drive than the driver would be aware of. In order to achieve the success we expected from this study, it would be necessary to perform it again on histamine-intolerant persons rather than normal persons. However, I doubt whether persons who already know that they do not tolerate alcohol would be willing to undergo this exertion even for a medical experiment. Our wine studies aroused a great deal of interest and response. An American journal requested us to publish our red wine provocation tests and asked us to write a short review about wine and headache (Jarisch and Wantke 1996; Wantke et al. 1994).

The fact that histamine intolerance is a rather common disease is demonstrated by the fact that, at many lectures within the country and abroad, I was frequently confronted with doctors (especially women) who said "I have that problem too."

The above mentioned leads to the conclusion that immediate-type allergies may be divided into three groups for teaching purposes: one group with the classical immediate allergy caused by specific IgE antibodies, a second group with histamine intolerance, and a third group which is a combination of the first two.

In the meantime we noticed that histamine intolerance caused by an excessive histamine load, such as drinking a bottle of red wine, lasts for just a day or two. This is in contrast to histamine intolerance caused by the intake of medications which are inhibitors of DAO. Thus, histamine intolerance may again be divided into two subgroups, i.e., one type is caused by food and resolves quite rapidly when the person adheres to a suitable diet, while the second type is caused by medications. Here the blockade of DAO may persist for a longer period of time.

In a wine maximization test, we investigated whether healthy probands who receive large quantities of histamine react in terms of their histamine and DAO parameters. We found that, despite the administration of increasing and large quantities of histamine, the persons' histamine levels remained the same. In these persons, histamine was adequately degraded by DAO. However, a maximal histamine load is followed by a peak increase in DAO levels. The body apparently presses out all residues of DAO, which is not produced in the small intestines alone, but in various other tissues as well (Wantke et al. 1999). This phenomenon is very similar to anaphylactic shock which is not accompanied by high histamine and low DAO levels as one would expect, but is accompanied by high histamine levels and simultaneous increases in DAO. This may be regarded as an inadequate attempt of the body to come to terms with the symptoms of shock.

2.10 Differential Diagnosis: Food Allergy (FA)

Wolfgang Hemmer

Patients with symptoms of histamine intolerance consult a doctor because they believe that they are unable to tolerate certain types of food and assume they are "allergic" to certain foods. As physical symptoms due to unknown causes must originate somewhere, the medically uninformed patient quite understandably attributes his/her condition to certain types of food. This is even more comprehensible in view of the fact that the subject of "healthy" and "unhealthy" food is gaining increasing importance in the public eye. Food intolerance is suspected in the presence of the most diverse symptoms, partly in a reflective manner. However, although it is very easy to establish the suspected diagnosis of food intolerance, it is very difficult to verify the same and find the actual causal agent in the individual case.

In contrast to intolerance reactions, allergic reactions are an expression of a hypersensitive immune system. A prerequisite for this condition is previous contact of the immune system with the allergen (which are nearly always proteins) and specific sensitization to this allergen. Thus, an allergy is an acquired or – from the viewpoint of the immune system – a "learned" disease. The fact that a person may still experience an allergic reaction when consuming a specific type of food for the first time is because sensitization will have occurred previously by a different route (for instance, a bird keeper's allergic reaction to millet after having been sensitized to bird seed via the lungs) or when the allergic reaction to a specific foodstuff has been triggered by an immunological cross-reaction (see below).

Food allergies are nearly always so-called immediate-type allergies or type I allergies. These are caused by class E antibodies (IgE). IgE antibodies occur in very low concentrations in the human body compared to other antibodies and are highly efficient. They bind to specific immune cells through a specific high-affinity IgE receptor. The immune cells store histamine within. These are mast cells on the one hand (skin, mucous membranes) and basophilic granulocytes on the other (blood). When a relevant allergen comes into contact with these cells loaded with IgE, binding of the allergen to the IgE antibodies causes a rapid release of stored histamine and the neoformation of further inflammatory substances (prostaglandins, leukotrienes, etc.), which trigger the acute allergic reaction. Typical symptoms include skin reactions (itching, redness, urticaria, edema), shortness of breath (asthma, swelling of the larynx), and cardiovascular problems (tachycardia, a drop in blood pressure), which may extend to the entire manifestation of anaphylactic shock. Quite often the patients also experience nausea, vomiting, and diarrhea, but gastrointestinal symptoms are generally not the primary ones in persons with genuine allergic reactions to food (in contrast to many intolerance reactions). Primary chronic gastrointestinal symptoms such as flatulence, abdominal pain, diarrhea, or soft stools are rarely caused by a food allergy (FA).

2.10.1 Primary ("Genuine") Food Allergy (FA)

Basically, food allergies may be divided into two types: the first are so-called primary (or genuine) food allergies in which sensitization occurs through the intestinal

tract. The main types of food are egg, milk, wheat, soya, peanuts, walnuts, and fish, all of which may trigger life-threatening allergic reactions. These food allergies mainly occur in early childhood and are commonly transient. In other words, they disappear on their own by the time the child reaches school age. This is especially true of egg, milk, and wheat. Nut and fish allergies, on the other hand, usually persist into adulthood. This fact is especially significant with regard to the diagnosis of allergy and counseling the patient.

In rare cases, a primary food allergy (FA) arises in adulthood. Some authors have identified the involved allergens as so-called type C food allergens and make a distinction between these and classical type A allergens of early childhood (egg, milk, etc.). A few important representatives of type C allergens are so-called lipid transfer proteins (LTP), which are a group of allergens possessing various degrees of cross-reactivity and occurring in many vegetable foods (fruit, vegetables, nuts). Due to their strong resistance to heat, gastric acids, and digestive enzymes, they may even trigger severe anaphylactic reactions. LTP allergies are especially common in Mediterranean countries, but relatively rare in Central Europe.

2.10.2 Secondary or Associated Food Allergy (FA)

The second large group of food allergies consists of secondary or associated food allergies, which may occur in patients with a preexisting respiratory allergy. Here it is not the foodstuff itself which causes sensitization. Rather, sensitization occurs earlier to specific inhalant allergens, such as Bet v 1, which is the main allergen in birch pollen. Proteins similar to Bet v 1 ("homologous" proteins) occur in a number of foodstuffs. Thus, cross-reactions following the ingestion of these foodstuffs may cause allergic symptoms. As inhalation allergies are very rare in early childhood and much more common after this period, secondary food allergies typically occur in adulthood and are by far the most common cause of food allergies in adults.

In Central Europe birch pollen is the most common cause of secondary food allergies and is associated with a long list of potential foodstuffs (Table 2.9). From the clinical point of view, the typical condition is a so-called oral allergy syndrome: the allergic reaction is mainly confined to the oral and pharyngeal region (itching, swallowing difficulties, hoarseness, swelling in the larynx, breathing difficulties). This is because the responsible Bet v 1-like allergens are rapidly destroyed in the stomach and are therefore usually unable to trigger generalized reactions. Cooking or roasting also destroys most of these allergens. However, some of the associated foodstuffs, especially soya in the form of soya drinks, may trigger severe reactions.

Analogously, there are confirmed interconnections between other vegetable or animal inhalation allergens and various foodstuffs, such as mugwort, house dust mite, latex, Benjamin's fig, cats, dogs, and pet birds. In contrast to food allergies associated with birch pollen, systemic and even life-threatening allergic reactions are common in this setting.

Advances in the field of molecular allergology in the last few years have contributed significantly to our understanding of these cross-reactions. In the large majority of the above-mentioned associations, the causative cross-reactive proteins in the sources of inhalation or associated foodstuffs are known today. Even the pollen of

Table 2.9 Secondary food allergies which may occur as a result of immunological cross-reactions in the presence of an allergy to inhalation allergens (such as pollen). Clinical intolerance usually develops toward just a few of the listed foodstuffs or may be entirely absent, depending on the individual pattern of sensitization, the severity of allergy, and the season. Data concerning the frequency of allergy and associated food intolerance are subject to regional variations and also depend on local eating habits

Inhalation allergy	Associated foodstuffs	Frequency of inhalation allergy	Frequency of food allergy in sensitized persons	Responsible cross-reactive allergens
Birch pollen	Pip fruits and stone fruits (especially apple and peach), hazelnut, walnut, almond, peanut, soya, fresh fig, carrot, celery, spices from the parsley family (e.g., caraway, aniseed, parsley, coriander, dill), potatoes (raw), kiwi, persimmon, strawberry, raspberry, jackfruit, mulberry	Very frequent	Very frequent	PR-10 proteins (related to Bet v 1)
Mugwort pollen	Celery, parsley root, spices (caraway, aniseed, coriander, cumin, curry), mango, lychee, pistachios, cashew nut, etc.	Frequent	Occasional	Partly unknown, partly LTP proteins
Profilin (panallergen in pollen)	Theoretically, all vegetable foods; common in actual practice: melon, banana, tomato, citrus fruits	Occasional	Occasional	Profilins
House dust mite		Very frequent	Rare	Tropomyosins, arginine kinases?
Benjamin's fig	Crustaceans (prawn, lobster, crab) and mollusks (mussels, snails, squid)	Rare	Frequent	Hevein (Hev b 6), β1,3-glucanases (Hev b 2)? And others?
Cat, dog, pet birds	Banana, avocado, sweet chestnut, kiwi, tomato, fig, papaya, etc.	Rare	Frequent	Cysteine proteases
	Fig, kiwi, papaya, banana, pineapple	Very frequent	Very rare	Serum albumins
	Pork (cat-pork syndrome), egg yolk (bird egg syndrome), in rare cases even poultry meat	Rare	Frequent	Serum albumins

LTP lipid transfer proteins

common ragweed (hogweed, ambrosia), which came from Hungary and is now spreading all over Central Europe, has been occasionally held responsible for specific types of associated food intolerance. According to more recent data, however, this is primarily based on cross-reactions with the ubiquitous "panallergen" profilin which occurs in all types of pollen and vegetable foods and therefore cannot be regarded as a ragweed-specific allergy.

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Disease Patterns in the Presence of Histamine Intolerance

3

Manfred Götz, Reinhart Jarisch, Christian Layritz,
Verena Niederberger, and Martin Raithel

3.1 Headache

Reinhart Jarisch

Headache (cephalea) is a common problem, especially in women. Usually the symptoms are attributed to the weather or the cervical spine. A prerequisite for the former is a specific type of hypersensitivity, while a prerequisite for the latter would be an injury, a degenerative disease, or a muscle tension. However, the fact is that both of these phenomena are cited as causes by patients much more frequently than would be justified on the basis of the slightest evidence. One takes headache for granted. Some patients even consider it normal.

M. Götz, MD (✉)
Department of Pediatric and Adolescent Medicine,
Pulmonary and Infectious Diseases, Wilhelminenspital der Stadt Wien,
Academic Teaching Hospital, Medical University of Vienna, Vienna A-1140, Austria
e-mail: m.goetz@aon.at

R. Jarisch, MD
Floridsdorf Allergy Center, Franz-Jonas-Platz 8, Vienna A-1210, Austria
e-mail: jarisch@faz.at

C. Layritz, MD
Department of Medicine 2, University Hospital of Erlangen,
Ulmenweg 18, Erlangen D-91054, Germany
e-mail: christian.layritz@uk-erlangen.de

V. Niederberger, MD
Department of Otolaryngology (ENT), Medical University of Vienna,
Waehringer Guertel 18-20, Vienna A-1090, Austria
e-mail: verena.niederberger@meduniwien.ac.at

M. Raithel, MD
Department of Medicine 1, University Hospital of Erlangen,
Ulmenweg 18, Erlangen D-91054, Germany
e-mail: martin.raithel@uk-erlangen.de

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This is an error. The sentence should correctly read *Women take headaches for granted and some (female) patients even consider it normal*.

Postscript: No man would regard a headache as a normal occurrence.

Post-postscript: When registering a patient's medical history, this goes so far as not to mention headache as one of the symptoms. It has to be specifically inquired.

Based on the clinical fact that the majority of persons who experience headache are women, one may suspect a certain association with histamine. A Danish study (Lassen et al. 1996) was focused on whether the inhalation of histamine in patients with migraine might lead to headache. Fifteen patients with migraine and 15 controls inhaled increasing doses of histamine and were asked about the occurrence of headache or migraine. Surprisingly, 11 migraine patients and even 8 healthy controls complained of headache after the inhalation. This shows that histamine may cause migraine and headache and that it also does so in healthy control persons and is apparently related to the magnitude of the dose.

For the majority of patients, headache in connection with food evokes the memory of consuming excessive quantities of red wine. It should be mentioned that headache and migraine may be caused by a large number of factors. Several thick textbooks have been published on the subject. I would like to confine this chapter to histamine as a potential cause of headache. The diagnostic investigation of this phenomenon is quite simple. Patients with recurrent headache, especially those in whom all previous investigations have been negative, should try to strictly avoid food and alcoholic beverages containing histamine and other biogenic amines for several weeks. Besides, it would obviously be meaningful to investigate the person's blood in respect of histamine and diamine oxidase (DAO). Among numerous patients with headache who benefited from a histamine-free diet, the following case was spectacular.

Case Report

A 26-year-old doctor who had just graduated from medical school reported that she had suffered from headache since the age of 7 (!). All previous check-ups she had undergone had been negative. She completed medical school with great difficulty because of her persistent condition. We counseled the patient and advised her to maintain a histamine-free diet as well as take H1 receptor blockers for a short period of time. The patient returned after 1 month. On being asked about her condition she replied, "I hardly dare 'touch wood' because I'm so scared the headache might return. I have had no symptoms for a month."

No case history in respect of headache ever impressed me as much as this one did. It clearly shows how easily these patients can be helped and the long-standing martyrdom some patients endure because they apparently do not receive appropriate help. The fact that frequent headaches lead to

analgesic abuse is well known. Besides, chronic use of analgesics is liable to cause massive side effects.

Headaches after a night of heavy drinking are commonly attributed to the excessive consumption of alcohol. It would be interesting to perform an experiment on oneself in this regard. In the evening one should take a large quantity of (preferably) red wine, which is known to cause a headache. When a headache occurs the next morning, one should take the same quantity of the same wine 2 days later, but with premedication in the form of an H1 receptor blocker an hour earlier. One will not have a splitting headache the next day. According to popular opinion, alcohol causes a headache. One can easily establish that this is not the case by taking a glass of schnapps (hard liquor) derived from grain. In colloquial German, this drink is known as a "clear" drink – not merely because it is transparent but apparently also because it helps to keep a clear head in terms of no headache. With regard to beverages that contain a large percentage of alcohol, the rule of thumb is that beverages as transparent as water are above suspicion in regard of histamine, but all colored alcoholic beverages contain histamine and should be avoided by persons with histamine intolerance. However, when consuming alcohol, one should consider the basic fact that acetaldehyde, a degradation product of alcohol, is an inhibitor of DAO per se. The additional ingestion of food containing histamine may cause additional problems.

In a pilot study, we investigated 35 patients with headache who had been examined previously by a neurologist. We investigated the patients in respect of histamine intolerance and determined their histamine levels in plasma and diamine dioxidase levels in serum. They were instructed to strictly maintain a histamine-free diet for 1 month and then report for a control investigation. Blood parameters determined before the start of the histamine-free diet and after 1 month were compared. Histamine levels dropped nonsignificantly ($p=0.07$), but diamine oxidase levels rose significantly ($p<0.001$) (Figs. 3.1, 3.2, and 3.3). Of 35 patients, 22 said they were free of symptoms. The frequency of headaches was reduced by more than 50 % in eight patients. Only five patients reported no change in their clinical symptoms and also revealed no change in histamine levels, but a rise in diamine oxidase levels was noted in four of five cases.

The patients were interviewed on the phone after 3–9 months. The pattern was largely the same. Three patients experienced worsening of their symptoms, which ceased after 1 month. Conversely, five patients experienced improvement of their symptoms. Many patients (22/26) reported renewed headaches when they failed to adhere to the diet (Steinbrecher and Jarisch 2005).

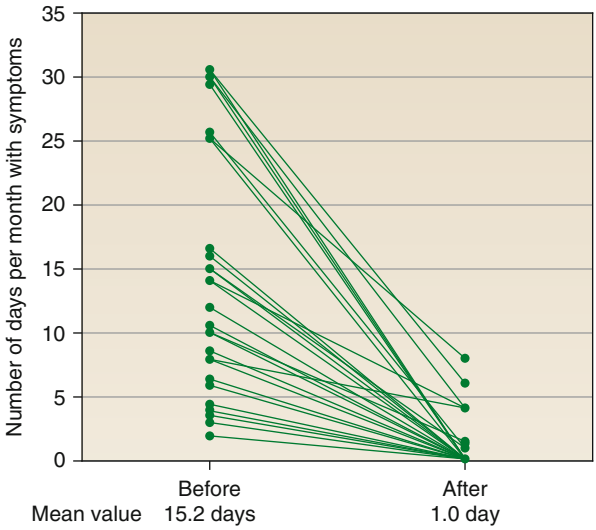


Fig. 3.1 Frequency of headache before and after a 4-week histamine-free diet in 30 patients with headache, who experienced subjective clinical improvement during the diet

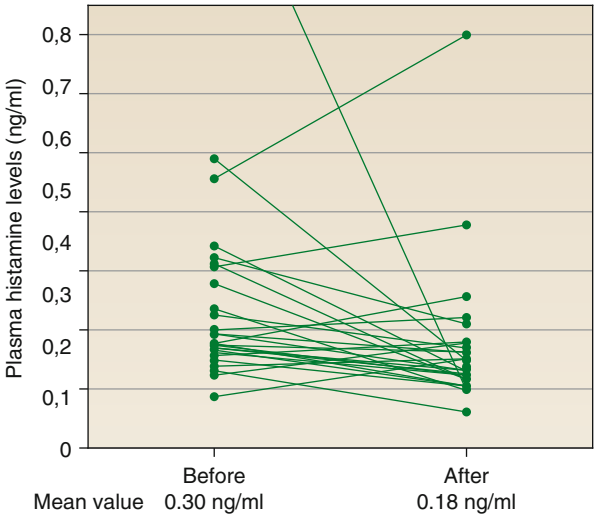


Fig. 3.2 Histamine levels before and after a 4-week histamine-free diet in 30 patients with headache who experienced subjective clinical improvement during the diet

The above mentioned clearly shows an association between headaches and the intake of histamine and biogenic amines. In addition to strict adherence to a histamine-free diet, in severe cases it may be useful to administer an (older) antihistamine that penetrates the blood-brain barrier (H1 receptor blocker). We still do not know whether histamine H3 receptor agonists improve the condition. Histamine H3 receptors occur especially in the brain and should therefore be the prime target of drug-based therapy.

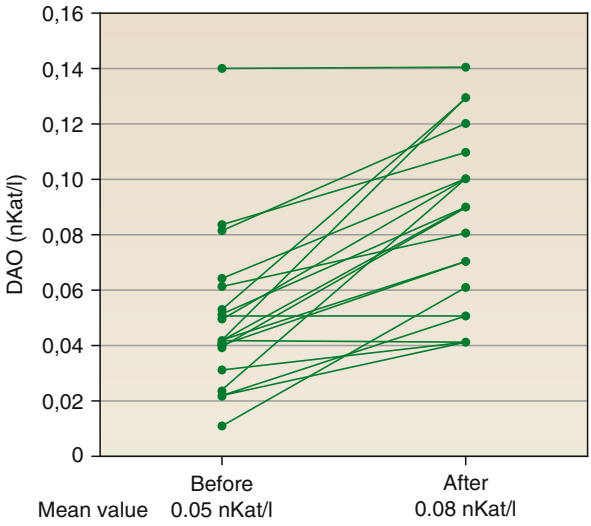


Fig. 3.3 Diamine oxidase (DAO) levels before and after a 4-week histamine-free diet in 30 patients with headache and subjective clinical improvement during the diet

3.2 Blocked or Runny Nose

Verena Niederberger and Reinhart Jarisch

The mucous membranes of the nose, which coat its inner aspect, contain small mucous glands that keep the nose moist. A dense network of veins lies below this surface. Histamine stimulates these blood vessels, causing them to dilate and release fluid into the surrounding tissue. This leads to swelling of the mucous membranes and constriction of the nasal pathways. Histamine also stimulates the mucous glands to secrete more fluid. Another mode of action of histamine is to irritate the nerves of the nose, which causes the urge to sneeze and the reaction to occur simultaneously on both sides, although only one side of the nose is stimulated by histamine.

These effects of histamine on the nasal mucosa are observed in specific patients who get a blocked or even runny nose when they drink wine. These effects are caused more frequently by red wine than by white wine, which may be explained by markedly higher histamine levels in red wine. The same symptoms may occur due to hypersensitivity to sulfite, which is also present in wine. Some patients report intolerance of beer, especially wheat beer. Intolerance of wheat beer is very common because it contains ten times more histamine than ordinary beer. Visible redness of the tip of the nose, which is also observed in many persons after they have consumed alcohol, is not caused by histamine but is a direct effect of alcohol, which dilates the blood vessels.

In terms of differential diagnosis, a number of diseases apart from histamine intolerance should be taken into account in cases of persons who suffer from a persistent runny or blocked nose over a long period of time. The most important of these diseases are listed in Table 3.1.

Table 3.1 Potential causes of a runny or blocked nose

Causes of persistent obstruction of nasal breathing	Causes of a persistent runny nose
Allergic rhinitis	
Histamine intolerance	
Unfavorable anatomy	Chronic inflammation of the paranasal sinuses
Nasal polyps	"Vasomotor rhinitis"

3.2.1 Allergic Rhinitis

The most common, and probably most significant, cause of a persistent runny or blocked nose is allergic rhinitis. During the medical interview with the doctor, the condition is usually assignable to a specific cause. The suspicion can then be quite rapidly confirmed by diagnostic investigations for allergy. When the nasal symptoms occur during a specific season, the condition is most often a pollen allergy (hay fever). Symptoms which are strongest in the spring, i.e., between February and April, are usually caused by hazel, alder, or birch pollen (so-called early flowering trees). Grass bloom occurs in May and June, followed by a high burden of ragweed and mugwort in August and September. In addition to these principal causes of pollen allergies, several other plants such as rapeseed, plantain, or nettle may cause difficulties in specific allergic persons during the intervening months as well.

Many patients with nasal symptoms throughout the year also have allergies, which are then most frequently caused by house dust mite or animal hair. The cause of animal hair allergy is usually very easy to establish because it mainly concerns pet owners, such as those of cats, dogs, guinea pigs, hamsters, or rabbits. Removing the pet from the living area, although a painful experience in psychological terms, usually alleviates or eliminates the symptoms. In persons who are allergic to house dust mite, contact with the dust mite causing the allergy usually occurs during sleep because these insects feed on flakes of shed skin scales from humans and find ideal living conditions in a warm and slightly moist bed. Therefore, large quantities of mites and their feces collect in mattresses in nearly all households. In the case of a patient with an allergy, it would be advisable to reorganize the household, such as using mattress covers impervious to mites or frequently washing one's pillow and covers at higher washing temperatures than 60 °C.

Antihistamines in tablet form, nasal sprays, or nasal steroid sprays may be used for the treatment of allergic rhinitis. A combination of these medications is effective in some patients. However, this is no more than combating the symptoms of allergy and does not alter the underlying disease. This type of treatment is suitable when a person has an allergic cold for a limited maximum period of a few weeks. When allergic rhinitis persists for a longer period of time and these measures do not achieve satisfactory alleviation of the symptoms, one should consider the possibility of inoculation for allergy. The current recommendation is to start the treatment early – in childhood or adolescence – because it has been found to prevent further deterioration of symptoms and progression of the condition to bronchial asthma.

3.2.2 Anatomical Changes in the Nose, Nasal Polyps, and Adenoids

A distorted nasal septum, an enlarged nasal turbinate, or a very constricted nostril may be the reason for a chronic blocked nose. When such alterations become very annoying, they can usually be resolved by surgery.

Nasal polyps may be another potential reason for a persistently blocked nose. The cause of such formations of the mucous membranes has not been conclusively established yet. However, they do not result from allergy or histamine intolerance. The symptoms of polyps and anatomical obstruction of the nose may be aggravated by the presence of allergy or histamine intolerance. Regrettably, many patients with nasal polyps cannot be treated satisfactorily. Although cortisone is effective in the short term, some patients with this problem need to undergo surgery repeatedly.

In children, especially those below 6 years of age, adenoids are quite a common problem. This may interfere with nasal breathing, block the ears, and cause snoring at night. Although adenoids in children tend to become smaller with advancing age, in terms of absolute size as well as in relative terms because of the growing size of the head, surgical removal is required in some cases.

3.2.3 Chronic Inflammation of the Paranasal Sinuses and Vasomotor Rhinitis

The principal differential diagnoses for a persistent runny nose include chronic inflammation of the paranasal sinuses. The cause is usually a constricted opening of the paranasal sinuses. Even a mild swelling of the mucous membranes may lead to complete obstruction of the accesses to the paranasal sinuses and a chronic self-sustaining inflammatory process.

A further reason for a runny nose, which occurs more frequently but not exclusively in advanced age, is so-called vasomotor rhinitis. Due to an excessive misrouted reaction of nerves in the nose following a change of temperature or even without a visible cause, the person has repeated bouts of watery secretion from the nose which can be extremely annoying.

3.3 Bronchial Asthma

Manfred Götz

Bronchial asthma is a chronic inflammatory disease of the bronchial mucosa, accompanied by the obstruction of air flow in the lower respiratory tract, which may improve or resolve completely after treatment or, infrequently, on its own. The cause of these problems is heightened responsiveness of the bronchial mucosa to various exogenous or endogenous stimuli. Allergic factors play a very major role in this phenomenon.

The patient's medical history, evaluation of lung function, response to drugs, and occasionally psychological factors are of prime importance for establishing the diagnosis. The principal sign is episodic wheezing and coughing, although a number of other diseases may be associated with similar symptoms. Today it is assumed that worldwide about 10 % of all children and adolescents suffer from asthma. The diagnosis of asthma may be more difficult in adults because environmental pollution, such as that resulting from industrial gases and especially tobacco smoke, may additionally damage the respiratory tract, resulting in asthma-like diseases like chronic bronchitis or chronic obstructive pulmonary disease. A gastroesophageal reflux may cause chronic recurrent "asthmatic symptoms" – even in children – and should be ruled out in patients who do not respond to therapy. Fortunately, only about 10 % of asthmatics are severely affected by the disease in terms of daily symptoms, limited physical capacity, abnormal lung function, and nocturnal dyspnea. Allergies play a very important role in nearly all of these patients.

Bronchial asthma is common in families with allergic disease. Thus, a hereditary predisposition may be presumed to exist. This genetic impact on bronchial asthma is mainly due to inheritance of the allergic disposition (atopy). Various chromosomes have been named as carriers of hereditary characteristics responsible for asthma and allergy, but no exact classification has been established to the present day. Interestingly, the genes responsible for IgE regulation (those responsible for allergy), bronchial hyperreactivity (hypersensitivity), and specific mutations of ß-adrenergic receptors (bronchodilator control centers) are located close to each other. This would explain the close relationship between allergic disposition and bronchial hypersensitivity.

Bronchial hypersensitivity to various stimuli, such as cold air, physical strain, bronchoconstrictive substances like methacholine or histamine, and hypertonic saline, is a frequently observed phenomenon among asthmatics – so much so that it was initially regarded as the principal characteristic of the disease. In the meantime we know that about 15–25 % of children and adults have such bronchial hypersensitivity even without symptoms of asthma. In addition to genetic factors, exogenous factors such as allergens, pollutants, and viral infections might cause a transient increase in bronchial sensitivity. Most asthmatics suffer from hypersensitivity which, however, cannot be demonstrated in all cases.

For about 40 years now, it has been known that asthma is basically a chronic inflammation of bronchial mucosa. Inflammatory cells like mast cells, eosinophilic granulocytes, and lymphocytes are involved in the chronic inflammation. Mast cell activation by various stimuli leads to release of histamine, which induces bronchoconstriction (constriction of the respiratory ducts), vasodilatation (dilatation of the blood vessels), and enhancement of vessel permeability. Very recent investigations have shown that histamine is responsible for remodeling the structure of the respiratory tract, which may intensify the chronic nature of the disease. Tryptase, a further mast cell product, intensifies the effect of histamine and also renders the reaction chronic. So-called interleukins (cell hormones) initiate the attraction of eosinophilic granulocytes. The cells contain a number of toxic substances, such as the eosinophilic cationic protein (ECP). These substances are known for their direct and

pronounced cell-damaging activity. Today we know that, in addition to the so-called humoral mechanisms mentioned above, T lymphocytes or cellular immunity plays a very decisive role in the chronification of the asthmatic process. Modern therapeutic approaches are aimed at influencing mast cells, eosinophils, and T lymphocytes. Even specific immune therapy (allergy vaccination) is an attempt to alter the T-lymphocyte pattern. It is successful when the treatment is continued for a sufficiently long period of time.

3.3.1 Asthma and Inhalant Allergens

In addition to physical strain and viral infection, the most common causes of asthmatic reactions are inhalant allergens. Inhaled foreign proteins, existing as airborne particles in the environment, may lead to the above-mentioned conditions, i.e., constriction of the bronchi and wheezing.

3.3.2 House Dust Mites

House dust mites are the most important inhalant allergens of all. They occur practically everywhere, and their growth is favored by moist living conditions or atmospheric humidity above 50 %. Clear associations have been established between the density of dust mites during the first few years of a child's life and sensitization to dust mites, i.e., the development of asthma. Dust mites favor environments shielded from light, such as beddings, carpets, sofas, cushions, mattresses, etc. They can be naturally repressed by reducing atmospheric humidity, which may however damage the human respiratory tract, and by cold.

3.3.3 Animal Allergens

The cat is a very potent source of allergens. This allergen is also found in areas never frequented by a cat. Other potential sources of allergens are dogs, rodents, and birds.

3.3.4 Pollen

Allergens of trees and grasses blooming early are the main inhalant allergens that cause asthma. Mold fungi (*Alternaria*, *Cladosporium*) are common in the late summer and fall. Their spores are much smaller than pollen and are therefore able to enter the lung easily. Obviously, a mixture of dust mites, animal epithelia, and mold fungi occurs in interior spaces. Recent inhalant allergens include latex (natural rubber), the fig tree (*Ficus benjamina*), and wild silk. There is no association between the milky sap of the fig tree and wild silk. All of the above-mentioned

substances may cause symptoms in the upper as well as lower respiratory tract. The investigation of asthma must include demonstration of inhalant allergens and appropriate countermeasures (removal of animals, renovation of living areas, optimization of ventilation, etc.). In rare cases contact with inhalant allergens early in life may establish tolerance, but usually causes sensitization. In sensitized persons renewed contact with an allergen results in an excessive reaction in terms of IgE antibodies, which may also be the reason for their clinical symptoms. Abnormal maturation of certain T cells occurs already in the intrauterine period. Thus, prenatal regulation and allergy prevention would be desirable, but cannot be performed to the present day. About 95 % of asthmatics can be treated very successfully by alterations of lifestyles, medication, and specific immunotherapy.

Failure of treatment is nearly always due to noncompliance, which is defined as nonadherence to the medical treatment plan. Fear of undesirable side effects of drugs, getting used to one's limited physical capacity, irrational fears, etc. are the main reasons for noncompliance. A detailed discussion of the compliance problem is time-consuming. The patient must be motivated seriously by competent specialists, such as doctors or respiratory therapists. As regards the drug-based therapy options available today, one should make generous use of anti-inflammatory drugs. Best effects have been achieved with steroidal anti-inflammatory drugs (cortisone derivatives) in inhalant form. Recent therapy supplements include long-acting bronchodilators and leukotriene receptor antagonists, which inhibit inflammatory processes. Acute attacks of dyspnea continue being treated with short-acting bronchodilators (such as beta-2-mimetics, including salbutamol). Patients with asthma should carry them as a metered-dose aerosol.

3.3.5 Asthma and Food

Foodstuffs and food additives may cause asthma attacks. There is no general rule as to which foodstuffs cause symptoms in asthmatics. Therefore, each patient should be assessed individually. Preservatives like metabisulfite, which is present in dried fruit, sausage, wine, and other beverages, are frequent triggers of allergy. Glutamate and tartrazine have been repeatedly mentioned as causes of asthma attacks. The most commonly involved foodstuffs are nuts, fish, cow's milk, eggs, berries, and fruits. They may cause an acute asthmatic reaction but are linked with generalized anaphylaxis when a reaction occurs and therefore promptly identified. Other immediate reactions to food include acute rhinoconjunctivitis, the oral allergy syndrome, urticaria (nettle rash), angioedema, gastrointestinal symptoms, and atopic dermatitis.

Table 3.2 shows some foodstuffs that cause cough and wheezing. These reactions are not always based on a genuine allergy; they may occur due to intolerance as well. Some food allergens absorbed by the oral route were found to increase a person's unspecific bronchial sensitivity. Interestingly, the respiratory tract of Indians is much more responsive to foodstuffs than the respiratory tract of Europeans.

Table 3.2 Cough and wheezing due to food (based on Wilson 1985)

Foodstuff	Trigger in percentage
Orange nectar	30
Nuts	21
Cola drinks	19
Chocolate	19
Milk	14
Ice cream	9
Eggs	5
Orange juice	4
Fish	2

Histamine is the best investigated inflammatory mediator of asthma. Inhalation of allergens is followed by a very rapid increase of histamine levels in blood plasma. Histamine degradation products are then eliminated in large quantities in the urine. Thus, histamine appears to be at least partly responsible for the asthmatic reaction. As mentioned earlier, it is mainly released by mast cells. Inhaled histamine may be used in a lung function laboratory to demonstrate bronchial hypersensitivity. Histamine appears to be of limited significance in chronic inflammatory processes, such as those characteristic of persistent asthma. Histamine acts on histamine receptors (control centers) which are responsible for bronchospasm in asthmatics. Additional reactions include dilatation of bronchial vessels, secretion of mucus, and function of various nerves. The majority of histamine receptors also mediate an inhibitory effect with regard to further release of histamine by mast cells. As in classical allergic reactions to food (IgE mediated), a person may also develop reactions to the biogenic amines contained in foodstuffs, of which histamine, tyramine, cadaverine, and putrescine are the most important ones. High histamine levels in food with or without the simultaneous intake of diamine oxidase inhibitors could markedly increase the risk of an acute bronchial reaction. Gastrointestinal diseases are also associated with a high risk of undesirable effects due to histamine-rich food because of the damaged physical barrier to the absorption of histamine in the gastrointestinal tract.

Food and semi-luxury foods, especially cheese and wine, contain high levels of histamine and other biogenic amines. The latter (biogenic amines) may inhibit the degradation of histamine. The authors of this book were able to prove, several years ago, that a histamine-free or low-histamine diet reduces the burden of enteral diamine oxidase; circulating histamine is thus eliminated more rapidly. In contrast to the use of antihistamines, which are generally believed to be of limited value in the treatment of bronchial asthma, a low-histamine diet was able to achieve significant clinical improvement. The fact that a high intake of histamine is associated with symptoms, and the fact that a low intake of histamine in one's diet is associated with a lesser burden of histamine degradation, is promising in terms of improving the course of the disease for asthmatics, especially because no entirely adequate substitute has been found yet for the histamine-degrading enzyme diamine oxidase. This has led to the general recommendation that asthmatics or persons with chronic rhinoconjunctivitis should carefully check their diet and avoid histamine-rich

products to start with. In addition to maintaining an appropriate diet, the person's individual responsiveness should be observed carefully. There is no doubt that a diet with low levels of biogenic amines cannot, by any means, replace the treatment of asthma. However, it certainly reduces the burden of the disease and achieves clinical improvement. These outcomes are logical and have been observed. As food allergies in conjunction with inhalant allergies and other triggers may lead to asthma, establishing the role of food per se is not quite simple. Appropriate elimination diets usually start to act after 2 weeks. Therefore, the change of diet must be maintained for several weeks before one can establish an improvement with certainty. If there is any doubt or uncertainty about the role of a specific type of food in respect of being a trigger of asthma, in some cases it will be impossible to avoid a double-blind placebo-controlled food provocation test. This must be performed during a short hospital stay.

3.4 Cardiac Arrhythmia

Martin Raithel and Christian Layritz

After the discovery of histamine in 1910, it was shown that histamine affects the heart, its muscle (the myocardium), the blood vessels, and the cardiac rhythm and may also trigger cardiac arrhythmia (Barger and Dale 1910). Several experiments have shown that histamine may trigger cellular events in the heart, such as cardiac arrhythmia (e.g., induction of abnormal automaticity; Giotti et al. 1966; Levi et al. 1981; Wit and Rosen 1983). Histamine accelerates the heart rate of human fetuses. It increases the rate of contraction in isolated atrial cells of rabbits. The blocking effect of the H2 antihistamine cimetidine indicates an effect via a specific H2 receptor. In 1966 Giotti showed that the large part of cardiac histamine originates from mast cells (Giotti et al. 1966). Recently, unusually high serum IgE levels were observed in cardiac patients; these were correlated with the severity of heart disease and arteriosclerosis (Wang et al. 2011). Histamine and IgE do not act as allergy signals here. Rather, they are produced in large quantities as part of the chronic inflammatory reaction of arteriosclerosis.

H1 receptors exist at the so-called AV node (junction between the atrium and the ventricle) and in the coronary vessels (vasoconstriction). H2 receptors are distributed in the heart muscle, the AV node, and the atrium, as well as in the coronary vessels (vasodilatation). H3 receptors exist in sympathetic nerve fibers (Nault et al. 2002). In a healthy cardiovascular system, the cardiac effects passed on by H1 and H2 receptors are very strictly regulated. However, histamine sensitivity can change rapidly in a diseased vascular system, a diseased myocardium, accompanying infectious or inflammatory reactions, oxygen deficiency, etc. Cardiac arrhythmia in the form of bradycardia (heart rate <60/min) as well as tachycardia (heart rate >100/min) have been observed in these settings (Levi et al. 1981; Nault et al. 2002; Petrovay et al. 2007).

Apart from the significance of a rising rate of cardiac arrhythmia in an aging population, the investigation of histamine metabolism in advanced age, the increasing number of allergic reactions, histamine intolerance (HIT), and mastocytosis (Friberg et al. 2003; Le Heuzey et al. 2004; Rueff et al. 2006) are also important.

According to the interdisciplinary data register for chronic inflammatory and allergic gastrointestinal diseases at the University of Erlangen–Nürnberg, about 15 % of registered patients with various immunological hypersensitivity reactions had one or several types of cardiac arrhythmia, which called for further investigation. In part, these reactions were associated with the intake of the allergen in the course of associated infection or due to other unknown factors (Petrovay et al. 2007). This issue is of enormous significance in view of the markedly higher numbers of hospitalization for atrial fibrillation in the last 20 years (2.2 million US citizens; 4.5 million Europeans). Numerous causes like aging, increase of heart failure, better registration of cardiac arrhythmia, etc. could be cited for the high rate of persistent or paroxysmal atrial fibrillation and all of its medical consequences (anticoagulation, medication, hospitalization, occupational disability) (Giotti et al. 1966; Le Heuzey et al. 2004). Nevertheless, in view of the extremely high costs of atrial fibrillation, it will be very important in the future to exactly register (in terms of diagnosis) and define patients with a disorder of histamine metabolism and greater release of histamine. For these patients, other basic therapy options (allergy avoidance, a low-histamine diet, antihistamines, etc.) will probably be more effective in the future than the therapeutic principles used for the treatment of idiopathic atrial fibrillation.

The following cases show that the problem of histamine-induced cardiac arrhythmia – such as sudden atrial fibrillation – is not significant in classical allergy alone. Specific activation of the immune system in the course of inflammation, a diagnostic investigation (application of contrast medium, cardiac catheter, endoscopy), or mastocytosis may lead to cardiac arrhythmia when specific threshold levels of histamine are exceeded or the tissue's tolerance of histamine is reduced (in the presence of accompanying diseases, for instance) (Petrovay et al. 2007; Schwab et al. 1999).

Allergy-Induced Cardiac Arrhythmia

A 59-year-old woman with atrial tachycardia (138/min) was admitted to the emergency department after she had inadvertently ingested chicken the previous evening although she was known to have a chicken allergy. The sequential administration of a beta-blocker, propafenone, and potassium for 3 h failed to reduce the patient's heart rate. Five minutes after the infusion of H1 and H2 antihistamines (ranitidine and clemastine), the patient's irregular atrial fibrillation reverted to a regular conduction system with a stable sinus rhythm. Her sinus rhythm was stable during the 6-h observation period. She was discharged from the hospital with oral antihistamine therapy.

Anaphylactic reactions and accompanying arrhythmia have been reported in the published literature and were traced to the release of histamine (Booth and Patterson 1970; Durie and Peters 1970; Schwab et al. 1999). Regrettably, with the exception of such isolated cases, we have no systematic data as to how frequently high histamine levels lead to (allergy-induced) atrial fibrillation and, most of all, which patients are affected by this condition.

Cardiac Arrhythmia Triggered by Infection

Another serious example was that of a 48-year-old man with mastocytosis, who experienced a severe viral infection of the upper respiratory tract under his standard medication. The symptoms of a severe cold were accompanied by various types of tachycardia, right ventricular load, and low blood pressure. Cardiological investigations with a cardiac catheter and a CT of the heart showed no pathological features in the coronary vessels or hypoperfusion. It was decided that the only potential causes could be inflammatory substances triggered by mastocytosis and the infection, and histamine. The dose of the antihistamine was doubled during the infectious phase, which led to gradual normalization of the patient's heart rate.

3.5 Gastric Symptoms

Martin Raithel

Gastric symptoms or symptoms in the abdominal or gastric region (dyspepsia, heartburn, pain) are attributed to a number of causes. Many of these symptoms may be modified or triggered by food or semi-luxury foods (alcohol, nicotine), stress, medication (cortisone, painkillers), or other basic diseases (such as inflammation of gastric mucosa, infection, overproduction of acids, tumor). In contrast to the *Helicobacter pylori* bacterium (Fig. 3.4), the unequivocal causal role of a specific foodstuff in the emergence of gastric ulcers or ulcers of the small intestines (so-called peptic ulcer disease) or an irritable stomach without ulcer (so-called non-ulcerous dyspepsia) has not been accurately confirmed yet (Schlicker and Göthert 2005). Food allergies (FA) or histamine intolerance (HIT) constitutes an exception. Immunological hypersensitivity to a specific type of food (allergy) or the ingestion of a foodstuff containing histamine may cause gastric symptoms in sensitive persons (HIT). This may be manifested as isolated gastric symptoms, may be coupled with other gastrointestinal symptoms from the oral cavity to the rectum, or may occur in conjunction with symptoms outside the gastrointestinal tract (eyes, respiratory tract, nose, skin, etc.) (Schlicker and Göthert 2005; Zopf et al. 2009).

Figure 3.5 shows that histamine exerts a stimulating effect on the regulated process of gastric acid production, while hormonal and neural factors also influence the secretion of acids. The primary effect of even a small increase in histamine beyond

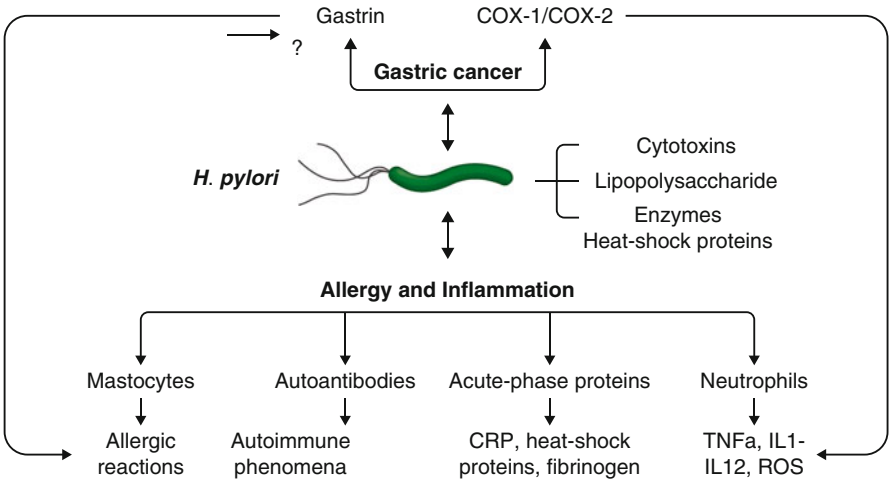
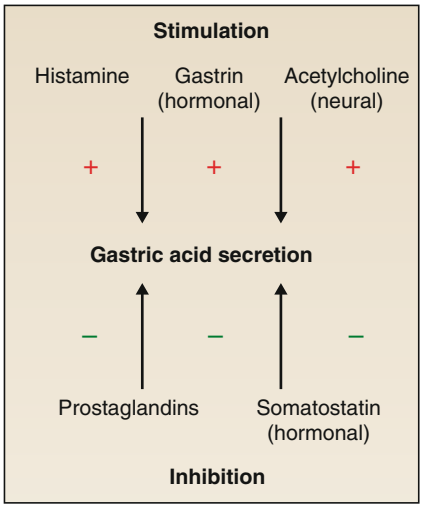


Fig. 3.4 Various aspects of *Helicobacter* infection in the stomach in the presence of gastritis, gastric cancer, food allergy, and histamine intolerance (Source: Adapted from Konturek et al. (2008))



Histamine (ng/ml × m^2 BSA)	Biological activity
0.15 – 0.45	Normal value Physiological functions
0.5 – 1.5	High secretion of gastric acids and mucus Contraction of smooth muscles Headache
1.0 – 5.0	Drop in blood pressure Accelerated pulse Cardiac arrhythmia kin reactions
2.0 – 12.5	Dyspnea, bronchoconstriction Bronchospasm
>7.5	Shock, cardiac arrest

Fig. 3.5 Physiological regulation of gastric acid secretion and biological effects of histamine

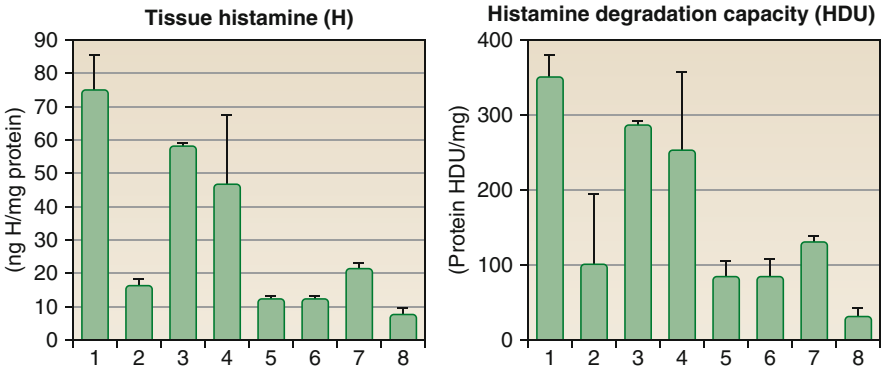
normal physiological levels is the stimulation of gastric acid and mucus production in the gastrointestinal tract (GIT), followed by the contraction of the smooth muscles, headache, and tissue swelling (edema) (Giera et al. 2008; Schlicker and Göthert 2005). This explains why symptoms of an irritable stomach or an irritable bowel frequently occur in the presence of FA or HIT, which are classified by doctors as non-ulcerous dyspepsia, recurrent gastric or esophageal acidosis, functional symptoms of the (upper) abdomen, or as psychosomatic phenomena, especially when

several diagnostic measures (investigation of blood and stools, ultrasound of the abdomen, the thyroid, the small bowel, endoscopies with biopsies, etc.) fail to reveal an organic pathological condition.

This has been demonstrated very clearly in mastocytosis: about 60 % of patients have pathologies in the stomach due to elevated histamine levels (Jensen 2000). In rare cases, severe inflammatory conditions including ulcers, iron deficiency, and anemia have been observed in the presence of HIT, FA, as well as mastocytosis (Jensen 2000; Kokkonen et al. 2001). Traditional medications for gastric ulcers (such as proton pump inhibitors or antibiotics to eradicate *Helicobacter pylori*) are not entirely effective in these cases or fail to achieve a sustained effect.

A patient with an allergic reaction in the upper GIT may have various specific symptoms ranging from nausea, heartburn, dysphagia, vomiting, gastric and intestinal pain, flatulence, and abdominal distension to even diarrhea. For a long time, it was inconceivable that the typical allergy substance histamine, which was commonly associated with no more than skin reactions, asthma, or allergic cold, could also cause gastrointestinal problems like nausea, stomach pain, and vomiting. The identification of HIT, FA, or mastocytosis in persons with recurrent or chronic gastric symptoms due to other causes requires highly differentiated gastroenterological, endoscopic-histological, and immunological investigation (Iacono et al. 2007; Jarisch and Hemmer 2001; Zopf et al. 2009), because persons with an irritable stomach or an irritable bowel problem include those with intolerance to other substances (such as salicylates in food or medication, carbohydrates), other basic diseases (such as pathologies of the pancreas, Crohn's disease), rare neuroendocrine diseases (such as gastrinoma), psychosomatic and neurovegetative diseases, etc. A local accumulation of mast cells and eosinophils in the stomach on histological tissue investigation would be a sign of FA or mastocytosis. However, in the absence of such histological features, one must specifically look for HIT as well as other rare diseases. In cases of suspected HIT, in addition to the determination of plasma histamine and methylhistamine in the urine, it would be useful to perform immunohistochemical investigation of the tissue for semiquantitative identification of diamine oxidase (DAO), comparative quantitative determination of DAO in serum and tissue, as well as diagnostic investigation of mediators in the blood and urine after the ingestion of a balanced diet and a potato–rice diet (Giera et al. 2008; Jarisch and Hemmer 2001; Wantke et al. 1993; Zopf et al. 2009). As the condition is known to be partly coupled with other diseases and psychosomatic conditions, a patient's gastric symptoms may not be assigned to HIT. Doctors are faced with the problem of having to coordinate the diagnostic investigation in a manner that other associated diseases are not overlooked in the presence of HIT (Giera et al. 2008; Hall et al. 2003; Jarisch and Hemmer 2001; Jensen 2000; Kokkonen et al. 2001; Raithel et al. 1999; Stolze et al. 2008; Zopf et al. 2009). The definitive diagnosis should be confirmed by histamine provocation only after dietetic measures for the purpose of reducing histamine levels and biogenic amines in food have not been clearly successful in terms of therapy (Giera et al. 2008; Stolze et al. 2008; Wantke et al. 1993).

As HIT may also occur in conjunction with a local allergy mediated by the gastrointestinal tract (Giera et al. 2008; Raithel et al. 1999), a guided endoscopic



Location	Physiological function of histamine
1 Stomach (corpus and/or antrum)	Acid production and gastric emptying
2 Duodenum	
3 Upper large bowel (jejunum)	Mucus secretion, chyme transport
4 Lower large bowel (ileum)	Mucus secretion, chyme transport
5 Beginning of the large bowel (cecum)	
6 Right-sided large bowel (ascending colon)	
7 Left-sided large bowel (sigmoid colon)	Stimulation of large bowel evacuation (motility)
8 Rectum	

Fig. 3.6 Physiological balance of tissue histamine levels and histamine degradation capacity in the gastrointestinal tract

segmental lavage (irrigation) of the stomach or the upper part of the small bowel is performed for reliable differentiation of a local type I allergy (immediate-type reaction). This is done to identify IgE antibodies formed in the gastrointestinal tract. Further immunological diagnostic investigation by means of oral provocation or biopsy testing (mucosa oxygenation) has been described in detail in Sect. 3.6 under "Diarrhea" (Giera et al. 2008; Zopf et al. 2009).

As histamine plays an important role in the stomach with regard to the secretion of hydrochloric acid, the stomach itself is very well provided with histamine-degrading enzymes (DAO and histamine N-methyltransferase). Figure 3.6 shows that a normal healthy person has relatively large quantities of tissue histamine in specific anatomical locations for the regulation of normal body functions as well as a large quantity of degradation enzymes to avoid any imbalance between histamine synthesis and histamine degradation. This explains why the stomach is less frequently involved in the symptoms of HIT compared to the lower GIT and the subsequent deeper portions of the intestines (middle to deep small bowel and large bowel). Young persons with histamine intolerance have symptoms which – on closer investigation – mainly concern the middle and lower portions of the intestines (diffuse abdominal pain, abdominal bloating, flatulence, colics, diarrhea). At a later age, when specific protective functions are no longer effective in the stomach (such as mucus production, protective tissue hormones, prostaglandins, etc.), HIT is also manifested in the upper gastrointestinal tract, accompanied by the most diverse symptoms.

While the maintenance of a histamine-free diet is an economical and effective therapeutic measure in persons with an irritable stomach and functional dyspepsia, the eradication of *Helicobacter pylori* may worsen the symptoms of HIT or allergy in the presence of an irritable stomach, FA, or HIT (Hall et al. 2003; Konturek et al. 2008). This is because some of the antibiotics used in this setting are inhibitors of DAO, may damage the gut flora, and may even induce antibiotic-associated diarrhea. As *Helicobacter pylori plays* a very complex role in the development of gastric cancer, allergy, and inflammation (gastritis) (Fig. 3.4), its eradication requires specific knowledge and targeted selection of suitable antibiotics, simultaneous administration of antihistamines, evaluation of potential drug interaction, and simultaneous or sequential probiotic therapy. Although a few signs indicate that *Helicobacter pylori* may reduce the severity of FA (Konturek et al. 2008), this pathogen should be treated appropriately because of the potential risk of gastric cancer and also because some persons sensitive to *Helicobacter* experience exacerbation of certain diseases (such as urticaria or atopia). As regards long-term treatment of gastric symptoms, it should be noted that the proton pump inhibitors used to curtail acid production (e.g., omeprazole, esomeprazole, pantoprazole) and histamine 2 receptor blockers may trigger the formation of allergy antibodies (IgE) in about 20 % of cases. Therefore, gastric acid blockers should not be administered without adequate reason for a long period of time.

Case Report

A physiotherapist (36 years old, 170 cm, 70 kg, moderate consumption of alcohol and moderate smoker, high levels of methylhistamine in the urine) had very obvious signs of HIT in the GIT after a trip to central France. The patient had no symptoms when consuming simple varieties of beer (about 5 % alcohol content) and German white wine (11–12 % alcohol content), but her latent HIT worsened during a day trip through the vineyards of Beaujolais. Various types of French cheese and red wine (13 % alcohol content) with various levels of histamine were offered at several stops. The patient initially experienced progressive flatulence and piercing abdominal pain, followed by tachycardia, diarrhea, and hypotension, which compelled her to leave the festive French dinner in the evening.

As alcohol inhibits the degradation of histamine, her continued ingestion of cheese during the day trip caused an excessive increase in histamine levels in the intestines (flatulence, pain, diarrhea), accompanied by relevant histamine absorption. Finally she had high plasma histamine levels as well (tachycardia, drop in blood pressure).

Similar hazardous combinations may occur when, in addition to the exogenous intake of histamine in food (such as cheese, tuna fish, vinegar, etc.), a person takes antibiotics (e.g., Augmentin) or other drugs (e.g., acetylcysteine) that block histamine degradation (Jarisch et al. 2001; Raithel et al. 1999; Schlicker and Göthert 2005). Infections constitute a further risk of such high

histamine levels. Immune activation causes high endogenous histamine synthesis due to the effect of interleukin-1 or due to bacterial histamine production (e.g., *Haemophilus influenzae*).

Based on the above-mentioned symptoms, the patient established an association between her complaints and the food or semi-luxury foods she had consumed. After a day of alcohol and food abstinence, the symptoms subsided completely within 24 h. The subsequent course of disease reflected the entire spectrum of HIT: she experienced recurrent bouts of flatulence, attacks of fatigue, and diarrhea. After several years of inconsistent therapy, she ingested tuna fish and experienced a common cold, followed by starting symptoms of shock (pre-anaphylaxis, irregular heart rate 134/min, hypotension 90/45 mmHg), generalized pruritus, and apathy. Based on the patient's history of HIT, she was given high-dose treatment with an H1 antihistamine (30 mg loratadine over 4 h) and took large quantities of fluid (3.5 l), which prevented emergency hospitalization.

3.6 Diarrhea and Allergic Gastrointestinal Diseases

Martin Raithel

Intestinal problems such as repeated bouts of flatulence, intestinal wind, soft stools, and diarrhea are reported by many adult patients. Like an irritable stomach (nonulcerous dyspepsia), a number of diseases may be responsible for this condition. However, quite often the clinician finds no pathological organic condition despite extensive diagnostic investigation. The patient's complaints are then attributed to a psychosomatic condition or an irritable bowel (irritable colon) (Kruis 2011). However, these symptoms may also be triggered by a food allergy (FA) in the gastrointestinal tract (GIT), histamine intolerance (HIT), or mastocytosis. Associated conditions such as food intolerance, restricted functional capacity, and ambiguity in regard of food or weight loss do not merely render a patient uncertain but also give rise to an extensive endoscopic examination of the GIT.

Depending on the individual disease pattern, the task of the physician in charge is to coordinate and organize various investigations by specialists like internists, gastroenterologists, allergy specialists, dermatologists, specialists in psychosomatic medicine, and nutrition experts (Zopf et al. 2009). It is estimated that about 10–25 % of all patients with an irritable bowel experience symptoms caused by histamine (Zar et al. 2001). Figure 3.7 summarizes the diagnostic steps required in cases of diarrhea and soft stools. It also takes various causes of diarrhea into account, such as carbohydrate intolerance, irritation after a gastrointestinal infection, gastrointestinal allergy, parasitic spread in the bowel, or other types of intolerance (such as salicylates in food). These should be clarified before the disease is classified as an inexplicable (idiopathic), neurovegetative, or psychosomatic condition (Zar et al. 2001; Zopf et al. 2009).

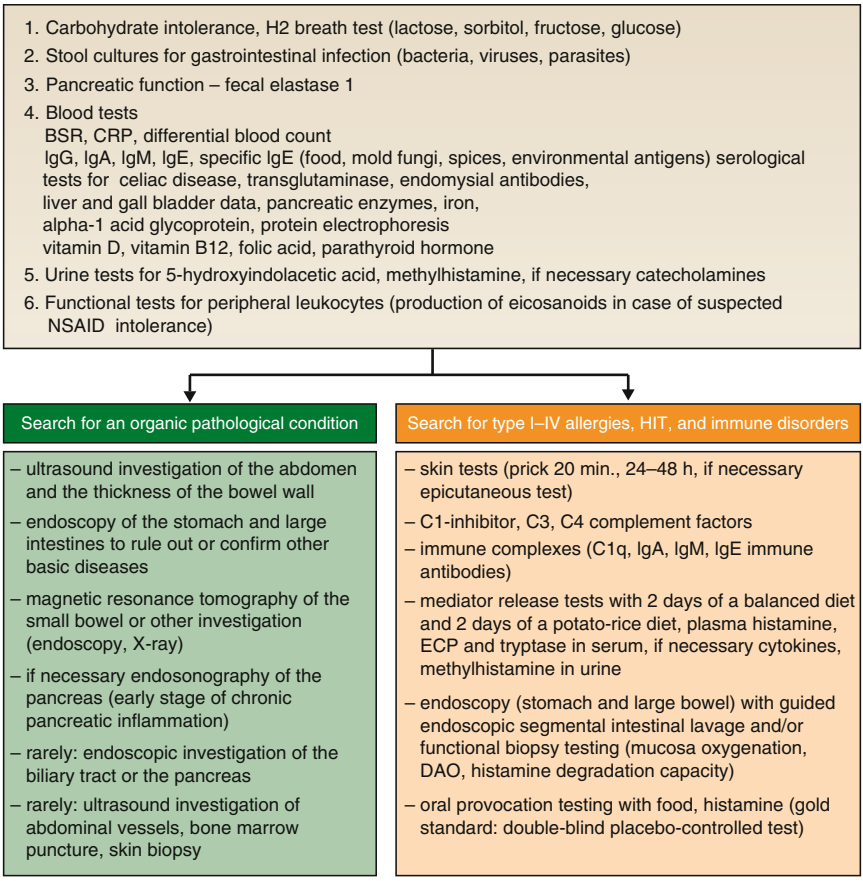


Fig. 3.7 Summary of differential diagnosis in cases of symptoms of an irritable bowel syndrome

3.6.1 Mechanisms and Classification of Histamine Intolerance (HIT)

HIT may be caused by various mechanisms (Table 3.3). The disruption of histamine metabolism is not confined to the gastrointestinal tract in all cases. However, as the gastrointestinal tract is able to form a large quantity of histamine because of its large mucosal surface (about 250 m^2) and histamine-degrading enzymes are very active at this location (also see Sect. 3.5 Gastric Symptoms), the GIT is frequently involved in HIT. Locations with high histamine levels are usually regions with a marked ability to degrade histamine as well. Histamine levels in the GIT are significantly and positively correlated with the degradation capacity of histamine in the GIT. A contradictory change in these variables results in imbalance. In other words, symptoms of HIT (such as diarrhea) occur in cases of high histamine levels and low degradation capacity, whereas low histamine levels and a high degradation capacity are associated with symptoms of histamine deficiency (such as constipation). The concentration of histamine degradation enzymes in intestinal tissue is manyfold

Table 3.3 Classification of disorders leading to histamine intolerance (HIT)

Cause of histamine intolerance	Class	Pathology
1. Greater availability of histamine	1a	Greater histamine synthesis due to endogenous or genetic causes, e.g., allergies, mastocytosis, leukemia, bacteria, etc.
	1b	Greater delivery of histidine, putrescine, or histamine due to exogenous causes, e.g., food, wine, vinegar, etc.
2. More sensitive histamine receptors	2A	Altered sensitivity of histamine receptors due to genetic factors
	2B	Acquired change in the sensitivity of histamine receptors, e.g., autoantibodies (?), cytokines, inflammation, infection, etc.
3. Disruption of enzymatic histamine degradation	3A	Genetic enzyme disorder at the level of Diamine oxidase Histamine N-methyltransferase
	3B	Acquired enzyme disorder at the level of Diamine oxidase Histamine N-methyltransferase
4. Disruption of cellular absorption (?)		

Table 3.4 Diseases outside the gastrointestinal tract with the potential to develop histamine intolerance

Atopic basic diseases[a]	Nonatopic basic diseases[a]
Atopic dermatitis (neurodermitis)	Food allergies (non-IgE) Delayed reactions Malabsorption syndromes
Bronchial asthma	Chronic urticaria
Allergic rhinoconjunctivitis (hay fever, pollinosis)	Nasal polyps
Food allergies (IgE) Oral allergy syndrome (pollen) Gastrointestinal allergy Anaphylaxis	Mastocytosis
Milk crust	Intolerance to nonsteroidal anti-inflammatory drugs (NSAID), salicylates, etc.
Urticaria	Intolerance to contrast media[b]

[a]Outside the gastrointestinal tract (extraintestinal atopic and nonatopic basic diseases)
[b]For additional data, also refer to basic gastrointestinal diseases

(>500-fold) higher than the quantity of these enzymes released into the blood (Kuefner et al. 2008; Raithel et al. 1998). Blood and tissue levels of histamine in the intestines are not correlated with each other.

Primary (congenital, genetically fixed) and secondary acquired forms of HIT are known to exist. Primary and secondary forms of HIT may be caused by greater availability of histamine, the presence of more sensitive receptors, disruption of histamine degradation, or its cellular absorption (Table 3.3).

As combinations of these mechanisms may also exist, the mechanisms and diseases listed in Tables 3.3, 3.4, and 3.5 should be subjected to careful diagnostic investigation.

Table 3.5 Diseases of the gastrointestinal tract with the potential to develop histamine intolerance

Underlying nonerosive gastroenterological diseases[a]	Underlying erosive gastroenterological diseases
Carbohydrate intolerance milk, fructose, sorbitol	Acute and chronic infectious diseases of the small and large bowel
Food allergies[b] (gastrointestinal allergies I–IV)	Chronic inflammatory bowel disease Crohn's disease Ulcerous colitis Indeterminate colitis
Unspecific or postinfectious alterations of the small or large bowel Collagenous/lymphocytic colitis NSAID intolerance Irritable colon	Rare inflammations of the small and large bowel (e.g., Behçet's disease)
Frequent occurrence of large bowel polyps and/or tumors	
Persistent infections[b]	
Celiac disease (sprue)[b]	
Eosinophilic esophageal, gastric, or intestinal disease[b]	
Mastocytosis[b], lymphoma[b], polyposis syndromes	
In rare cases, diseases of the small bowel	

NSAID nonsteroidal anti-inflammatory drugs
[a]Listed in the order of frequency
[b]In severe cases the condition has been known to progress to erosive disease

The most common disorders are those of enzymatic histamine metabolism (degradation of histamine through diamine oxidase (DAO) or histamine N-methyltransferase) as a result of specific underlying diseases outside the bowel or in bowel disease (secondary forms of acquired HIT, Tables 3.4 and 3.5). Changes in the intestines, such as a permeability disorder, epithelial damage, or mild inflammation, may be clinically unapparent.

Further mechanisms of HIT include an overload on histamine degradation due to the excessive intake of histamine in food (enteral histaminosis) and/or blockade of these degradation enzymes due to alcohol, medication, or other substances (Kuefner et al. 2008; Petersen et al. 2003; Raithel et al. 1998; Zopf et al. 2009). On average, DAO levels in FA are about a third lower than those in healthy persons (Fig. 3.8). Histamine-intolerant persons may, in part, demonstrate greater reductions in DAO activity.

Some persons with FA, neurodermitis, bronchial asthma, or HIT may have variations of the DAO gene (polymorphisms) and/or histamine N-methyltransferase (Hagel et al. 2012; Kuefner et al. 2008; Maintz et al. 2011; Petersen et al. 2003;

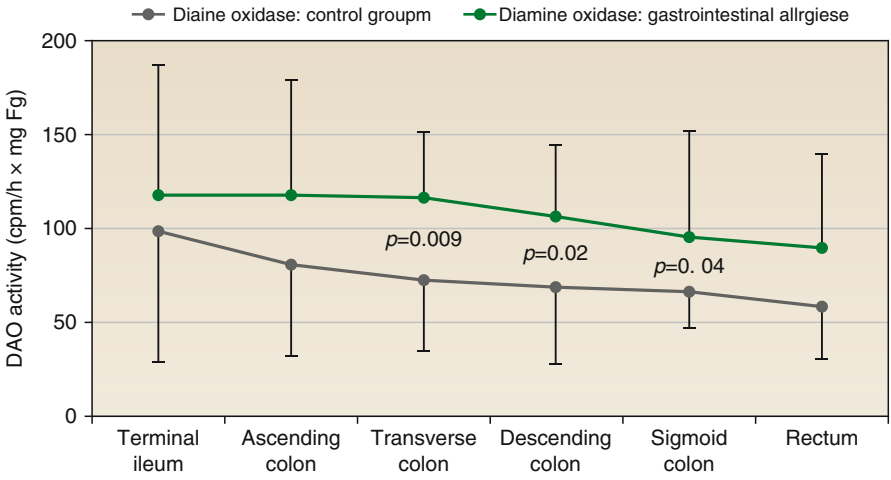


Fig. 3.8 Diamine oxidase activity in the lower gastrointestinal tract as a reason for using a low-histamine diet or antihistamines in persons with a food allergy or with histamine intolerance (Raithel et al. 1998)

Preuss et al. 1998). These genetic variants are not always associated with dysfunction of the corresponding degradation enzyme or the manifestation of HIT; other mechanisms may also contribute to this condition (Kuefner et al. 2008; Maintz et al. 2011; Petersen et al. 2003).

However, loss of the ability of the intestinal epithelium to degrade histamine (allergy, inflammation, intestinal bacteria, etc.) causes endogenous histamine to be degraded slowly. This results in concentration-dependent histamine-induced symptoms within the bowel (diarrhea, abdominal pain flatulence, etc.) as well as outside the bowel (headache, urticaria, asthma, drop in blood pressure, etc.). A poor ability to degrade histamine may also cause exogenous histamine in food to trigger clinical symptoms like itching, diarrhea, urticaria, or cardiac arrhythmia (Maintz et al. 2011; Petersen et al. 2003; Preuss et al. 1998; Zopf et al. 2009). Quite often it is not clear whether the observed reaction is a genuine allergic reaction to a foodstuff (allergy types I–IV), whether a pseudoallergic mechanism has led to the release of histamine (e.g., strawberry, tomato, or citrus fruit intolerance), or whether (spoiled) food was already contaminated with toxic quantities of histamine (>150 mg histamine, intoxication).

Diseases of the GIT may be divided into erosive and nonerosive underlying diseases. This classification is used not only for histological investigation but also for endoscopic or additional endomicroscopic examination during gastrointestinal endoscopy. Experienced endoscopists are able to classify the condition as HIT, food intolerance, or gastrointestinal allergy on the basis of the condition of the mucous membranes and the endomicroscopic appearance alone. This is important because HIT is most commonly overlooked in persons with nonerosive disease. In these patients with FA, a capsular endoscopy was needed to objectively establish the fact

that about 85 % of them had inflamed mucous membranes in the entire small bowel (in a normal person, this is the site of highest DAO levels in the body). This would explain the emergence of HIT in some patients (Hagel et al. 2012).

3.6.2 GI-Mediated Allergies and Histamine Intolerance

3.6.2.1 Diagnostic Investigation

An allergic gastrointestinal disease is suspected when, after exclusion of the above-mentioned conditions, a patient has still recurrent or chronic complaints after ingesting food, the mucous membranes are normal, a patient has unspecific signs of inflammation in the intestines, or (optionally) eosinophilia is established in the blood or intestinal tissue. In these situations, merely "considering the possibility of allergy or HIT" may help many patients because a brief (1 week) low-allergen potato–rice diet conducted on a trial basis or a subsequent low-histamine diet might serve as an economical means of alleviating the problem (established globally) (Jarisch 2008; Raithel and Hahn 1998; Raithel et al. 1998; Zar et al. 2001; Zopf et al. 2009). Investigation of the urine in respect of methylhistamine and histamine while maintaining a balanced diet for a minimum period of 2 days and a potato–rice diet for 2 days provides early evidence of increased histamine production and elimination. The GIT can be very well assessed by the investigation of methylhistamine in the urine because a large part (about 60 %) of histamine formed endogenously in the intestines reaches the liver through the portal vein and is stably converted into methylhistamine at this site (Raithel and Hahn 1998; Winterkamp et al. 2003). DAO takes over the degradation of the remaining free histamine on the surface of the intestinal mucosa (exogenous histamine) or histamine methylated in cells (endogenous histamine) when it reaches the blood and lymphatic fluid from the cells. Proper diagnostic investigation of these aspects is facilitated by the instructions provided by Synlab Fachlabor Weiden (Weiden/Opf., Germany) (Raithel and Hahn 1998; Winterkamp et al. 2003; Zopf et al. 2009). The advantage of this primary simple screening test is the fact that it measures the quantity of histamine released in various types of allergy (type I–IV) (Fig. 3.9) and is not merely an indicator of IgE-mediated FA. Its disadvantage is that it does not specifically prove the presence of FA but is also positive in cases of other histamine-producing diseases (such as mastocytosis, carcinoid, bone marrow disease, etc.).

The purpose of further diagnostic investigation is to determine the foodstuff(s) that causes the symptoms and to ascertain the underlying allergy mechanism responsible for the condition (Hagel et al. 2012; Zar et al. 2001; Zopf et al. 2009):

- Specific IgE antibodies to a type of food (allergy type I)
- Food-induced consumption of complement factors (allergy type II)
- Food-induced formation of immune complexes (allergy type III)
- Lymphocytes specifically sensitized to the triggering foodstuff (allergy type IV)

Evidence of these immune phenomena may be found in the skin, in the blood, in the intestines, or in other organs. It is important to obtain evidence of food-specific immune phenomena in the first place. The fact that one should look for locally

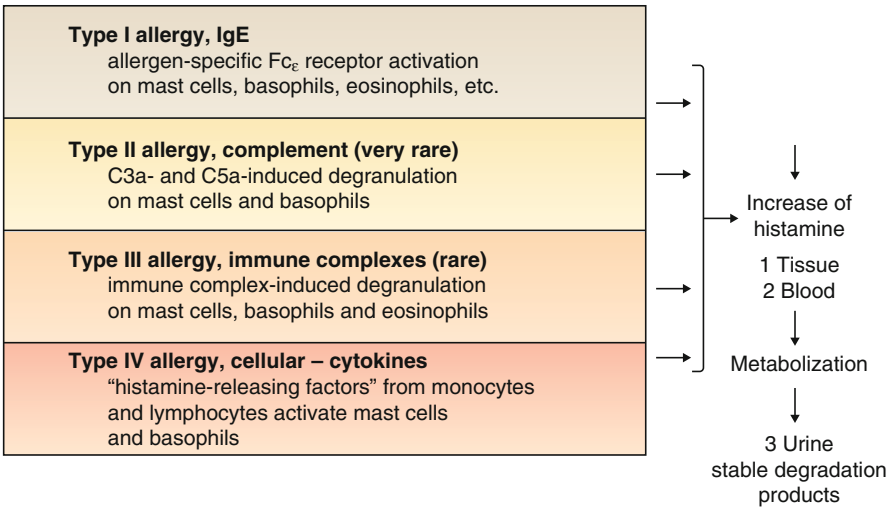


Fig. 3.9 Involvement of histamine release reactions in various types of allergy

formed allergy antibodies or the cited allergy mechanism not only in the blood but also in gastrointestinal mucosa is frequently overlooked (Lin et al. 2002; Raithel et al. 2006; Schwab et al. 2001; Winterkamp et al. 2003; Zopf et al. 2009). Currently it is not enough to perform skin tests with brief reading times (so-called prick test, 20 min) and/or merely look for IgE antibodies in the blood (type I allergy). One should also look for non-IgE-mediated and delayed allergy types (types II–IV), because the GIT is affected by non-IgE-mediated allergies as well as local IgE-mediated allergies (entropy); the latter are not seen in the blood (Arslan et al. 2006; Hagel et al. 2012; Lin et al. 2002; Paajanen et al. 2005; Zopf et al. 2009).

Endoscopic lavage was developed for specific diagnostic investigation of the bowel. Significant immune parameters such as immunoglobulin E, proteins in mast cells and eosinophils, tumor necrosis factor, etc. can be determined in the irrigation fluid of the human bowel (Raithel and Hahn 1998; Schwab et al. 2001). Thus, modern endoscopy helps the investigator to establish the allergy at the location of the disease (stomach, upper or lower small intestines, large intestines). This procedure is complemented by tissue investigation (histology) and imaging procedures. When endoscopic lavage reveals signs of food allergy, one may prescribe a diet on the basis of the investigation (<3 foodstuffs). Alternatively, one may assess the clinical relevance of the allergen by exposing the patient to it (in vivo provocation) or on a biopsy specimen of bowel mucosa (ex vivo provocation) (Arslan et al. 2006; Lin et al. 2002; Niggemann et al. 2006; Paajanen et al. 2005; Raithel and Hahn 1998; Raithel et al. 2006; Schwab et al. 2001; Zopf et al. 2009). During provocation on the patient, one looks for a reproducible reaction to the allergen (Arslan et al. 2006; Niggemann et al. 2006). During provocation of the intestinal biopsy specimen (mucosal oxygenation) (Raithel and Hahn 1998; Raithel et al. 2006), the investigator looks for any significant release of specific allergy mediators. When the test on

the patient (clinical symptoms) or the biopsy test (pathological release of allergens) yields a positive result, one initiates a strict allergen-free diet (abstinence). In both types of tests, one may investigate food, mold fungi, spices, pollen, foods cross-reacting with pollen, and environmental antigens. The type of test one uses depends on the patient's symptoms, the suspected type of allergy, the potential hazards of provocation, the patient's time, and funding by medical insurance companies. As many patients with GIT symptoms due to allergy or HIT are subjected to endoscopy, it would seem opportune to investigate the patient's intestinal mucosa (mucosal oxygenation) (Raithel et al. 2006). However, this investigation is performed in a standardized way at just a few centers and requires approval (of costs) from the patient's medical insurance company.

When the above-mentioned diagnostic steps and those listed in Fig. 3.7 for the identification of allergy types I–IV yield no evidence of gastrointestinal FA and the patient still has clinical histamine-mediated symptoms, one specifically looks for a disruption of histamine metabolism. As a blood test for the detection of DAO alone is not sufficient for this purpose, the standard diagnostic steps of clinical testing and intestinal biopsy should be performed (Jarisch 2008; Kuefner et al. 2008; Maintz et al. 2011; Petersen et al. 2003; Raithel et al. 1998). In the interdisciplinary register of chronic inflammatory and allergic gastrointestinal diseases at Erlangen, patients with HIT were identified by a number of tests and test combinations.

Diagnostic options for histamine intolerance:

- Medical history and physical examination
  - Tests for mediator release in the blood (single test):
- Plasma histamine, ECT, and tryptase in serum, if necessary cytokines
  - Functional mediator release tests with at least 2 days of a balanced diet and 2–14 days of a hypoallergenic low-histamine potato–rice diet
  - Combined determination under a balanced diet and after a potato–rice diet, both for the purpose of comparison (therapy effect)
- Plasma histamine, serum DAO, ECP, and tryptase in serum, if necessary cytokines, histamine, and methylhistamine in 12-h urine
  - Endoscopy with removal of a biopsy specimen (nitrogen)
  - Histological assessment (density of mast cells), if necessary DAO immune histochemistry and determination of histamine levels in the tissue, if necessary further mediators
  - Determination of isolated enzyme activity of DAO and HNMT
- Determination of biologically available total histamine degradation capacity
  - Oral provocation testing with 50–150 mg histamine or placebo
  - Emergency on-call service (if necessary ICU monitoring)
  - Symptom score, monitoring blood circulation, peak flow measurement, etc.
  - Mediator release tests, plasma histamine, if necessary DAO, and other parameters

Although oral provocation with 75–150 mg histamine is the gold standard to prove the presence of HIT, this test, even if performed under standardized clinical testing conditions, does not yield reproducible symptoms in all patients. This may be due to the absence of specific factors that favor the occurrence of histamine-induced symptoms in daily life (such as specific combinations of foodstuffs,

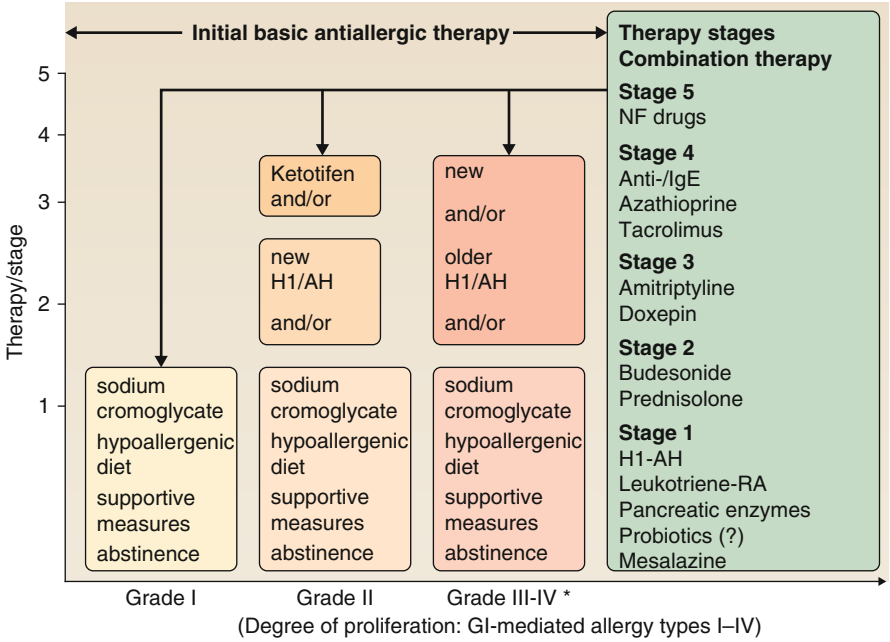


Fig. 3.10 Principles of stagewise therapy for food allergy and histamine intolerance

alcohol, psychological stress, etc.). Therefore, laboratory analysis of DAO or histamine N-methyltransferase activity complements the clinical diagnostic procedure of oral histamine provocation for the purpose of identifying false-negative provocation tests (Kuefner et al. 2008; Maintz et al. 2011; Petersen et al. 2003; Raithel et al. 1998).

3.6.2.2 Additional Modifying Factors

As the clinical manifestation of allergy or HIT may not be caused by the allergen or the foodstuff containing amine alone, but is favored by other conditioning factors such as specific underlying diseases (Figs. 3.9 and 3.10), the presence of alcohol or nicotine, drugs that enhance permeability (such as painkillers, nonsteroidal anti-inflammatory drugs, aspirin, etc.), spices (e.g., curry, chilly), salicylates in food (e.g., pineapple, curry, berries), physical or mental strain, and physical factors, one should take accompanying factors into account.

Unspecific supportive therapy measures in cases of food allergy and histamine intolerance:

- The patient should be referred to the nutritional therapist, individual diet plans should be worked out, and the patient should receive suggestions for a diet with balanced quantities of nutrients.
  - Low-histamine diet.
  - Abstinence from unspecific histamine liberators (e.g., tomato, strawberries, etc.).
  - If necessary the use of a hypoallergenic liquid diet.

- If necessary substitution of pancreatic enzymes.
  - Eliminate accompanying factors that favor the manifestation of allergy (augmentation factors).
  - Physical strain and mental agitation (stress).
  - Physical factors (cold, heat, alcohol, spices, etc.).
- Treatment of other underlying diseases.
  - Review concurrent medication in respect of:
    - Constituents (starch, soy, corn flour, etc.)
    - Immunoactive substances (ACE inhibitors, antiepileptic agents, NSAID, etc.)
- Inhibitors of histamine catabolism (antibiotics, mucolytic agents, etc.).
  - Abstinence from substances that increase permeability and abstinence from smoking:
- Alcohol, spices, NSAID, salicylates in food, etc.
  - Look for other types of intolerance:
- Carbohydrate malabsorption, salicylates, etc.
- Rule out loss of bile acid, bacterial overgrowth in the small intestines, and exocrine pancreatic failure; therapy if necessary.
- Investigation by the psychosomatic specialist and monitoring, if necessary therapy.
- Attempt treatment with probiotics and normal intake of coffee.

Endogenous factors that may modulate the manifestation of FA or HIT include genetic factors (hereditary predisposition), the autonomic nervous system (coping with stress and modulation of stress), as well as digestive functions through the secretions of the stomach, gall bladder, and pancreas. This is also evidenced by the fact that persons with disrupted gastric acid production, sprue (hypersensitive to wheat or gluten), chronic inflammation of the pancreas (pancreatitis), or an IgA antibody deficiency may have elevated IgE antibody levels and therefore be prone to a higher risk of allergy (Raithel et al. 2003; Schleimer 2000; Zar et al. 2001; Zopf et al. 2009).

Especially chronic inflammation of the pancreas accompanied by reduced production of digestive enzymes (so-called exogenous pancreatic failure) has been associated with nearly tenfold higher serum and stool IgE levels than those in healthy persons, because the allergens are not effectively destroyed due to the absence of pancreatic enzymes (Raithel et al. 2003). Based on these conclusions, pancreatic enzymes may also be used for the treatment of FA (Fig. 3.10).

Further modulation of allergy activity and the severity of HIT may be achieved by the endogenous hormonal response, such as the estrogen-progesterone ratio or the response of the hypothalamus–pituitary–adrenal axis. Daytime fluctuations in cortisol levels may be used to modulate the severity of allergy and histamine symptoms in such a way that a person has less frequent asthma attacks in the morning, or provocation tests performed early in the morning yield less severe results than those performed in the evening. Even the number and the activity of allergy cells in the blood may vary considerably (Schleimer 2000).

3.6.2.3 Important Aspects of Food

As many persons with FA demonstrate a change in histamine sensitivity because of their disrupted histamine metabolism, initially a low-histamine diet is recommended for persons with severe manifestation of the disease or an ambiguous disease pattern. This signifies abstinence from red wine, cheese, tuna fish, vinegar, sauerkraut, chocolate, and a few other foodstuffs and beverages (also see Sects. 3.7 and 3.8) in order to avoid intolerance reactions (Jarisch 2008; Kuefner et al. 2008; Maintz et al. 2011; Petersen et al. 2003; Raithel et al. 1998; Zopf et al. 2009). At the start of treatment, unspecific histamine liberators such as strawberries, citrus fruits, or tomatoes should also be avoided. Further important measures to reduce intestinal permeability include the administration of zinc, treatment of loss of bile acids (bile acids release histamine), adequate and proportional intake of fat (e.g., curd 20–40 %), and sufficient quantities of vitamins B1, B12, C, folic acid and copper, and, if necessary, pancreatic enzymes. As some patients with HIT have been known to follow a one-sided diet with a large quantity of carbohydrates, it is extremely important to return to a balanced mixed diet (carbohydrates 50 %, protein 20 %, fat 30 %).

Other biogenic amines in food may modulate the symptoms of FA, HIT, or associated underlying diseases (Häberle 1987; Jarisch 2008; Kuefner et al. 2008; Maintz et al. 2011). On in vivo intestinal biopsy, Backhaus et al. showed that of the three important polyamine precursors (putrescine, spermine, and spermidine), putrescine is a significant histamine-releasing molecule (Backhaus et al. 2003; Häberle 1987). Putrescine probably signals histamine release and stimulates intestinal peristalsis. However, in persons with disrupted histamine degradation, this may easily cause symptoms. The clinical conclusion is that food containing putrescine (and also food containing a few other biogenic amines) should be avoided during severe disease activity (Backhaus et al. 2003; Häberle 1987; Jarisch et al. 1993). These associations are possibly more complex because bacteria may also produce putrescine and histamine. This gives rise to the question: To what extent could bacteria and intestinal flora be involved in the manifestation of HIT? Putrescine, other biogenic amines, and histamine appear to compete for the enzyme DAO. Thus, the transformation of histamine is reduced in the presence of high putrescine levels.

3.6.2.4 Specific Therapy

Of specific therapy methods for the treatment of FA or HIT, eliminating the foodstuff (allergen) that triggers the condition or abstinence from the foodstuff containing (hist)amine is certainly of utmost value (Boyce et al. 2010; Zopf et al. 2009). Quite often this results in complete remission of the symptoms. Abstinence of any kind is markedly superior to pharmacological therapy, more economical than the latter, and most easily used when the allergy or intolerance is limited to one or a few allergens or foodstuffs. The patient should be specifically instructed by the nutritional therapist about the prevalence of the allergen or the foodstuff containing (hist) amine. In addition to the prohibition of specific foods, dietetic alternatives should be suggested. This should include an individual diet plan based on proportionate quantities of various nutrients and adequate fat.

Immunological changes due to strict elimination of the allergen or a diet containing histamine cause abatement of allergic symptoms, a drop in IgE levels, excretion of methylhistamine, reductions in levels of major allergens in the bowel (histamine, tryptase, etc.), and improvement of the barrier function of the intestines. This is frequently coupled with a rise in DAO, thus leading to the resolution of secondary acquired HIT.

In addition to abstinence, the specialist should establish, at an early point in time, whether specific oral, sublingual, or subcutaneous immune therapy (hyposensitization) may be administered in the presence of allergy (such as FA cross-reacting with pollen) and whether the patient requires emergency medication at home if there is a risk of anaphylaxis.

3.6.2.5 Unspecific Supportive Therapy

The above-mentioned specific therapy may be optimized by the use of numerous supportive therapy measures in persons with a food allergy or with histamine intolerance (see above and Fig. 3.10) before one uses nutrition therapy consisting of hypoallergenic substitute foods or drug treatment.

3.6.2.6 Supplementary Nutrition Therapy

Nutrition therapy for allergy is similar to that used for the treatment of Crohn's disease. It may consist of specific polymeric diets with specific nutrients (such as Modulen IBD) and elemental diets with amino acids (such as E028), oligopeptide solutions (such as Provide Extra), etc. Interestingly, all of these hypoallergenic foods are free of histamine and also effective in the presence of associated underlying diseases (Jarisch et al. 1993; Schwab et al. 1998).

These substances are either taken in adjuvant form – in quantities of 500–1,500 kcal/day – along with the tolerated diet or in conjunction with a potato–rice diet (if necessary supplemented with hypoallergenic foods such as lamb, green salad, broccoli, etc.). In patients with severe disease involving several allergens, children, or persons with malabsorption syndromes who are in poor nutritional condition, these foods are used as the exclusive diet (>1,500–2,500 kcal/day) for a short period of time (Schwab et al. 1998; Zopf et al. 2009).

3.6.2.7 Stagewise Drug Therapy

When the above-mentioned therapy measures fail to alleviate the patient's symptoms to an acceptable extent, one should first administer antiallergic drugs such as sodium cromoglycate (sodium cromoglycate mast cell stabilizer; available in Germany as Colimune and Pentatop) and histamine 1 receptor antagonists (more recent H1 antihistamines like desloratadine, levocetirizine, rupatadine, etc.; older H1 antihistamines like ketotifen, clemastine, dimetindene, doxepin, etc.) either alone or in combination with histamine 2 receptor antagonists (e.g., ranitidine and famotidine) (Paolieri et al. 1998). Figure 3.10 shows the various principles of stagewise therapy. "Primary antiallergic therapy" may be prescribed initially as basic therapy by any physician. It is marked by a low rate of side effects and high efficiency. After consulting a specialist, the stages of combination therapy are used in patients with greater disease activity, a high degree of endangerment (anaphylaxis), or chronic disease.

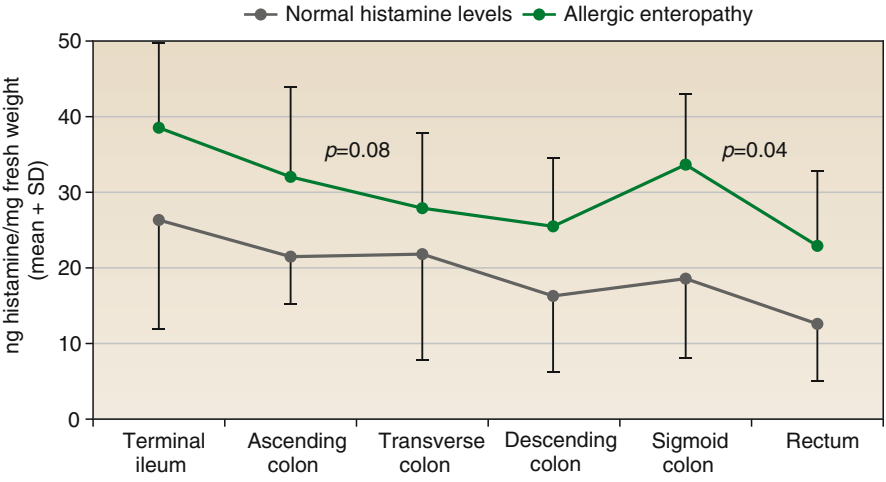


Fig. 3.11 Tissue histamine levels in the lower gastrointestinal tract as a basis for the application of a low-histamine diet, mast cell stabilizers, and antihistamines in persons with a food allergy

3.6.2.8 Mast Cell Stabilizers and Antihistamines

Drugs that stabilize allergen-specific effector cells mainly include cromoglicic acid, ketotifen (a weak mast cell stabilizer), and a few recent H1 antihistamines. With regard to the stabilization of allergy cells (mast cells, eosinophils), gastrointestinal allergy should not be equated with HIT. In allergy a person's hypersensitivity is mediated by specific immune mechanisms, but in HIT the hypersensitivity is caused by histamine overload, highly sensitive histamine receptors, or inhibition of histamine degradation (also see Table 3.3 Classification of histamine intolerance). Thus, the stabilization or inhibition of allergy cells and the underlying immune mechanisms (such as the formation of IgE antibodies) is the main focus of drug treatment of allergy, whereas the treatment of HIT is focused on blocking/reducing the quantity of available histamine itself. Figure 3.11 shows that FA is generally associated with consistently high histamine levels due to activated mast cells in the lower GIT. This explains why dietetic measures are immediately followed by the use of mast cell stabilizers, H1 and H2 antihistamines (Raithel and Hahn 1998; Raithel et al. 1998, 2006, 2007; Zar et al. 2001).

Sodium cromoglycate reduces cellular release of mediators and thus blocks the allergic reaction (Boyce et al. 2010; Zar et al. 2001) in IgE-mediated allergy as well as specific types of non-IgE-mediated allergy. Sodium cromoglycate is not absorbed to a relevant extent in the intestines and therefore exerts just a local effect in the gastrointestinal tract. The substance is associated with a low rate of side effects and is most commonly used to treat local GI-mediated allergy (grade I, only the intestines are affected) (Boyce et al. 2010; Marshall 2000; Raithel et al. 2007; Zar et al. 2001). Three to five doses are administered daily before meals. The dose is increased gradually to 2 g/day or 30–40 mg/kg body weight in adults. If no effects are noted even after administering more than 2 g/day, the patient has an allergy mechanism that cannot be inhibited by cromoglicic acid (a different mast cell subtype? type IV

allergy?), or diagnostic investigations in respect of other types of intolerance and mediators have been inadequate (such as salicylate intolerance). The different therapy responses to cromoglicic acid in FA have been investigated in more than 50 studies. Depending on the patient population, remission rates of 40–90 % have been reported (Boyce et al. 2010; Collins-Williams 1986; Marshall 2000; Raithel et al. 2007; Zar et al. 2001). Gastrointestinal symptoms of allergy such as diarrhea, abdominal pain, or flatulence are associated with a therapy response of about 75 %. Extraintestinal symptoms (migraine, atopic dermatitis, chronic urticaria) do not respond well to treatment with sodium cromoglycate. Due to its favorable mast cell-stabilizing effects in the GIT, sodium cromoglycate is used even in cases of suspected gastrointestinal allergy. Such trial therapy should be administered at a sufficiently high dose for at least 4 weeks in order to establish its efficacy (Collins-Williams 1986; Raithel et al. 2007).

Based on its chemical acid structure, sodium cromoglycate may cause rare side effects in persons who do not tolerate citrus fruits, organic acids, or salicylic acid (NSAID or salicylate intolerance). This may occasionally worsen gastrointestinal complaints. When this occurs, the physician should utilize the opportunity and test the person in regard of acids and salicylates (Raithel et al. 2005). In some persons who do not tolerate cromoglicic acid, one may identify salicylate intolerance as the cause of the underlying gastrointestinal symptoms. This disease pattern would then call for another dietetic measure, namely, abstinence from foodstuffs containing salicylic acid, 5-aminosalicylic acid (and nonsteroidal drugs), and colorants (e.g., citrus fruits, curry, certain spices, blackberries, and potato) (Raithel et al. 2005).

3.6.2.9 Ketotifen and Older Antihistamines

Ketotifen also achieves a moderate attenuation of allergy cells. It is absorbed at the systemic level and, like older antihistamines, has sedating (fatigue) and anticholinergic effects. Therefore, ketotifen or older antihistamines are used after basic therapy measures such as sodium cromoglycate have proved ineffective (Fig. 3.10). Owing to its side effect spectrum, ketotifen is dosed gradually. One starts by administering the substance in the evening in cases of extraintestinal symptoms such as asthma, urticaria, or rhinoconjunctivitis (Marshall 2000). As an H1 receptor blocker, ketotifen was found to exert beneficial effects in the treatment of eosinophilic gastroenteritis, chronic inflammatory bowel disease, and HIT (Boyce et al. 2010; Collins-Williams 1986; Raithel et al. 2007).

3.6.2.10 Newer Nonsedating Antihistamines

Newer antihistamines (e.g., fexofenadine, levocetirizine, desloratadine, rupatadine) also achieve stabilization of allergy cells to a certain extent and very effectively block histamine at peripheral histamine receptors. Therefore, they are mainly used when extraintestinal organs (such as the skin, lung, or nose) are involved in FA (extraintestinal disease, grades II–IV), HIT, or mastocytosis. Even in cases of gastrointestinal disease, H1 and H2 antihistamines alleviate symptoms like abdominal pain, diarrhea, colic attacks, or dyspepsia. However, one should keep in mind the fact that much higher doses are required for the GIT (two- to fourfold higher daily

doses of desloratadine, levocetirizine, rupatadine, etc.) than in cases of allergic rhinoconjunctivitis (Raithel et al. 2007), depending on the quantity of released histamine. Newer antihistamines are associated with much lower side effect rates than older antihistamines (Marshall 2000; Schwab et al. 2001). They mediate additional anti-inflammatory effects, which is advantageous in the presence of specific associated diseases (such as ulcerous colitis or microscopic colitis). They may be taken before as well as after meals and are quite important in acute or shock treatment (Raithel et al. 2005).

Older antihistamines with tranquilizing and sedating effects are beneficial when FA is complicated by, or associated with, agitation, anxiety disorders, or a pronounced psychomotor constitution, somatoform disorders, sleep disorders, or concurrent episodes of depression.

The persistence of severe primary idiopathic intestinal (non-immunological) HIT without an accompanying food allergy – which remained for more than 20 years – is described in the following case report (Case 1). The second case shows how difficult it can be to detect a local gastrointestinal allergy, which occasionally provides the explanation for the evolution of the entire disease pattern.

3.6.2.11 Further Drug-Based Therapy Options

Figure 3.10 shows that in difficult cases, modern stagewise therapy may be supplemented with numerous therapy options at experienced centers. These therapy options include leukotriene receptor agonists (Montelukast), which have a relatively low side effect profile.

Further effective therapy alternatives include conventional (prednisolone) or topical (budesonide) cortisone preparations, the use of anti-IgE antibodies (omalizumab) or immunosuppressants. Whether the alteration of intestinal flora by probiotics achieves effective improvement of FA or HIT in the long term is currently under investigation.

Case Report 1

Two men had been suffering from chronic diarrhea for more than 20 and 30 years, respectively. Numerous investigations failed to reveal any pathologies in the gastrointestinal tract or other organ systems. Thus, all attempts to treat the condition failed. HIT, evidenced by high excretion of methylhistamine and histamine in the urine, served as the crucial diagnostic sign. A potato–rice diet was prescribed. This was followed by a low-histamine diet and the administration of H1 receptor blockers for a short period of time. These measures led to cessation of diarrhea in both cases. The patients achieved an entirely new sense of life. Owing to the patients' immediate and remarkable response to therapy, oral histamine provocation to confirm the diagnosis was deemed unnecessary.

The patients' prolonged period of suffering is explained by the fact that HIT was only manifested in the gastrointestinal tract as diarrhea but was not

manifested in other organs (such as skin rash, low blood pressure, etc.). Therefore, all treating physicians focused on the GIT. After all causes of diarrhea had been ruled out, the sole alternative that remained was the notion of intolerance. These cases prove that intolerance reactions (e.g., HIT, salicylate, or sulfite intolerance) may occasionally be manifested in isolated fashion, atypically, or in the form of several symptoms in an organ system. A few diseases that may progress in such (masked) form have been reported in the published literature (e.g., FA, postprandial rhinitis, celiac disease, rheumatoid arthritis, etc.) (Arslan et al. 2006; Lin et al. 2002; Paajanen et al. 2005; Raithel et al. 2005; Zar et al. 2001). Therefore, when routine diagnostic procedures prove fruitless in individual cases, one should always take the possibility of such rare diseases into account.

Case Report 2

Another case of a 60-year-old woman with chronic inflammation of the large bowel (so-called collagenous colitis) illustrates the entire problem of local FA in the GIT. Due to collagenous colitis, the patient had been experiencing 8–12 bouts of diarrhea daily for more than 10 years. Several attempts to treat the condition with prednisolone, Imodium, probiotics, 5-aminosalicylic acid, and budesonide had been largely unsuccessful. The patient was given aspirin for the treatment of an obstruction of vessels in the ocular fundus. Under 9 mg budesonide (topical steroid), she still experienced 5 stools per day.

Determination of methylhistamine in the urine under a balanced diet and a potato–rice diet showed consistently high values on several occasions (12–15 µg methylhistamine/mmol creatinine × m^2 body surface area). The patient underwent gastroenterological investigation with specialized diagnostic procedures for allergy, which revealed evidence of lactose malabsorption (lactose intolerance) as well as allergy antibodies (IgE, local type I allergy) in the large bowel.

As the patient's methylhistamine levels in the urine did not fall under the potato–rice diet, we first suspected a rare potato or rice allergy. However, the corresponding antibodies were found neither in the blood nor in the intestines. As potato contains salicylic acid, peripheral blood cells were tested in respect of salicylate intolerance (Raithel et al. 2005). This test clearly revealed salicylate intolerance, although the patient consistently took salicylic acid in the form of aspirin. Apparently, this patient's salicylate intolerance was manifested by just one symptom, namely, inflammation of the large bowel. Based on this finding, aspirin was replaced by a different platelet-inhibiting drug (Plavix). For the first time the patient's diarrhea resolved. Budesonide could be discontinued and an antihistamine was administered.

During the regeneration diet (starting with rice), the patient observed that she always experienced painful bloating sensations and partly mucinous stools when she ingested banana. This caused the physicians to look for specific antibodies to banana and other cross-reacting types of fruit. IgE antibodies to banana were found, indicating a so-called cross-reaction between latex, banana, and pineapple. After eliminating banana, pineapple, and other cross-reacting fruits (kiwi, melon, etc.) from her diet, the patient ceased to experience diarrhea. Now she needs no medication other than a single antihistamine taken once daily in the evening.

Thus, the final diagnosis was GI-mediated allergy and associated NSAID intolerance (salicylate intolerance). In the meantime, this disease pattern of collagenous or microscopic colitis has been observed in several patients on medication (aspirin). This apparently causes a disruption of intestinal permeability, which permits the person to become sensitized to food and then develop an allergy mediated by the gastrointestinal tract (Raithel et al. 2005).

3.7 Irritable Bowel Syndrome

Reinhart Jarisch

Diarrhea is the cardinal symptom of the irritable bowel syndrome. The condition is presumed to be of psychovegetative origin. We are all aware of stomach pain and diarrhea before examinations at school – which disappear immediately once the stress is over. We decided to investigate whether the irritable bowel syndrome is possibly triggered by lactose intolerance (LIT) and/or intestinal fructose intolerance (FIT).

In a placebo-controlled double-blind study, 230 patients who fulfilled the ROM-II criteria of the irritable bowel syndrome received a lactose-free or fructose-free diet for 3 weeks. They were then investigated in regard of lactose and intestinal fructose intolerance by the use of the hydrogen breath test. We expected to delineate four groups: FIT positive, LIT positive, FIT and LIT positive, and FIT and LIT negative. The patients were randomly assigned to the diets at the start of the investigation. Thus, they received the appropriate or inappropriate diet purely by coincidence.

Patients who received the appropriate diet improved significantly after 3 weeks. This was obviously an expected outcome. However, it came as a great surprise that even patients who maintained the "wrong diet" (such as patients with lactose intolerance on a fructose-free diet) were improved to a highly significant extent ($p < 0.001$). Patients who were shown to have neither FIT nor LIT also improved very markedly by adhering to one of the two diets.

How does one explain these facts? This disease pattern appears to be caused by a different and "superior" phenomenon such as stress before examinations, as described above. Possibly, some persons experience their entire lives as a stressful

experience. On the other hand, this "negative" outcome also has a "positive" side. It would explain, with great ease, why so-called alternative medical procedures are effective in the presence of this disease: no matter what diet a patient is prescribed, it always helps. The physician, the talk with the physician, and the feeling of having been helped is, in itself, a form of therapy. So are we dealing with a psychological cause?

3.8 Low Blood Pressure (Hypotension)

Reinhart Jarisch

One of the physiological (normal) functions of histamine is to achieve vasodilatation. Therefore, it is quite comprehensible why persons with a histamine degradation disorder and consequently increased histamine levels in the blood may also have low blood pressure (hypotension). Interestingly, patients are known to have low blood pressure for years but accept it as the "will of God," so to speak. Physicians also regard only high blood pressure as a disease. Therapeutic measures used thus far to treat low blood pressure have been rather modest – ranging from the intake of fluid in the morning while "still in bed" to sports and the administration of so-called cardiovascular agents. As a rule, none of these measures is very effective.

Therefore, in patients with low blood pressure, it would be quite worthwhile to take the possibility of histamine intolerance and the corresponding measures (described above) into account. However, the opposite (i.e., hypertension) may also occur.

Case Report
I know a lady (a doctor) who, after ingesting hard cheese, repeatedly experienced hypertensive crises which could not be controlled by therapy. Once she stopped ingesting this type of cheese, the crises ceased to occur. As histamine does not only dilate peripheral vessels and leads to hypotension in the majority of cases, but also constricts central vessels, some patients may develop hypertension rather than the expected condition of hypotension.

3.9 Urticaria

Reinhart Jarisch

The subject of urticaria would fill an entire textbook. Publications on the subject provide sufficient data about the condition.

To establish the cause of urticaria, the simplest thing to do is to look for recently used medications and their potential intolerance. On occasion, NSAID intolerance

(intolerance of nonsteroidal anti-inflammatory drugs like aspirin) may be combined with chronic urticaria (Asero et al. 2001).

Worm infections, whose many features include high total IgE levels, may be the cause of urticaria.

The first condition is fairly common. The latter hardly occurs in our latitudes. When urticaria is really found to have been caused by a worm infection, total IgE levels will be reduced by the power of ten after 14 days of treatment with Pantelmin tablets given 2 × 1 for 3 days, because the half-life of IgE is just 2–3 days.

Serum IgG autoantibodies directed against the α-chain of the FcεRI receptor have been identified as a marker and pathogenetic factor in about one third of patients with chronic urticaria (Fiebiger et al. 1995).

Urticaria is presumed to be caused by food allergy. However, a genuine food allergy is very rarely the cause. Among about 400 patients with urticaria, we found an association between urticaria and food intolerance in about 10 % of cases; a very small number of these were genuine food allergies. Intolerance of biogenic amines is much more common among these patients. However, those with intolerance of biogenic amines also comprised just about 10 % (Jarisch et al. 1999; Pollock et al. 1991).

In patients with urticaria, which is a supreme example of a histamine-related disease, it would be meaningful to use all possible measures to reduce histamine levels. Therefore, the patients are asked to abstain from food containing histamine and other biogenic amines. This reduces histamine levels rapidly and, provided the patient's tolerance limit is not undershot, also improves or cures the condition.

The most recent position paper recommends up to four tablets of an antihistamine for the treatment of chronic urticaria (Zuberbier et al. 2009). Assuming that histamine plays a causal role, one should also take a histamine-free diet into consideration.

When antihistamines prove ineffective, the condition may be due to leukotrienes, or leukotrienes in addition to other causes. In these cases one should attempt treatment with leukotriene receptor antagonists (Montelukast®) (Pacor et al. 2001).

3.10 Mastocytosis and Mast Cell Activation Syndrome

Martin Raithel

3.10.1 Definition

The symptoms of mastocytosis are a supreme example of systemic histamine intolerance (HIT). The term mastocytosis encompasses a heterogeneous group of diseases marked by the proliferation and accumulation of mast cells in various tissues (Ellis 1949). All subtypes of mast cells contain histamine and can be activated to secrete histamine as well as about 40 other inflammatory substances (including tryptase, eicosanoids, etc.). Stress, mental tension, and estrogens may intensify or

modulate the effects of classical mast cell stimuli (Akin 2005; Ellis 1949; Molderings et al. 2006).

The following are important *stimuli of mast cells* in mastocytosis:

- Food, drink, and tobacco (alcohol, seafood)
- Strain and physical and emotional stress
- Physical factors (heat, cold, sunlight, pressure, friction)
- Bacterial toxins
- Insect venom (especially bee and wasp stings)
- Medicinal products (acetylsalicylic acid, codeine, morphine, polymyxin B, dextran, amphotericin B, heparin, contrast media containing iodine)

Mastocytosis is a consequence of functional activating mutations in various cell proteins (e.g., tyrosine kinases c-kit), which leads to persistent activation of the affected mast cells (Akin 2005; Molderings et al. 2006). Mastocytosis is marked by increased numbers of mast cells, in activated condition, often immature, which do not proceed to normal apoptosis.

HIT is a predominant feature because mast cells are a principal mediator and contain a large quantity of histamine and because, under physiological conditions, a very low concentration of histamine is present in the body. Symptoms occur rapidly when this limit is exceeded (e.g., plasma levels >0.35 ng/ml × m^2 body surface area; see Sect. 3.5 Gastric Complaints). The effects of histamine are passed over to tissue through four histamine receptors. According to the classification of HIT (refer to Sect. 3.6 Diarrhea), in mastocytosis HIT is mainly caused by greater availability of endogenous histamine in metabolism (Molderings et al. 2006; Raithel et al. 2011). One must specifically determine whether this dominant mechanism is associated with additional mechanisms (such as the intake of exogenous histamine). This would include a search for intestinal IgE antibodies, the determination of diamine oxidase (DAO) and histamine N-methyltransferase in the tissue, etc. Apart from histamine, the above-mentioned mast cell mediators may cause specific symptoms (Akin 2005; Molderings et al. 2006; Raithel et al. 2011). As nearly all patients with systemic mastocytosis have high histamine levels, treatment with antihistamines and a low-histamine diet is successful in more than 75–80 % of patients.

3.10.2 Classification of Various Forms of Mastocytosis

Mastocytosis may be divided into forms that only affect the skin (urticaria pigmentosa) and those that concern one or several internal organs (systemic mastocytosis) (Table 3.6). Once an organ is affected, the patient may develop initial symptoms of HIT. The severity and frequency of symptoms secondary to histamine increase with advancing organ disease. Reactive mast cell accumulation and the mast cell activation syndrome should be differentiated from the various forms of mastocytosis listed in Table 3.6 (Akin 2005; Molderings et al. 2006; Raithel et al. 2011).

Table 3.6 Classification of various forms of disease in mastocytosis

Stage	Severity
I	*Cutaneous mastocytosis* (*only the skin is affected*)
1	Urticaria pigmentosa (typical skin rash of mastocytosis)
2	Solitary or multiple mastocytoma (the accumulation of mast cells is limited to a small area on the skin)
3	Diffuse cutaneous mastocytosis (involvement of the skin without urticaria pigmentosa; in case of massive involvement of the skin, large quantities of mast cell products are released and the patient has systemic symptoms)
II	*Systemic mastocytosis with or without involvement of the skin* (mast cell infiltration in at least one internal organ: usually the bone marrow, the gastrointestinal tract, the liver, or the spleen)
III	*Mastocytosis with accompanying hematological disease* (e.g., leukemia)
IV	*Lymphadenopathic mastocytosis with eosinophilia* In some cases there may be further changes in blood count and bone marrow (enlarged splenic and lymph nodes with mast cell infiltrates and a large quantity of eosinophils in the blood)

3.10.3 Symptoms of Mastocytosis

The severity of symptoms may differ markedly from person to person, depending on the factors affecting histamine metabolism, the immune system, the autonomic nervous system, etc. Further variables include mediators secreted in addition to histamine (Raithel et al. 2011), concurrent factors (e.g., drugs, food, intestinal flora, etc.), and existing or acquired underlying diseases (such as bee or wasp venom allergy, osteoporosis, etc.).

The symptoms range from simple fatigue and mild malaise to anaphylactic shock (after a bee or wasp sting, for instance) or, in very rare cases, leukemia. Over time the symptoms may become more severe or may occur more frequently. However, the symptoms of the disease may also be improved for a long period of time. The type and severity of symptoms may vary from one episode to the next. The foremost symptoms of urticaria pigmentosa include transient reddening, tingling, burning of the skin, itching, and urticaria (nettle rash). Patients with systemic mastocytosis may additionally develop nausea, vomiting, abdominal cramps, diarrhea, excessive production of gastric acids, and even gastric or duodenal ulcers (Akin 2005; Molderings et al. 2006; Raithel et al. 2011). Besides, bone atrophy (osteoporosis), joint or muscle pain, enlargement of the liver and/or spleen, bladder pain, allodromy or tachycardia, low blood pressure, shortness of breath, dizziness, fatigue, weakness, loss of weight, respiratory disorders, and even bronchial asthma may occur. Other manifestations of the disease include depression, memory and concentration disorders, headache, intolerance of heat and cold or changes in temperature, and syncope.

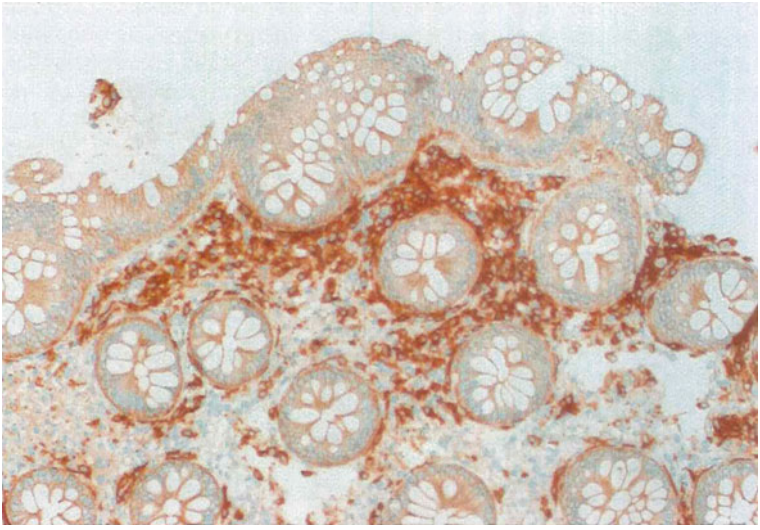


Fig. 3.12 Immunohistochemical presentation of systemic mastocytosis in the small bowel with multifocal accumulations of pathological mast cells (>15 adjacent brown-stained mast cells per field of view)

3.10.4 Diagnostic Investigation of Mastocytosis

Clinical description of the constellations of symptoms listed above may be aided by a checklist to assess the presence of mastocytosis (for details refer to www.uni-bonn.de/~umv701, Molderings et al. 2006). Besides, one looks for pathologically increased levels of typical mast cell mediators like tryptase or chromogranin A in the blood, which constitute an expression of abnormal mast cell accumulation. One also determines whether histamine metabolites like methylhistamine are excreted to a greater extent by the urinary pathway and whether there is a rise in IgE levels or eosinophils in the blood (atopy) (Akin 2005; Ellis 1949; Molderings et al. 2006; Raithel et al. 2011). Pathological increases in these mast cell messenger substances call for a through differential diagnostic investigation while taking clinical symptoms into consideration. The differential diagnosis is of diagnostic, therapeutic, and prognostic relevance because food allergies (FA), NSAID intolerance, drug or insect venom allergies, and other diseases may cause symptoms similar to those of a so-called mast cell mediator syndrome.

The clinical diagnosis or the suspicion of mastocytosis is eventually confirmed by a tissue biopsy (skin, liver, intestines, or bone marrow) and/or mutation analysis (e.g., c-kit mutations). Figure 3.12 shows severe mastocytosis in the bowel in a patient with colic attacks, diarrhea, and weight loss. To prove the presence of systemic mastocytosis, one must demonstrate mast cell infiltrates in at least one extracutaneous organ (Akin 2005; Molderings et al. 2006). This may be achieved by performing an ultrasound investigation of the abdominal cavity (if necessary with liver puncture), taking biopsy specimens from the gastrointestinal tract (GIT)

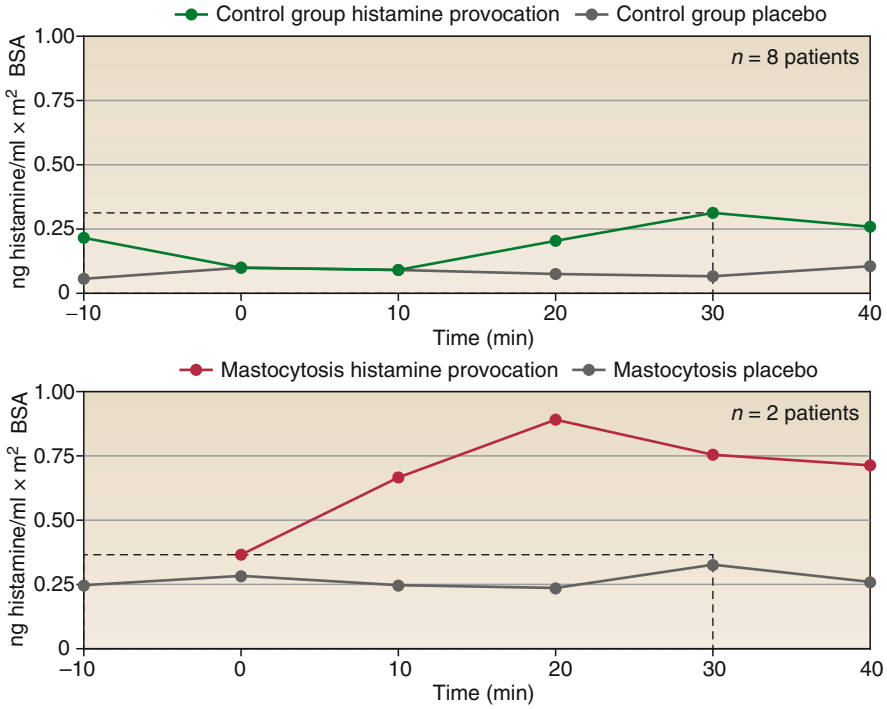


Fig. 3.13 Standardized histamine provocation (75 mg oral) in persons with mastocytosis and controls

during a gastrointestinal endoscopy, or even a bone marrow biopsy (iliac crest) (Akin et al. 2010; Perbellini et al. 2008; Raithel et al. 2011; Valent et al. 2007).

3.10.5 Treatment of Mastocytosis

To the present day we have no cure for mastocytosis. The treatment is aimed at reducing the release of mast cell products and/or inhibiting mast cell activity (Butterfield 1998; Escribano et al. 2006; Molderings et al. 2006; Raithel et al. 2011). Therefore, the crucial measure is to avoid factors known to trigger a reaction in the individual patient, such as drugs, food and semi-luxury foods, histamine liberators, or situations that activate the immune system (such as infection, insect venom, vaccines, etc.), as well as specific physical and mental stresses (see above).

Figure 3.13 specifically shows that individual patients with mastocytosis may also react to mental stimuli (such as stress, agitation) in terms of histamine release because of their yet immature mast cells. In contrast to healthy persons and those with FA, patients with mastocytosis receiving standardized histamine provocation with placebo (mint tea) at the intensive care unit were found to show variable rates of visible symptoms (flush, agitation, tachycardia) as well as objective increases in

plasma histamine levels. Apparently, a test situation of this type in patients with mastocytosis causes the release of neurotransmitters. These, in turn, are able to release histamine to a greater extent from the proliferating immature mast cells (Giera et al. 2008). Therapy options in this setting include stress regulation, regular breaks for relaxation, the administration of older antihistamines with a sedating effect (such as doxepin or clemastine), or once to twice weekly administration of low-dosed soporifics (so-called benzodiazepines, for instance, 1.5–5 mg of bromazepam or oxazepam in the evening). This is because mast cells also have receptors for these soporifics (benzodiazepine receptors). Thus, the neural stimulus acting on mast cells is partly blocked without inducing soporific-like effects at these doses.

The treatment of mastocytosis primarily consists of so-called H1 receptor blockers (such as diphenhydramine, fexofenadine, desloratadine, rupatadine, etc.) to reduce the stressful symptoms (e.g., reddening of the skin, diarrhea, etc.). On the other hand, gastric and abdominal symptoms caused by acidity respond well to H2 receptor blockers (such as ranitidine or famotidine) or proton pump inhibitors (such as pantoprazole). Quite often one has to administer H1 and H2 receptors jointly and/or dose them higher because the quantity of released histamine may be manyfold higher than normal tissue or blood levels (Escribano et al. 2006; Molderings et al. 2006; Raithel et al. 2011). A further important substance is sodium cromoglycate (available in Germany as Colimune and Pentatop). Like ketotifen this is a mast cell stabilizer which, in many cases, blocks gastric and intestinal mast cells very effectively. The exact guidelines concerning these mast cell stabilizers, antihistamines, and supplementary and supportive therapy measures are described in Sect. 3.6 Diarrhea (Butterfield 1998; Escribano et al. 2006; Molderings et al. 2006).

Patients who secrete large quantities of mast cells (histamine, eicosanoids, etc.) as a reaction to excipients (mainly lactose, maize starch, preservatives and colorants, ethanol) contained in medicinal preparations are especially difficult to treat (Molderings et al. 2006; Raithel et al. 2011). When the required active substances are not available as proprietary medicinal products without the excipients associated with intolerance, one may ask the pharmacist to produce a tolerable version of the medicinal product without the excipients, Besides, one must look for associated diseases (such as lactose malabsorption, NSAID intolerance, rare allergy to preservatives). In addition to histamine, the so-called eicosanoids (prostaglandins, leukotrienes, PAF, thromboxane) formed from cellular metabolism may cause symptoms (after the intake of salicylates or preservatives, for instance), although the patient may be taking sufficient antihistamines (Raithel et al. 2011). Leukotriene receptor antagonists (e.g., Montelukast) or the H1 and PAF receptor blocker rupatadine is suitable for this purpose (Raithel et al. 2011). Since acetylsalicylic acid, nonsteroidal anti-inflammatory drugs, and even salicylates in food may cause severe reactions (such as shortness of breath, flush, bowel inflammation, shock) because of the formation of leukotrienes, it would be advisable to first test the patient in respect of salicylate intolerance and determine his/her ability to tolerate salicylates (NSAID intolerance) (Schäfer et al. 1999). In case of a negative test outcome one may, if necessary, test acetylsalicylic acid at a very low dose, administered as a supine infusion under medical supervision, and keep emergency drugs ready for

immediate use. In contrast to these leukotriene-forming substances in patients with mastocytosis, a few rare patients with mastocytosis have been reported to develop large quantities of prostaglandins (flush, dizziness). Paradoxically, acetylsalicylic acid (such as ASS or aspirin) was helpful in these patients.

PUVA may be successfully used in patients with skin symptoms. The patient is given a substance (psoralen) to swallow or rub in, which renders the skin more photosensitive. The skin is then radiated with UVA, which exerts a favorable effect on the release of mast cells in the skin (Godt et al. 1997). In cases of severe symptoms that do not respond to the above-mentioned measures, or in cases of anaphylactic reactions, it may be meaningful to use systemic corticosteroids, anti-IgE antibodies (omalizumab), cyclosporine, or interferon (Molderings 2011; Godt et al. 1997),

Patients with mastocytosis should always be thoroughly informed about the possibility of shock and its emergency treatment. In cases of severe disease activity, the presence of an insect venom allergy, or markedly increased serum tryptase levels, one should always keep a so-called emergency set ready, consisting of H1 and H2 antihistamines, liquid cortisone preparations, and epinephrine as an emergency injector (Butterfield 1998; Escribano et al. 2006),

3.11 Histamine Metabolism in Chronic Inflammatory Bowel Disease

Martin Raithel

Several advances have been made in the last few decades as regards research in inflammatory bowel disease (IBD). However, the exact triggering agents of this type of bowel inflammation are still unknown (Sánchez-Fayos et al. 2009). The involvement of the immune system is emphasized by the therapeutic effects of 5-aminosalicylic acid (mesalazine), which has largely anti-inflammatory and antihistaminergic effects. It is also emphasized by cortisone preparations which act as immunosuppressants and biological cytokine antagonists (anti-TNF antibodies). According to current knowledge, this condition is marked by an abnormal and excessive immune response or disrupted immune regulation, resulting in intensified formation of proinflammatory messenger substances of the immune system (Sánchez-Fayos et al. 2009). Analogous to food allergies (FA), one first suspects a loss of specific protective factors (tolerance) in IBD or the irritable bowel syndrome. Such loss, in conjunction with specific genetic factors, environmental factors (food, nicotine), and local complex immune dysregulation (e.g., interleukin 6, intestinal flora), may lead to various disease patterns (Fig. 3.14) (Eigenmann 2009; Krauss et al. 2010; Sánchez-Fayos et al. 2009).

Dysregulation of the immune system in IBD also leads to the activation of allergy cells, histamine synthesis, and changes in histamine degradation enzymes (among other effects). Therefore, the significance of FA and histamine intolerance (HIT) has been addressed since the very first description of IBD. These patients' clinical characteristics show that atopic diseases are common in IBD: 27–50 % of patients have

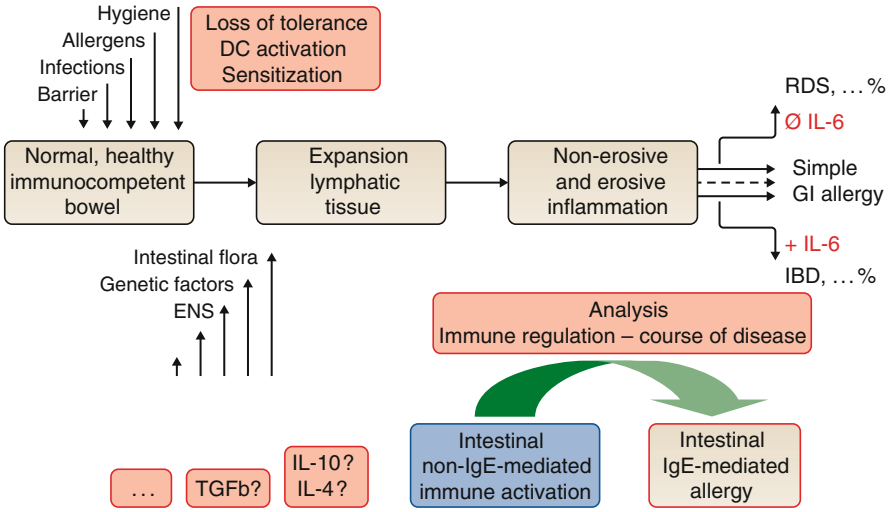


Fig. 3.14 Immunopathogenesis in gastrointestinal allergy, inflammatory bowel disease, and irritable bowel syndrome

Table 3.7 Clinical and immunological characteristics of German patients with chronic inflammatory bowel disease

Characteristics	Crohn's disease[a] ($n=29$)	Ulcerative colitis[a] $n=15$	Age-, gender-, and occupation-matched controls $n=44$
Atopic disease	18 (62 %)	10 (67 %)	22 (50 %)
Positive skin test (prick test)	10 (34.5 %)	8 (53.3 %)	15 (34.1 %)
Plasma histamine (>0.35 ng/ml×m² BSA)	8 (27.6 %)	8 (53.3 %)	3 (6.8 %)
Food allergy (any type)	7 (24 %)	3 (20 %)	7 (16 %)
Oral allergy syndrome	4 (13.7 %)	3 (20 %)	1 (11.3 %)
Gastrointestinal allergy and extraintestinal symptoms	3 (10.3 %)	2 (13.3 %)	2 (4.5 %)
Allergy among relatives	14 (48 %)	5 (33 %)	30 (68 %)
IBD among relatives	8 (28 %)**	0 (0 %)	1 (2.2 %)

BSA body surface area
**$p=0.032$
[a]All patients without acute inflammation (remission)

high plasma histamine levels in the stage of remission (Table 3.7). The frequency of clinically demonstrable FA is high in IBD. Classical IgE antibodies in the bowel are found in Crohn's disease, ulcerative colitis, or microscopic colitis in 10–30 % of cases (Table 3.7; Fig. 3.15). Except for a few published cases in which abstinence from the allergen led to sustained resolution of bowel inflammation (Raithel et al. 2007; Weidenhiller et al. 2005), we still do not know whether these local allergy antibodies act as triggers of IBD or merely arise in the course of inflammation (Moneret-Vautrin et al. 2001; Raithel et al. 1999; Van den Bogaerde et al. 2002).

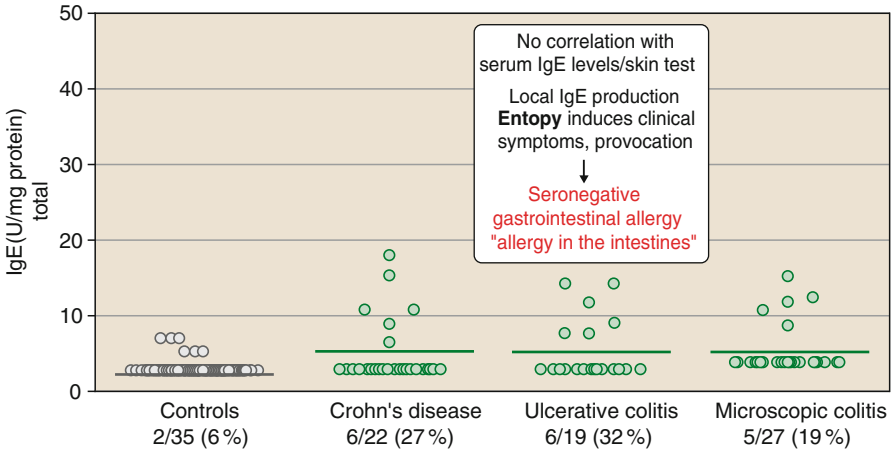


Fig. 3.15 Evidence of local IgE antibodies in the gastrointestinal tract by endoscopically guided segmental lavage of the intestines in chronic inflammatory bowel disease and microscopic colitis

Regardless of this fact, it is important to locate such local IgE antibodies in the bowel because they may lead to allergic symptoms in addition to those caused by IBD. The allergic symptoms may complicate the course of disease and the patient's diet to a significant extent in IBD (Moneret-Vautrin et al. 2001; Raithel et al. 1999, 2007; Van den Bogaerde et al. 2002; Weidenhiller et al. 2005).

Basic activation of immune cells in the bowel may not be caused by allergy-dependent mechanisms alone (IgE antibodies or non-IgE-mediated allergy) (Eigenmann 2009; Krauss et al. 2010; Moneret-Vautrin et al. 2001; Raithel et al. 1999, 2007; Weidenhiller et al. 2005). It may also occur due to numerous nonallergic mechanisms because mast cells – for instance – may react to a number of stimuli (such as bacterial antigens, neurotransmitters, cytokines, etc.; Raithel et al. 1995, 2007; Sánchez-Fayos et al. 2009). Mast cells in the bowel are activated in the acute stage of IBD, are associated with signs of degranulation, and release large quantities of histamine although elevated histamine levels are not always found in blood plasma (Raithel et al. 1995, 2010). The large quantity of histamine released in the bowel leads to the secretion of water and electrolytes, as well as pain and contraction of smooth muscles. In addition to histamine, the condition is marked by the presence of other aggressive proteins from immune cells, leading to the destruction of intestinal mucosa and the epithelium (ulcers, fistulas, etc.). This explains the loss of histamine degradation enzymes like diamine oxidase (DAO) and histamine N-methyltransferase. This phenomenon, in conjunction with activated mast cells, elevated histamine levels in the tissue, and intensified histamine secretion on the intestinal surface, leads to secondary acquired HIT which causes additional clinical problems (Raithel et al. 1995, 2010; Schmidt et al. 1990; Wantke et al. 1994).

As the loss of DAO in Crohn's disease is mainly caused by the bowel inflammation, the patient's histamine intolerance resolves when IBD is treated effectively

(Raithel et al. 1995, 2010). In the acute phase, the use of a (hist)amine- and putrescine-reducing diet or a histamine- and putrescine-free diet is an important measure in addition to drug therapy (Schmidt et al. 1990; Wantke et al. 1994). This is also reflected in so-called enteral nutritional therapy: hypoallergenic and histamine-free preparations (e.g., E028, Modulen IBD, ProvideExtra) are used in the acute phase or to prevent renewed exacerbations.

Comparison of Crohn's disease and ulcerative colitis shows that the latter is associated with a higher risk of allergy, which is partly explained by the so-called Th2 immunopathogenesis of ulcerative colitis and its common association with pollen allergy, neurodermitis, and bronchial asthma. Histamine levels in the acute phase of inflammation are higher in ulcerative colitis than in Crohn's disease [9], while DAO activity may be permanently reduced. This may be due to the patient's greater atopic disposition and the immaturity or consistent regeneration of the intestinal epithelium. Possibly, reduced DAO levels in this setting express the known risk of malignant degeneration in poorly treated ulcerative colitis (Raithel et al. 1998; Schmidt et al. 1990).

These pathophysiological histamine reports led to the use of sodium cromoglycate, antihistamines, and 5-aminosalicylic acid (mesalazine) for the treatment of IBD. The effects of these substances include their ability to block histamine release. As recent investigations have shown, supplementing the standard treatment of IBD with low-dosed application of 10 mg loratadine did not influence plasma histamine levels to a significant extent, but was able to alleviate the patients' clinical symptoms and reduce the dose of cortisone by about 5–15 mg per day (Raithel et al. 2010; Wantke et al. 1994). These data indicate that the treatment of IBD could be improved further by raising the antihistamine dose to a sufficiently high level of about 30–50 mg per day.

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Drug Intolerance

4

Knut Brockow and Reinhart Jarisch

4.1 Drug Allergy

Reinhart Jarisch

Intolerance reactions to drugs are usually manifested as skin rashes. The latter may have a diverse appearance and can be reliably diagnosed only by a dermatologist.

In cases of nettle rash after the intake of a drug, the clinician usually considers a so-called type I allergy. However, in some cases, the test performed after such manifestations shows no evidence of an IgE antibody-mediated allergy in the blood or the skin. In these cases, one should take a potential histamine effect into account.

Besides, the person may have a histamine degradation disorder in addition to the allergy. This should be considered especially when the allergic reaction assumes drastic proportions after the intake of a drug. In this context, it should be noted that some drugs inhibit diamine oxidase. In other words, the intake of these drugs may trigger allergic or allergy-like symptoms at a later point in time. Paradoxically, some drugs used to treat cardiac arrhythmia actually cause arrhythmia, but the condition resolves after discontinuation of the drug and a simultaneous histamine-free diet.

A number of drugs used to treat obstructive bronchitis or asthma may actually be inhibitors of diamine oxidase and thus permit a potential histamine burden to occur or may lead to the deterioration of symptoms. Besides, some drugs used to treat cardiac arrhythmia may be inhibitors of diamine oxidase and – if the arrhythmia has been triggered by histamine – may worsen the disease. The strongest inhibitors of diamine oxidase are listed in Table 4.1.

K. Brockow, MD (✉)
Department of Dermatology and Allergology Biederstein,
Technische Universität München, Biedersteiner Strasse 29, Munich D-80802, Germany
e-mail: knut.brockow@lrz.tum.de

R. Jarisch, MD
Floridsdorf Allergy Center, Franz-Jonas-Platz 8, Vienna A-1210, Austria
e-mail: jarisch@faz.at

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Table 4.1 The top 11 most frequently sold drugs that block the histamine-degrading enzyme diamine oxidase (DAO)

Active substance	Examples
Acetylcysteine	For example, Aeromuc, Pulmovent
Ambroxol	For example, Ambrobene, Ambroxol, Broxol, Mucosolvan, Mucospas
Aminophylline	For example, Euphyllin, Mundiphyllin, Myocardon
Amitriptyline	For example, Saroten, Tryptizol, Limbritol
Chloroquine	For example, Resochin
Clavulanic acid	For example, Augmentin
Isoniazid	Isoniazid (INH) – single agents and combination products
Metamizole	For example, Buscopan comp, Inalgon, Novalgin
Metoclopramide	For example, Ceolat comp., Paspertase, Paspertin
Propafenone	For example, Rhythmocol, Rytmonorm
Verapamil	For example, Isoptin

Patients who are treated with these drugs should avoid food containing histamine because histamine cannot be adequately degraded due to the inhibition of DAO. Therefore, histamine in the alimentary canal may trigger headache, rhinitis, urticaria, diarrhea, hypotension, cardiac arrhythmia, or bronchial asthma

Case Report

A man received anti-arrhythmic agents for the treatment of cardiac arrhythmia. The medication did not improve his condition. Rather, his condition deteriorated under the treatment. After discontinuation of the drug, which is an inhibitor of DAO, and simultaneous abstinence from food containing histamine or other biogenic amines, the patient was relieved of his symptoms.

4.2 Intolerance of Anti-inflammatory and Pain-Relieving Drugs

Reinhart Jarisch

So-called antirheumatic agents, i.e., anti-inflammatory or pain-relieving drugs, may release additional histamine in persons with allergy, which then causes an intensified histamine effect (Table 4.2) (Wojnar et al. 1980). This reaction should be taken into account in patients with hay fever as well as those with allergic bronchial asthma. These drugs either should not be given at all or should be given only when the patient receives H1 receptor blockers simultaneously. However, some anti-inflammatory drugs inhibit the allergen-specific release of histamine in persons with an allergy and are therefore specifically suited for these persons (Table 4.3).

Table 4.2
Anti-inflammatory or analgesic drugs that increase allergen-specific histamine release in persons with an allergy

Active substance	Examples
Meclofenamic acid	Meclomen
Mefenamic acid	Parkeme
Diclofenac	Dedolor, Deflamat, Diclo B, Diclobene, Diclomelan, Diclostad, Diclovit, Dolo-Neurobion, Fenaren, Magluphen, Neodolpasse, Neurofenac, Tratul, Voltaren
Indometacin	Flexidin, Indobene, Indocid, Indohexal, Indomelan, Indometacin, Indoptol, Luiflex, Ralicid
Flurbiprofen	Froben
Naproxen	Naprobene, Nycopren, Proxen
Ketoprofen	Keprodol, Profenid
Acetylsalicylic acid	Aspirin

Table 4.3
Anti-inflammatory drugs that inhibit allergen-specific histamine release in persons with an allergy

Active substance	Examples
Fenbufen	Lederfen
Levamisol	Ergamisol
Ibuprofen	Avallone, Brufen, Dismenol Neu, Dolgit, Ibudol, Ibupron, Kratalgin, Nurofen, Tabcin, Ubumetin, Urem

4.3 Allergy to Radiocontrast Agents

Knut Brockow

Radiocontrast agents are highly concentrated solutions of benzene compounds containing iodine and are routinely used in diagnostic radiology to improve the visualization of organs and body structures (such as vessels) (Brockow et al. 2005). Undesirable effects after the application of radiocontrast agents are not uncommon.

4.3.1 Clinical Appearance

Only some of the undesirable effects after exposure to radiocontrast agents are caused by an allergy and call for a test (Brockow and Ring 2010). Some symptoms, such as a sensation of warmth after the injection, malaise, deterioration of kidney function, or headache, may be explained by the normal "toxicity" of the highly concentrated solutions; these reactions can not be tested. Independent unspecific reactions may also occur. However, typical hypersensitivity reactions to radiocontrast agents, marked by symptoms of anaphylaxis as well as delayed body rashes (exanthema), must be investigated further (Table 4.4) (Brockow and Ring 2010).

Table 4.4 Symptoms of hypersensitivity reactions to radiocontrast agents

	Immediate reactions (usually within 1 h)	Late reactions (usually after >1 h)
Skin	Itching Nettle rash (urticaria, angioedema) Redness	Itching Maculopapular rash due to drugs (raised red rash) In isolated cases Nettle rash, redness Specific skin rashes (including fixed drug eruption, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, pustular rash, hypersensitivity syndromes)
Gastrointestinal tract	Abdominal pain, nausea, diarrhea, vomiting, bowel movement	
Respiratory tract	Hoarseness, cough, dyspnea (asthma attack, swelling of the respiratory tract), sneezing attacks, runny nose	
Cardiovascular system	Drop in blood pressure, rapid heartbeat	
	Circulatory shock (possibly with loss of consciousness)	
	Respiratory arrest or cardiac arrest	

These reactions occur in approximately 3 % of applications of radiocontrast agents and are usually mild. The majority of patients who experience an immediate reaction within 60 min after the administration of radiocontrast agents develop itching and wheals (urticaria, occasionally even angioedema) (Table 4.4) (Brockow et al. 2005). Severe consequences like dyspnea or circulatory reactions are rare (about 0.03 % of cases). Even death has been reported in isolated cases. The majority of patients with delayed reactions to radiocontrast agents develop maculopapular exanthema (itchy skin rash with redness) a few hours or a few days after the administration of the agent (Fig. 4.1).

The sole reliable risk factor indicative of such hypersensitivity reactions is previous reactions in the patient's medical history. Hypersensitivity to radiocontrast agents is usually independent of an iodine allergy, although the agents do contain iodine in bound form. In a study comprising 19 patients with hypersensitivity to radiocontrast agents, only three patients developed symptoms after the administration of high doses of iodine (Scherer et al. 2010). Thus, the large majority of patients appear to be hypersensitive to the benzene structure or side chains and not to iodine.

4.3.2 Diagnostic Investigation

It would be meaningful to perform allergy tests in persons with hypersensitivity reactions to radiocontrast agents (Brockow et al. 2005). Release of histamine or tryptase during an immediate reaction provides an indication of a potential allergic reaction.

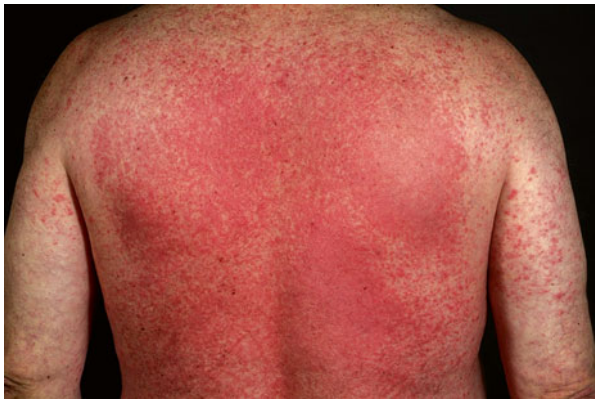

Fig. 4.1 Maculopapular eruption mainly in the trunk, in a person with a contrast medium allergy 7 days after the administration of iomeprol

As far as possible, further testing should be performed within a period of 6 months after the reaction (Brockow et al. 2009). Skin tests are performed in cases of immediate reactions (anaphylaxis) by means of skin prick and intracutaneous testing, and the outcome of the test is read after 20 min. In cases of delayed reactions (exanthema), one additionally performs the patch test and reads the outcome after 2 and 3 days. The prick test and the patch test may be performed with undiluted solutions. The intracutaneous test should be performed with tenfold dilutions, in order not to develop unspecific reactions on the skin (Brockow et al. 2009). As cross-reactions may occur between various radiocontrast agents, sometimes it is meaningful to test a number of X-ray contrast media and find a substance that causes no reaction on the skin test and will possibly be tolerated by the patient in future contrast-assisted radiological investigations (Fig. 4.2).

Laboratory tests for allergies to radiocontrast agents have been poorly investigated. Some laboratory tests (such as the measurement of in vitro CD63 expression on the basophil activation test in cases of immediate reactions or the lymphocyte transformation test or the lymphocyte activation test in cases of delayed reactions), may be useful in some patients on an experimental basis (Brockow and Ring 2010).

An allergy can be proven by skin or laboratory tests only in some patients who are allergic to radiocontrast agents. A negative test result does not reliably rule out hypersensitivity, but a positive test helps to identify those substances that must be avoided in the future. In cases of delayed reactions, one may perform a provocation test with a substance that tested negative on the skin test and thus prove the patient's tolerance of the substance.

4.3.3 Prophylaxis and Further Procedures

In patients with previous hypersensitivity reactions who need contrast-assisted radiological investigations, one should perform a skin test and, if necessary, a laboratory test. When the skin test to radiocontrast agents yields a positive reaction, the

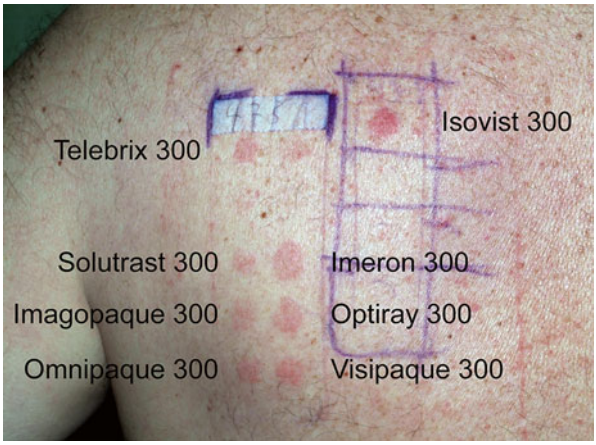

Fig. 4.2 Reading of the result of the patch test after 72 h in a person with positive skin reactions not only to the causal substance iomeprol (Imeron 300®) but also to other radiocontrast agents

substances that tested negative may usually be given without any risk. If the test including the causal radiological contrast medium remains negative, the power of the test is lower and a negative test for a specific radiocontrast medium does not guarantee the patient's tolerance of the respective agent. In cases of delayed reactions, one may perform stepwise provocation testing (Caimmi et al. 2010). In cases of immediate reactions, usually the patient is given preventive premedication (Tramer et al. 2006). For this purpose, one administers antiallergic drugs, corticosteroids (such as 50 mg prednisone 13, 7, and 1 h earlier), and H1/H2 antihistamines (such as 1 ampoule of dimetindene ± ranitidine 1 h previously) before the investigation. These substances further reduce the risk of a renewed reaction. One deals in similar fashion with patients who have experienced late skin eruptions to radiocontrast agents in the past.

4.4 Histamine and Drugs, Anaphylaxis

Reinhart Jarisch

In Austria alone, more than 200 drug addicts die every year. These deaths are usually attributed to an overdose or interactions with other drugs.

However, in actual fact, chemists at the Department of Forensic Medicine, University of Vienna, repeatedly found very small quantities of heroin in the blood – a fact that is indicative of other causes of death. Heroin and similar drugs are known to be histamine liberators. Thus, it may be assumed that histamine contributed significantly to death in these cases.

This hypothesis is corroborated by studies which showed markedly increased tryptase levels postmortem. Even in animal experiments, elevated histamine levels were registered in the blood after the administration of drugs.

Table 4.5 Relevant blood parameters (mean value + standard deviation) in drug addicts receiving substitution therapy, persons with an insect venom allergy, and healthy controls

	Drug addicts ($n=34$)	Persons with an insect venom allergy ($n=48$)	Controls ($n=80$)
Histamine (ng/ml)	0.61 ± 0.35	0.23 ± 0.06	0.13 ± 0.06
Diamine oxidase (U/ml)	12.3 ± 4.90	17.2 ± 9.00	16.7 ± 7.32
Tryptase (µg/l)	5.98 ± 0.8	4.04 ± 1.86	4.15 ± 2.08
Lp-PLA_2 (ng/ml)	348.9 ± 72.7	334.6 ± 73.2	314.4 ± 42.3

Lp-PLA_2 lipoprotein-associated phospholipase A_2

We therefore investigated drug addicts on substitution, receiving Substitol, and found nearly fourfold (!) higher basic histamine levels (Maurer et al. 2014). Besides, diamine oxidase levels were significantly lower than those in normal persons. Tryptase was significantly increased and the same was true of Lp-PLA_2 (Lp-PLA_2 = lipoprotein-associated phospholipase A_2). Lp-PLA is a synonym for PAF (PAF = platelet-activating factor), which is frequently found in large quantities in cases of anaphylaxis (Table 4.5).

These reports are indicative of a high risk of anaphylaxis. To put it more specifically, one needs just a mild stimulus to trigger allergic shock (anaphylaxis) in this setting.

These conclusions may help to avoid drug-related deaths. On the other hand, these conclusions are important for all persons, because allergic shocks after wasp or bee stings as well as after the intake of medication and at the start of operations are not very uncommon.

This also means that one can identify persons at risk of anaphylaxis in advance. Anaphylactic shock is often preceded by an excessive reaction, which is usually ignored by the patient and not investigated further. Anaphylactic shock still is a poorly researched subject. As it occurs very suddenly, it is regarded as a sinister illness, nearly always causing panic among medical staff.

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Surgery and Dental Operations

5

Reinhart Jarisch

5.1 Collapse at the Dentist

Reinhart Jarisch

No one likes to visit the dentist – not only for time reasons but also because the dentist usually causes pain. To avoid such pain one makes generous use of local anesthetics. Patients occasionally experience circulatory collapse after such injections and become unconscious. The local anesthetic is presumed to be the cause. A person may be allergic to local anesthetics, but this is rarely the case.

A histamine effect during the dental treatment is much more common. In the past, patients used to sit in the dentist's chair as they would in an ordinary chair – with the head above and the legs below. Fear is associated with the release of histamine, especially when it is accompanied by pain. If the patient undergoing treatment does not tolerate histamine, the quantity of released histamine is not degraded adequately. This leads to vasodilatation, a drop in blood pressure, and collapse.

Modern dentists take this circumstance into account and usually treat their patients in supine position. In fact, sometimes the patient's head is positioned lower than the legs. Collapse is a rare or nonexistent condition at these dental offices.

It should be noted that not only surgical interventions at the dentist's office but also surgery in general is associated with the release of histamine. In other words, the moment the surgeon places the scalpel on the patient's body, the latter releases histamine.

One may conclude the following in regard of the patient and the dentist: pain and fear cause greater release of histamine and therefore involve the risk of collapse. Fear can be controlled by several measures, such as autogenic training. Some persons are even able to process their problems rationally and thus avoid fear (a classical example is Niki Lauda, who analyzes problems thoroughly until all

R. Jarisch, MD
Floridsdorf Allergy Center, Franz-Jonas-Platz 8, Vienna A-1210, Austria
e-mail: jarisch@faz.at

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facts are thoroughly known, and their very knowledge eliminates fear). Fear usually arises when a person does not know what awaits him/her.

Furthermore, in a conversation with the dentist, the patient may inform the dentist early of the fact that he/she would like to have a local anesthetic in the event of pain. If the patient knows about his/her histamine intolerance, he/she should inform the dentist of the same and he/she should block the effects of histamine by taking an H1 receptor blocker as premedication.

Obviously, food containing biogenic amines should not be ingested 24 h before visiting the dentist.

From the dentist's point of view, the option of treating the patient in supine position or in head-down position minimizes the risk of hypovolemic shock. Especially when the patient is female and about 40 years of age, the dentist should be prepared for the fact that she may be at high risk of histamine intolerance and should try to obtain confirmation of the suspected diagnosis by asking leading questions. The dentist may actively counteract the problem by giving the patient an H1 receptor blocker before the treatment. As modern H1 receptor blockers act very rapidly even when taken orally, this should not pose any problems. In cases of patients with a history of ambiguous incidents after receiving a local anesthetic, it would be advisable to consult the allergy specialist. The latter could determine the questionable local anesthetic in a skin test or pretest a different local anesthetic to establish its safety before the dental intervention.

5.2 Histamine and Periodontal Disease

Reinhart Jarisch

Histamine also plays a role in periodontal disease. Bacteria in the gingival sulci (such as *Tannerella forsythensis* or *Prevotella intermedia*) produce histamine. The more numerous types of bacteria one finds, the greater is the likelihood of myocardial infarction (odds ratio up to 2.0) (Andriankaja et al. 2011). Histamine levels in blood and saliva are in equilibrium. By determining histamine levels in the saliva, one can confirm the diagnosis of periodontitis. The test is easy to perform. Test kits are provided by Greiner Bio-One company.

In the presence of periodontal disease, we found more than tenfold higher values in the blood. Particularly diabetics are at risk (Venza et al. 2006). Histamine levels in saliva may also be determined to control therapy after dental treatment in gingival sulci.

5.3 Surgical Procedures

Reinhart Jarisch

During operations the anesthetist is repeatedly confronted with a drop in blood pressure and respiratory problems. Quite often the anesthetist is taken unawares

by the problem because the patient's medical history reveals no sign of such disease.

One should be aware of the fact that histamine is released during any dramatic incident. Any impact on the body, accident or injury due to accident, or the placement of a scalpel on the patient's body at the start of an operation causes histamine to be released in large quantities. In a patient with histamine intolerance, the large quantity of histamine may lead to a drop in blood pressure and/or respiratory disorders. Therefore, premedication with antihistamines (the administration of H1 receptor blockers) before the operation is highly recommended. A study published in the Lancet on this subject very clearly shows that perioperative risks (i.e., risk during an operation) can be markedly reduced by administering an antihistamine as premedication (Lorenz et al. 1994).

Thus, one may conclude that, before an operation, the anesthetist's or the internist's general question in regard of previous allergy as well as the question of histamine intolerance is important. Regrettably, the latter question is nearly always overlooked, although it may be extremely important. The patient in the operating room, waiting to undergo surgery, is neither exposed to house dust mites nor pollen nor animal hair. Histamine intolerance, on the other hand, is something "he always carries around with him." He reacts accordingly at any time to histamine loads.

Therefore, the investigating physician is advised to inquire about a potential allergy as well as a histamine degradation disorder.

The patient scheduled to undergo surgery is advised to take premedication in the form of an H1 receptor blocker, ideally agreed upon with the surgeon.

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Histamine Intolerance in Women

6

Reinhart Jarisch

6.1 Dysmenorrhea (Menstrual Pain)

Reinhart Jarisch

Some women experience severe cramps on the first day of their menstruation (dysmenorrhea). These symptoms do not respond to ordinary pain-relieving agents.

The uterus has histamine receptors (binding sites). The uterus contracts at the onset of menstruation. When the effect of histamine is at its highest, such cramps in the uterus may well be triggered by histamine. This hypothesis is confirmed by the clinical observation that the administration of an H1 receptor blocker on the first day of menstruation may prevent pain. Pain that occurs on subsequent days of menstruation should, however, be treated with ordinary painkillers.

Dysmenorrhea affects more than 50 % of all menstruating women and causes severe physical impairment in 10–15 % of cases (grade 3 dysmenorrhea with markedly limited activity, poor response to analgesic therapy, and accompanying symptoms such as headache, fatigue, vomiting, and diarrhea).

Primary dysmenorrhea is attributed to increased or abnormal uterine activity and poor uterine blood circulation. These conditions are caused by high concentrations of prostaglandin F2α and vasopressin (Dawood 1985; Sessa et al. 1990). Secondary dysmenorrhea, on the other hand, is caused by various pathological changes in the lesser pelvis, such as endometriosis, adenomyoma, polyposis, pelvic inflammatory disease, stenosis of the uterine cervix, ovarian cysts, adhesions, and uterine malformations.

A major characteristic of primary dysmenorrhea is the absence of causative pathological changes in the lesser pelvis and the onset of symptoms in conjunction with, or shortly after, the start of menarche. Menstrual pain starts on the first day of menstruation and may persist for 48–72 h. Primary dysmenorrhea has been attributed to

R. Jarisch, MD
Floridsdorf Allergy Center, Franz-Jonas-Platz 8, Vienna A-1210, Austria
e-mail: jarisch@faz.at

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elevated prostaglandin F2α and vasopressin levels. However, we suspect that histamine, due to the activation of uterine H1 receptors, is significantly involved in the increased uterine contractility associated with dysmenorrhea.

Vasopressin and prostaglandin F2α are considered to be effective uterine stimulants; they increase uterine contractility, reduce blood flow, and cause pain (the measurement of prostaglandins in the endometrium, in menstrual blood, and in plasma reveals markedly enhanced levels in patients with dysmenorrhea).

In epidemiological studies, food, drinking, and smoking habits, as well as factors associated with the menstrual cycle, were investigated as potential risk factors of dysmenorrhea.

- In the published literature, a high risk of dysmenorrhea has been reported in persons who consume egg and cheese, among women who smoke, those who experience early menarche and stronger and prolonged bleeding, and women who use an intrauterine device.
- A low risk of dysmenorrhea has been noted in women who consume large quantities of unsaturated fatty acids, surprisingly among those who consume alcohol, those who use oral contraceptives (which are also used for the treatment of dysmenorrhea), and postpartum.

The strong contractile effect of histamine on the myometrium has been frequently discussed (Bergant et al. 1993; Cruz et al. 1989; Martinez-Mir et al. 1992), but has never been potentially linked to the pathogenesis of dysmenorrhea. The responsiveness of mast cells in relation to the menstrual cycle and their histamine release have been investigated in a few studies. Experiments in rats revealed high uterine histamine levels, mediated by estradiol, and also greater uterine contractility, which might be a sign of the modulation of myometrial histamine receptors secondary to ovarian steroids (Rubio et al. 1992).

High excretion of histamine metabolites was registered in human urine at the time of ovulation. Here also one suspects the effect of estrogens (especially estradiol) on histamine liberators or histamine synthesis. Kalogeromitros clearly demonstrated the impact of the menstrual cycle on skin prick tests by registering the highest responsiveness (wheal size) at the time of ovulation (day 12–16) and in conjunction with the highest plasma estrogen levels (Holinka and Gurpide 1984).

However, considering the fact that patients with dysmenorrhea frequently had higher estradiol levels before menstruation than did asymptomatic reference groups (Sessa et al. 1990; Viggiano et al. 1988), one may well suspect a potential effect on mast cell degranulation and consequent histamine release here as well.

Hormonal regulation of diamine oxidase was also investigated. In an animal model (rat), uterine DAO activity was found to be increased by 17β estradiol, whereas hepatic diamine oxidase levels were significantly reduced (Sessa et al. 1990). However, experiments on human uterine specimens revealed no change in enzyme activity (Holinka and Gurpide 1984).

To corroborate the hypothesis that dysmenorrhea might be primarily caused by histamine, we determined histamine and DAO levels in a patient shortly before, during, and after menstruation. We found that some women experience a drop in

diamine oxidase levels and a consequent severe effect of histamine at the start of menstruation. Thus, in pregnant women with early labor pain, one should take a histamine effect into account. A histamine-free diet would be very meaningful in these specific cases.

6.2 Pregnancy and Allergy

Reinhart Jarisch

The question as to whether one should initiate or continue specific immunotherapy during pregnancy is avidly discussed. The current recommendation is that in patients who are allergic to insect venom, immunotherapy should be continued with appropriate precautionary measures during pregnancy, but in patients who are allergic to pollen or house dust mites, one should interrupt immunotherapy and resume it after the birth of the child. One usually overlooks the fact that many women report feeling very well in regard of their allergy during pregnancy, that their hay fever or even their asthma had entirely disappeared during pregnancy, and that the symptoms reappeared after the birth of the child.

To clarify this phenomenon, one should be aware of the fact that excessive quantities of diamine oxidase (DAO) are produced in the placenta. This appears to be related to the fact that the growing infant tries to protect itself from uterine contractions because the uterus is sensitive to histamine. Merely, the ingestion of Emmental cheese or other food containing histamine would cause abortion of the infant. The overproduction of DAO is needed to enable children to be born and for safety reasons. It is required for the growth and survival of the infant. The excess DAO benefits the mother as well because a potential allergy (histamine release) in the baby is also treated by the excess DAO. Clinical experience has taught us that the quantity of DAO is rather important to assess the severity of an allergic reaction. Thus, it is quite comprehensible why some patients have a so-called type I allergy (such as hay fever or allergic bronchial asthma) which tests positive on the skin test and the blood test (RAST), but the patients experience no symptoms because the large quantity of DAO obviously prevents or minimizes the occurrence of an allergic reaction.

To corroborate the above thesis, we investigated plasma histamine and serum DAO levels in 83 pregnant women at various time points during their pregnancy. We found that pregnancy is associated with a significant drop in histamine levels and a massive rise in DAO levels. From the 12th week of gestation, all of the patients had high DAO levels (Fig. 6.1). From the 17th week of gestation, all of our patients had normal histamine levels. The drop in DAO levels between the next-to-the-last and the last measurement is remarkable. The child was born 10 days before the last test. Thus, it was evident that the overproduction of DAO ceased once the mother had passed the placenta. Falling DAO levels may be explained by the half-life of the existing DAO.

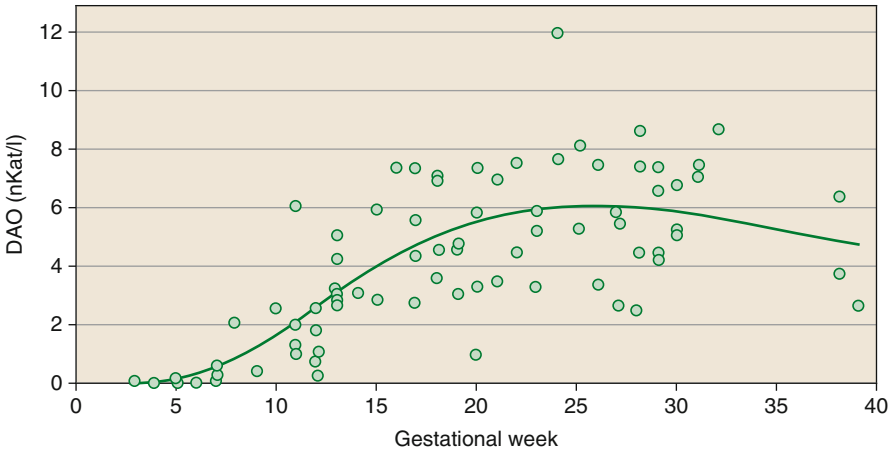

Fig. 6.1 Diamine oxidase levels (DAO levels) in serum in 83 pregnant women. Enzyme activity increases from the middle of the first trimester and reaches about 100-fold of normal levels in the second and third trimester

Case Report

The patient had borne two children and had experienced major difficulties during pregnancy. Owing to the risk of impending abortion or premature termination of pregnancy, she had to be hospitalized for several months. She told me that she had received tocolytic agents but also a large number of foodstuffs containing histamine. The patient was one of the few who had nearly all symptoms known to occur in the presence of histamine intolerance. She said she could probably have avoided several weeks of hospitalization if she had known at the time that food containing histamine could exert a harmful effect on her pregnancy. Incidentally, she became a midwife later on!

My conclusion is that women who experience difficulties during pregnancy should request investigation in respect of histamine intolerance and should, in any case, avoid food containing biogenic amines.

6.3 Nausea and Vomiting in Pregnancy

Reinhart Jarisch

Nausea and vomiting are very troublesome during the first 3 months of pregnancy. They do not occur in all women but do occur with greater or lesser severity in many. In a recent publication in the *New England Journal of Medicine*, one of the most renowned medical journals in the world, antihistamines were listed as the treatment of choice for this condition (Niebyl 2010).

If antihistamines are effective in women who experience nausea and vomiting during pregnancy, the opposite is true, i.e., histamine may be the cause of nausea.

In the same article, the authors mention a hormone (human chorionic gonadotropin or hCG) as the cause of these symptoms. The rise and fall in hCG levels correlated "exactly" with the occurrence and resolution of nausea, but not quite: the two curves were shifted in time. Thus, when nausea resolves, 50 % of the hCG is still present in the blood. Since antihistamines effectively counteract nausea and have no effect on hormones, the theory regarding hCG as the cause of nausea appears to have been disproved.

We now know that antihistamines are recommended as the treatment of choice for nausea and vomiting in seasickness. In a study in the German navy (see Chap. 10), we showed that chewable tablets containing 500 mg of vitamin C counteract nausea and vomiting. Obviously, chewable vitamin C tablets (Cevitol® chewable tablets) should be considered for the treatment of nausea in pregnancy. A study on this subject is yet to be performed.

One pregnant staff member (and two other pregnant women) was relieved of nausea by taking chewable vitamin C tablets. She was able to take care of her first child and also return to work. However, as the saying goes, one swallow does not make a summer; the test might have yielded a negative outcome. Nevertheless, the intake of chewable vitamin C tablets is always worth a try when a woman experiences nausea and vomiting during pregnancy.

6.4 Histamine and Obesity

Reinhart Jarisch

When obese persons visit an allergy outpatient center, it is always because they believe their obesity must be due to an allergy. This belief results from their exasperation and their fervent wish: something other than their passion for food must be the cause of their excessive weight. Such wishful thinking is supported by nutritional counselors who make allergies responsible for obesity – which obese persons obviously like to hear.

> The fact is, obese persons do not have allergies.
> The fact is, histamine makes a person slim.

The reason is that histamine downregulates a person's body weight. Persons with neurodermitis are extremely slim, no matter what they eat, and persons with an allergy are never fat. In very rare cases, there may be exceptions. Drugs that stimulate the histaminergic system (H3 receptor antagonists) are the most promising drugs for the treatment of obesity (Jørgensen et al. 2007; Barak et al. 2008). Conversely, antihistamines of the older generation tend to increase weight – a fact which used to be mentioned in the package inserts as well. This effect is most pronounced in the case of astemizole (Hismanal®), which was withdrawn from the

market because of its potential ability to cause cardiac arrhythmia. Histamine-deficient mice (so-called histidine decarboxylase knockout mice: the enzyme that is able to form histamine from histidine is blocked in these mice) may easily turn overweight when given a fatty diet (Fülöp et al. 2003; Jørgensen et al. 2006).

Regrettably, obese patients must be informed of the fact that allergies are not causally involved in their condition (tests on food allergens, frequently performed despite this fact, have all been negative).

However, I believe that we still have a solution for obese persons: If too little histamine causes obesity, more histamine would probably cause the opposite, i.e., reduce weight. Therefore, I believe that a low-histamine diet is important and is the basis of therapy for histamine-intolerant persons, but the opposite – a diet rich in histamine – should reduce weight (Malmlöf et al. 2006). This means that one should ingest foods like tuna fish (contains a lot of histidine, the precursor of histamine) daily (Kasaoka et al. 2004). Women should benefit most from this method (Kasaoka et al. 2005). A study on this subject in humans has not been performed yet, but the thesis appears very logical to me and is certainly worth a try.

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Neurodermitis

7

Reinhart Jarisch

The parents of many young children dread the diagnosis of neurodermitis, because they presume it is an incurable chronic disease. The fact is that neurodermitis, also known as atopic eczema, is a genetic disease with a propensity for dry skin and eczema. An agonizing itch is also reported in many cases. A food allergy in childhood has been noted in about one quarter of cases. From the age of 6 years onward, the child develops inhalant allergies like allergic rhinitis or bronchial asthma (Borkowski et al. 1998; Isolauri et al. 1997).

Histamine intolerance is observed at similar rates (Maintz et al. 2006; Worm et al. 2009). Clinically, one may suspect HIT in patients who report redness in the mouth after ingesting ketchup or tomatoes. By the determination of histamine and DAO in blood and by maintaining a histamine-free diet for 14 days and then retesting blood for histamine and DAO, the suspicion is confirmed when the person's blood values return to normal after the diet or the child's skin symptoms improve.

At a lecture in Vienna about climate and skin diseases, Professor Paul Bergstresser from Houston/Texas mentioned that neurodermitis does not exist in Florida. A talk with a dermatologist in Miami convinced me of the truth of this statement. This observation clearly shows that the climate of Florida, which consists of persistent sunshine and a moist, warm atmosphere due to the evaporation of sea water, is the primary therapeutic factor in neurodermitis.

Carrying these facts forward to Europe, this means that neurodermitis is practically nonexistent in southern Spain, southern Italy, and southern Greece and that the largest number of cases of neurodermitis occur in Scandinavia and northern England (its prevalence is 24 % in these regions). Accordingly, the majority of scientific publications on this subject were performed in Scandinavia. From a purely geographic point of view, Austria lies between Scandinavia and Sicily. Thus, Austria is "southern" in the summer and "northern" in the winter. This concurs with the observation of parents of atopic children.

R. Jarisch, MD
Floridsdorf Allergy Center, Franz-Jonas-Platz 8, Vienna A-1210, Austria
e-mail: jarisch@faz.at

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In Austria as well, neurodermitis is healed to a large extent in the summer and deteriorates in the winter. Thus, it may be concluded that diets in Italy, Austria, and Sweden do not differ significantly. Even in Europe it can be proven that neurodermitis is no primary food allergy. A recently published study is interesting in this regard: it showed that the prevalence of neurodermitis in Italy is 7 % northern Italy and 0–2 % in southern Italy. As the food consumed in Europe is largely the same, and Italians ingest pasta, schnitzel, and pizza just as often as do Austrians or Swedes, it may be assumed that food is a factor of marginal importance in neurodermitis (Borkowski et al. 1998; Businco et al. 1998).

The following major therapeutic approaches may be derived from these observations:

- The use of a humidifier set to 50 % atmospheric humidity for the cold (dry) season from October to April
- UVA radiation during the darker time of the year (winter)

It has now become common practice to measure vitamin D3 levels and provide substitution in case of low vitamin D3 levels.

As regards clothing, one should avoid sheep's wool because the latter is not well tolerated by children with atopic diseases.

The efficacy of so-called Mayo Clinic dressings may be attributed to the principle of providing moisture. The patient is thoroughly greased with ointments, thick cotton dressings are placed on the skin, and the patient is wrapped like a mummy. The beneficial effect appears to be based on the fact that occlusion dressings cause greater penetration of the ointment and the patient lies in a humid environmental chamber (due to his/her own perspiration).

The nonatopic person with normal fatty skin experiences massive dehydration of the skin in the winter, at subzero temperatures (while skiing, for instance), accompanied by mild itching and chapped lips. Thus, it is quite clear why these clinical features are potentiated in atopic persons. Even in atopic babies wearing diapers, neurodermitis is manifested in regions other than those covered by diapers. This appears to be related to the production of humidity by urine beneath the tight-fitting diapers.

The problem is complicated by the fact that so-called transepidermal water loss is twofold higher in atopic persons than it is in nonatopic persons and may be fourfold higher during a flare of neurodermitis. Many parents have found that the use of an ointment alone is not very effective. Ointments help only when the children are kept in a suitably moist (50 % atmospheric humidity) environment. In terms of therapy this means that the use of oil baths (such as an oil bath with pH 5 Eucerin®) is very important. Besides, the production of surface lipids in normal persons is intensified by ultraviolet irradiation. Therefore, in the summer we have a normal fatty skin, while even healthy persons have a dry skin in the winter because of the absence of ultraviolet radiation.

Persons with neurodermitis most commonly experience itching. This is caused by histamine, among other factors. This easily explains why H1 receptor blockers constitute an effective supportive measure in therapy, such as desloratadine which is contained in Aerius®, and levocetirizine which is contained in Xyzall® (both

available in Austria). However, dermatologists usually recommend sedating antihistamines of the older generation.

Fear of cortisone is unjustified. Topical corticosteroids are usually frowned upon by the majority of persons with neurodermitis. These ointments have a bad reputation because of overuse.

However, studies on neurodermitis have shown that a person suffering from the disease is obviously unable to respond to inflammatory stimuli by producing adequate quantities of endogenous cortisol. Therefore, the short-term use of steroid ointments is by no means an overdose. Rather, it balances the paucity of endogenous cortisol. Short-term (1 week) use of a steroid ointment is clearly indicated during acute inflammation. However, after 1 week one should immediately switch to nonsteroidal emollients. Calcineurin inhibitors such as pimecrolimus ointments, administered twice weekly, proved to be useful as long-term therapy.

Thus, neurodermitis may well be described as a cortisol deficiency disease. Our own studies showed that persons with neurodermitis frequently have reduced ACTH levels. ACTH is the regulatory hormone responsible for the endogenous production of cortisol. At the same time it is a stress hormone. This explains why children with atopic disease tend to be hectic and nervous and are considered hyperactive by their parents. We know, from our own studies, that vitamin B6 is able to normalize reduced ACTH levels and makes the children quieter. Furthermore, the administration of vitamin B6 (½ mg per kilogram body weight per day) for 1 week leads to complete or almost complete resolution of eczema. As vitamin B6 is known to exert therapeutic effects in neurodermitis when a person has a deficiency of this vitamin, many patients ask whether they can take vitamin B6 through their diet. Our experience has shown that the deficiency is better treated by drug-based administration of vitamin B6. However, a vitamin B6 diet is also an alternative.

The ingestion of food containing vitamin B6 does not cause a direct rise in vitamin B levels. Rather, the protein-to-vitamin-B6 ratio is important.

Vitamin B6 is needed to degrade proteins. When one consumes an egg, which contains proteins as well as vitamin B6, one does give the body vitamin B6, but the body needs more vitamin B6 to degrade the protein than is contained in the egg. Therefore, in the final analysis, the body is deprived of vitamin B6. The enclosed list (Table 7.1) shows that patients who constantly ingest foodstuffs labeled minus or 2 minus may develop a vitamin B6 deficiency.

Sometimes patients experience a massive exacerbation of neurodermitis. This usually occurs in the course of viral infection or due to so-called superinfection. The latter is mainly caused by *Staphylococcus aureus* infection. Therefore, in cases of massive atopic eczema, one should take superinfection secondary to staphylococcus into account and prescribe an antibiotic that effectively counteracts staphylococcus. Clinical experience has shown that steroid ointments are ineffective in these cases.

Neurodermitis may also be negatively influenced by a fungal infection caused by *Pityrosporum ovale*, the pathogen responsible for Pityriasis versicolor. Therefore, after a staphylococcus superinfection, it would be sensible to use appropriate treatment like Fungoral (antifungal) shampoo.

Table 7.1 Food with high levels of vitamin B6

– B6 balance < –0.20 mg/100 g
Avocado, bananas, elderberries
Soy beans, peppers, sweet potato, green beans, leek
Wheat germ, wheat bran, millet, unpolished rice
Wholemeal wheat bread, flour of a low type number
Walnuts, chestnuts, hazelnuts
Liver, goose meat
Salmon, sardine, trout, mackerel, lobster
Food enriched with B6 (e.g., fruit juice, cocoa beverages, cornflakes)
+ B6 balance +0.05 to +0.20 mg/100 g
Dried fruit, pineapple, grapes, melons
Most types of vegetables
Granary bread
Chicken, pork
Herring, tuna fish
Honey
± B6 balance +0.05 to –0.05 mg/100 g
Other types of fruit
Polished rice, flour of a low type number, rye-wheat (mixed) bread
Mushrooms
Egg yolk
Milk products other than cheese
Beef, calf, turkey, sausages of high quality
Halibut, eel
– B6 balance –0.05 to –0.20 mg/100 g
Beans
Corn flour, white bread, pasta
Curd, white mold cheese
Rabbit, lamb
Plaice, codfish, carp, mussel, shrimps
Chocolate
– B6 balance > –0.20 mg/100 g
Peanuts, almonds
Egg white
Other types of cheese
Sausage of low quality
Gelatins

Vitamin B6 is consumed as a coenzyme during protein degradation. Therefore, persons taking a protein-rich diet are advised to take larger quantities of vitamin B6. The table is not directly oriented to the vitamin B6 content of food but takes the B6-to-protein ratio of the respective foodstuff (B6 balance) into account. Food with a negative balance (so-called B6 feeders) should be avoided by persons with atopic disease and histamine intolerance. The German Society of Nutrition recommends a daily dose of 1.6–2.0 mg vitamin B6 for adults

Obviously, one should perform an allergy test and determine sensitization to inhalant and/or nutritive allergens. If the person has an inhalant allergy to house dust mites, it would be necessary to perform restorative measures in the living environment. In cases of simultaneous inhalant symptoms, it would be appropriate to administer specific low-dosed immunotherapy as well. However, the skin may worsen in the initial phase of immunotherapy, necessitating a limited maintenance dose.

If a person is allergic to pollen, which may be accompanied by a pollen-associated food allergy (such as birch or ragweed), he/she should avoid the respective foods. Persons allergic to birch pollen usually do not tolerate apples, carrots, and nuts, as well as soy bean products, kiwi, and raw figs. Those with a ragweed allergy usually do not tolerate celery, absinth, chamomile, sunflower seed, sunflower honey, aniseed, dill, fennel, coriander, caraway seeds, and parsley.

Besides, one should consider the fact that a person may be sensitized to the panallergen profilin. In this case he/she may have a more wide-ranging hypersensitivity to diverse types of pollen by way of a cross-reaction, or even to food. These problems are resolved by performing an allergy test and/or asking an allergy specialist to interpret the results of the test.

Besides, a person may develop cutaneous sensitization by way of allergic contact eczema. Thus, performing an epicutaneous test or even an "atopy patch test" would be meaningful.

One should keep in mind the possibility of bronchial involvement, which may necessitate a routine lung function test.

Clinical practice has shown that 95 % of cases of atopic dermatitis may be rated "mild" and can be controlled well or cured by the above-mentioned therapies. Massive spread is observed in just about 5 % which, especially in cases of longstanding disease or lichenification (thickening of the skin), require more intensive in-hospital treatment and special dermatological care afterward.

According to published reports, aggressive therapy procedures such as treatment with interferon gamma are associated with very low rates of clinical success (apart from side effects). These therapies are no longer a subject of discussion. Positive results have been obtained after the administration of cyclosporine. However, it should only be used in severe cases and under in-hospital supervision. New calcineurin inhibitors like tacrolimus 0.03 % in ointment form and pimecrolimus 1 % as cream are useful when the patient experiences an exacerbation of eczema, especially on the face, throat, and areas of intertrigo. They help to reduce steroid use as well as the number of exacerbations.

Finally, there is good news for parents. It has been proven that atopic children are highly intelligent – a fact that parents have discovered the painful way, because their children are skilled at operating all technical devices in the household. Their mothers are unable to switch off the devices as rapidly as the children switch them on.

All in all, neurodermitis is easily diagnosed by the specialist, although it may be associated with very diverse clinical symptoms in various age groups. Diagnostic

procedures for allergy should be performed by an experienced allergy specialist. The treatment must be administered with a lot of common sense. Taking all of these factors into account, neurodermitis is by no means a fearful chronic condition, but a skin disease that can be easily steered when treated appropriately.

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Allergen-Specific Immunotherapy

8

Reinhart Jarisch

Allergen-specific immunotherapy (previously known as desensitization, hyposensitization, or specific immunotherapy) is standard treatment for allergic diseases, accepted internationally and recently also by the WHO (World Health Organization). Allergen-specific immunotherapy is able to restore a dysregulated immune system to its normal state (Malling et al. 1993).

Allergies may be described as a false alarm of the immune system. They make no sense and only cause trouble. The problem involved in allergic reactions is inflammation, which is quite meaningful in the presence of infection, but triggers disease in allergic conditions. The question arises: Who, in actual fact, are the "enemies"?

The enemies include pollen of trees, grasses and weeds, house dust mites, and animal epithelia, all of which are so small that they are practically invisible to the naked eye. They do not constitute a hazard for the body or the immune system but are still perceived as enemies by the immune system. I get the impression that the immune system looks at a fly under a magnifying glass and reports that the body is being attacked by an elephant. No matter how trite this sounds, it offers very clear therapeutic approaches. To elaborate further on this simple example, when one steps on a chair, jumps from it, and sprains the ankle without experiencing a distension, a tear of ligaments, or a fracture, the ankle swells. In other words, an inflammation occurs. Any person who has witnessed a sports event knows that a cold spray or ice cubes are used in this setting, with the single purpose of suppressing the senseless inflammation.

The inflammatory reaction that accompanies allergic diseases is as meaningless as the inflammation that occurs in sports injuries. In the nose the mucous membranes of the nose become swollen and watery fluid is secreted. In the lungs the bronchial mucosa becomes swollen and the muscles at the outlet of the pulmonary alveoli become constricted. This makes it difficult to exhale; the non-utilizable residual

R. Jarisch, MD
Floridsdorf Allergy Center, Franz-Jonas-Platz 8, Vienna A-1210, Austria
e-mail: jarisch@faz.at

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volume of the lung increases. An insufficient quantity of air is inspired because the residual air in the lung prevents inspiration. To return to therapy, it becomes evident that drugs – whether antihistamines or even cortisone – effectively counteract the swelling of mucous membranes, as well as suppress secretion and inflammation, but this effect is transient. It persists as long as the treatment is administered.

The therapeutic principle of allergen-specific immunotherapy, on the other hand, is to normalize the dysregulation of the immune system. Thus, in terms of immunology, its purpose is to induce tolerance.

The principle of the allergen-specific immunotherapy is that one administers continuously increasing doses of the allergen the person is allergic to and thus habituates the immune system to the substance. The immune system starts to tolerate the substance. When renewed contact with the allergen occurs, the body develops just a mild, or no, inflammatory reaction. One may well ask why this does not work the natural way, since we are subject to increasing quantities of pollen during the pollen season. The difficulty of natural pollen exposure is that we experience no load for a long period of time and are then exposed to maximal quantities of pollen rather rapidly. This could be compared to a sportsman who does not train at all for 6 months and is suddenly asked to jump from a height of 1.8 m or even 2 m. If he were to train consistently throughout the year and steadily raise the yardstick to higher levels, after 6 months he would well be able to jump from a height of 1.8 or even 2 m.

The same is true of allergen-specific immunotherapy. The immune system is gradually exposed to the dose it is expected to tolerate. Several studies have shown that allergen-specific immunotherapy is effective after just 4 months. To achieve a sustained effect for several years or even the entire duration of one's life, we believe that the maintenance dose should be continued for 2 years. According to international opinion it should be administered for more than 3 years. A further advantage of allergen-specific immunotherapy is that the risk of simple hay fever developing into bronchial asthma is reduced by a half, while the risk of developing further allergies is also reduced by a half (Des Roches et al. 1998).

In allergen-specific immunotherapy the patient is given an allergen he/she does not tolerate. Thus, one may well anticipate an intolerance reaction after every injection. The fact that this is not the case and intolerance reactions occur very rarely is related to the quality of currently available vaccines on the one hand and a moderate dose titration system on the other. We believe that certain measures must be undertaken to further minimize the residual risk of a systemic reaction due to allergen-specific immunotherapy.

The antihistamine premedication we presented in 1988 has now been confirmed by several colleagues abroad on the basis of placebo-controlled double-blind studies (Jarisch et al. 1988, 1993 and Wantke et al. 1993b). It was found that consistent premedication with antihistamines or the administration of an H1 receptor blocker 30 min to 1 h before allergen-specific immunotherapy reduces the risk of side effects by the power of ten or more (Wekkeli et al. 1989 and Müller et al. 1993).

At the 2012 annual meeting of AAAAI (AAAAI = American Academy of Allergy, Asthma & Immunology) in Orlando, premedication with antihistamines was explicitly listed as one of the several measures to prevent anaphylactic shock.

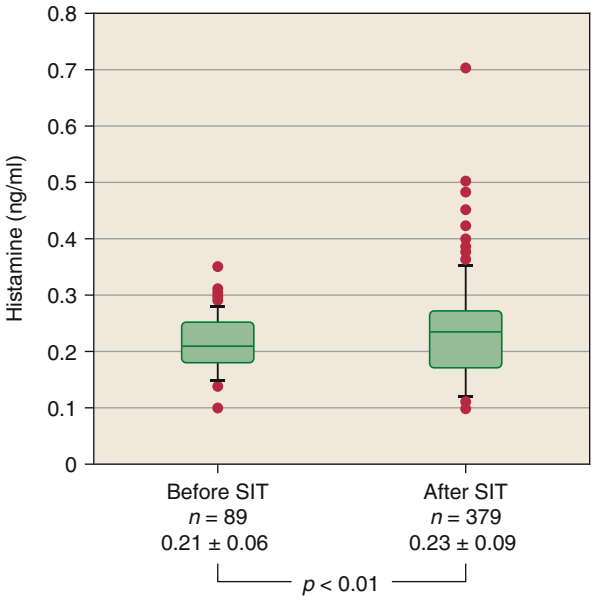

Fig. 8.1 Histamine levels in 468 persons with allergies receiving ongoing allergen-specific immunotherapy, measured in blood samples taken before ($n = 89$) and after ($n = 379$) injection of the immunotherapeutic agent

Blood samples taken from approximately 500 persons before and after allergen-specific immunotherapy showed significantly higher histamine levels after the immunotherapy than before (Fig. 8.1).

Furthermore, based on our current experience, we recommend abstinence from food containing histamine for a period of 24 h before the administration of allergen-specific immunotherapy, because such food imposes an additional burden on the immune system. Besides, some drugs are inhibitors of diamine oxidase (DAO) and are able to block the histamine-degrading enzyme (DAO) for several weeks. Two case reports will be presented here to illustrate this point.

Case Report 1

In Denmark a patient with an insect venom allergy received so-called rush immunotherapy, consisting of increasing doses administered as 3–4 injections per day. The patient was a sailor who spent the intervals between the injections drinking beer. Beer contains several substances, including histamine. It also contains alcohol and its degradation product acetaldehyde, which is an inhibitor of DAO. The patient promptly experienced anaphylactic shock after the last injection. The authors of the study were unable to locate the cause. We believe the patient's consumption of beer was responsible for his condition.

Incidentally, the instruction leaflet for allergen-specific immunotherapy mentions that one should not consume alcohol before the treatment.

One of our own cases of a mild systemic reaction corroborates the thesis that the administration of drugs that are potential inhibitors of DAO might be causally involved in side effects.

Table 8.1 Case report illustrating the potential significance of DAO inhibitors (here acetylcysteine) as a cause of systemic side effects in allergen-specific immunotherapy (SIT)

	Histamine (ng/ml)	Tryptase (µg/l)	DAO (nkat/l)	Vitamin B6 (nmol/l)
After 15 min	1.2	18	0.21	180
After 1 week	0.2	6	0.04	141
After 5 weeks	0.2		0.04	70
After 9 weeks	0.1		0.06	52

The patient (see Case Report 2) was receiving allergen-specific immunotherapy for grasses and rye for a period of 24 months. Medical history: Aeromuc (acetylcysteine) for 1 week; the last dose was given 4½2 days before the SIT injection

Case Report 2 (Table 8.1)

A man, approximately 20 years of age, was allergic to grass and rye pollen. His values were as follows: RAST grass 4.9, RAST birch 2.0 (RAST = radioallergosorbent test). He received allergen-specific immunotherapy for 2 years. The treatment was administered in conjunction with consistent antihistamine premedication. The patient tolerated the immunotherapy with no reactions. However, at the last scheduled injection (21st maintenance dose), he developed a mild systemic reaction in the form of irritation in the throat, pressure in the chest, swelling of lips, generalized redness of the skin, low blood pressure (110/70), and a pulse rate of 76 beats/min. Besides, the patient had a strong local swelling at the injection site. After intravenous treatment with Solu-Decortin® and Fenistil®, his symptoms abated rapidly.

Blood tests performed after 15 min showed that the patient's plasma histamine levels were sixfold higher and his DAO levels threefold higher than normal (Wantke et al. 1993a). His histamine levels returned to normal after 1 week and remained stable thereafter. His DAO levels returned to normal only after 9 weeks. At the time of the anaphylactic shock, his tryptase levels (an indicator of anaphylaxis) were also high but returned to normal rapidly. The patient's vitamin B6 levels fell continuously over the 9-week period.

He was asked specific questions about his condition. His medical history revealed that he had been taking Aeromuc (acetylcysteine) for 1 week. He had taken the last dose 4½ days before the injection. We believe this drug had triggered anaphylaxis. One may well ask why anaphylaxis occurred although the patient's DAO levels were threefold higher than normal. It has been mentioned in the published literature that, during anaphylactic shock, the body presses out its very last reserves of DAO to resist the shock. The fact that anaphylactic shock occurs despite this effort is because histamine levels rise much higher than do DAO levels (Mondovi et al. 1975).

Table 8.2 Subjective assessment of the success of allergen-specific immunotherapy in 850 persons with allergies to pollen, house dust mites, and insect venom

Subjective improvement after specific immunotherapy (SIT)
No improvement (<10 %) 4 %
Improvement by 10–49 %: 8 %
Improvement by 50–90 %: 76 %
Improvement >90 %: 12 %

Table 8.3 Association between histamine intolerance (HIT) in the patient's medical history and the efficacy of specific immunotherapy (SIT) in 34 failures and 104 patients in whom immunotherapy was very successful

Subjective improvement due to SIT	With HIT	No HIT	
<10 % ($n=34$)	10	24	$p<0.001$
>90 % ($n=104$)	10	94	$p<0.001$

Thus, it may be concluded that abstinence from food containing histamine for 24 h before the injection and the avoidance of drugs that could be potential blockers of DAO are important aspects of allergen-specific immunotherapy.

Allergen-specific immunotherapy was clinically successful and elicited a favorable response. Of 850 patients treated by us, 88 % reported improvements of their symptoms by 100–50 %, 8 % reported improvements of 50–10, and 4 % reported no improvement (Table 8.2). Basically no vaccine is effective in all persons. Vaccination failures are still an unresolved problem and a subject of ongoing immunological research.

It was quite logical to speculate that the failure group possibly suffered from previously undiagnosed histamine tolerance. Therefore, we examined patients in whom immunotherapy had been unsuccessful and compared them to those who achieved clinical improvement by more than 90 % (Table 8.3).

A highly significant difference was observed between the groups. Thus, it may be concluded that allergen-specific immunotherapy will not be successful in histamine-intolerant patients. Besides, the risk of side effects is naturally high. We therefore believe that, as long as the patient suffers from histamine intolerance, he/she should not be given immunotherapy.

To be absolutely certain that the drug was the causal agent in our patient with a grass pollen allergy, we performed an investigation in regard of spontaneous basophilic histamine release. Based on experience we know that persons with histamine intolerance have high levels of histamine release. However, our patient had normal values. Besides, the patient was again given acetylcysteine after a few weeks and its effect on DAO levels was investigated. After taking the drug for 1 week, the patient's DAO levels dropped by 35 % while an increase of 24 % was noted in a control subject. Thus, it is almost certain that the side effect had been caused by the drug given to the patient, namely, ACC®.

All in all, currently standardized vaccines have achieved a very high level of quality. The problem of immunotherapy is no longer related to the vaccine – which is standardized – but to patients who react very differently to immunological treatment. The task of the allergy specialist is to filter out those patients who are not

likely to benefit from allergen-specific immunotherapy. By treating those patients who are eligible for immunotherapy, we will be able to achieve better success rates than we have achieved in the past.

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Vitamin B6 and Histamine

9

Reinhart Jarisch

Vitamin B6 is a collective term for all 3-hydroxy-2-methylpyridines which act as vitamins. Vitamin B6 substances like pyridoxine, pyridoxal, pyridoxamine, and their phosphorylated metabolites are all equally effective. Pyridoxal-5-phosphate and pyridoxamine-5-phosphate fulfill the functions of a coenzyme in the organism.

One of the many functions of vitamin B6 is the degradation of glutamate. In addition to histamine, glutamate is a potential trigger of the so-called China restaurant syndrome in persons with a vitamin B6 deficiency. However, the EU regulations do not mention an established maximum daily dose for glutamate (E621 to 625). Vitamin B6 is recommended for the treatment of the China restaurant syndrome as well as the premenstrual syndrome. However, the efficacy of vitamin B6 for these two indications has not been conclusively proven yet (Biesalski et al. 1997).

We found low levels of vitamin B6 in children with atopic dermatitis. These returned to normal after the administration of vitamin B6 and the patients' atopic dermatitis was also improved. Besides, the children became quieter.

The data published in the Austrian Nutrition Report of 1998 are interesting in this regard. Of persons aged 6–18 years, 65 % had slightly reduced and 8 % markedly reduced vitamin B6 levels. The mean value in adult women aged 36–55 years was no higher than 80 % of the recommended level. In pregnant women in the 22nd to 35th weeks of gestation, the mean value was no higher than 65 % of the recommended level (Elmadfa 1998).

The original quote, translated into English, is as follows (Elmadfa 1998):

> A much more critical situation was noted in respect of the subjects' vitamin B6 status: only 8-18% of the reports were in the normal range as regards the ability to activate EGOT (erythrocyte glutamate-oxaloacetate transaminase, a vitamin B6-dependent enzyme). Approximately one third of the reports were assigned to the markedly reduced range. With regard to the absorption of vitamin B6 as well, we found a situation that clearly called for improvement. In study B, only 1.8% of women achieved the level recommended by the

R. Jarisch, MD
Floridsdorf Allergy Center, Franz-Jonas-Platz 8, Vienna A-1210, Austria
e-mail: jarisch@faz.at

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German Society of Nutrition, which is 0.25mg vitamin B6/MJ). Despite frequent use of multivitamins, the prevalence of suboptimal levels of vitamin B6 is very high. Other studies also mention marginal levels of vitamin B6 during pregnancy. This exerts a negative impact on the infant's vitamin B6 levels as well. Therefore, it is most essential to provide the body with larger quantities of this nutrient through food. Potent sources of vitamin B6, in addition to meat and fish, include vegetable foods like potato, banana, whole meal products, and some types of vegetables.

The data show that a part of the Austrian population suffers from a vitamin B6 deficiency. The fact that we found low vitamin B6 levels in children with atopic dermatitis as well as those with significant swelling after mosquito bites, and the patients' clinical symptoms abated once the deficiency had been eliminated, justifies the thesis that the patients' vitamin deficiency might be related to their disease (Koller et al. 1992).

This thesis is further confirmed by the fact that soldiers of the Brazilian army receive vitamin B6 as a prophylactic measure when they work in the jungle and are exposed to massive mosquito bites at this time. We also know that children with a proven vitamin B6 deficiency who report marked local swelling after mosquito bites are able to tolerate the bites better and experience less swelling when they are given vitamin B6. The latter inhibits the degranulation of mast cells, and this leads to histamine release (Gonzales Alvarez and Garcia Mesa 1981). The importance of vitamin B6 becomes evident when one looks at the list of vitamin B6-dependent enzymes. One textbook about vitamins lists 13 enzymes of this type.

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Histamine and Seasickness

10

Reinhart Jarisch

10.1 Introduction

Seasickness, also known as motion sickness or kinetosis, occurs on land, at sea, and in space travel. It is usually triggered by vehicles of motion or transportation, such as carousels, cars, buses, trains (tilting trains), ships, planes, or space travel. Mild seasickness on the backseat of a car or a bus is a well-known phenomenon (Jarisch 2009). The fact that many astronauts became space sick, such as the first Russian astronaut Gagarin, and the fact that an American space mission nearly ended in a crash landing because of space sickness are less known.

Interestingly, even "ski sickness" has been reported. It is attributed to vestibular overstimulation when maneuvering on uneven ground, insufficient visual control (especially in fog), or lesser ophthalmological problems (such as myopia and astigmatism, or refraction error). Furthermore, altered somatosensory input due to unsuitable ski shoes or skis, fear of heights, fear of mountains, high speed, and the effect of changes in atmospheric pressure on the ear appear to play a role in this condition (Hausler 1995).

The significance of this disease is highlighted by the fact that more than 2,800 scientific investigations have been published to date on the subject. Yet, the surprising fact is that a textbook on the subject – in the German or in the English language – has not been published yet. Salient conclusions from scientific research are summarized here, especially those of our own research. The purpose of this summary is to be able to cope better with seasickness in the future.

R. Jarisch, MD
Floridsdorf Allergy Center, Franz-Jonas-Platz 8, Vienna A-1210, Austria
e-mail: jarisch@faz.at

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10.2 History of Seafaring

Usually motion sickness is regarded as an intolerance reaction on ships (seasickness). The history of seasickness is as old as that of seafaring. Seamen in previous centuries used to suffer from two major conditions: scurvy (vitamin C deficiency) and seasickness. The difficulties experienced on warships in early times were less due to the guns of the enemy than due to scurvy and seasickness on one's own ship.

While circumnavigating Cape Horn in 1497, Captain Vasco da Gama, a Portuguese seafarer, lost 100 of his crew of 160 men due to scurvy. It took a few centuries to realize the significance of fresh fruit, especially lemon and oranges, for the treatment of scurvy.

James Lind, a Scotsman from Edinburgh (1731–1794), discovered the cause of scurvy (1748), which was then published in 1754. In 1775 Captain Cook (England) was the first to prove that prolonged sea voyages were not the sole cause of scurvy. According to a report of the royal Austrian navy in 1864 concerning the battleship named *Kaiser*, 800 of 900 sailors were affected by seasickness, including engineers and stokers.

Although the ingestion of citrus fruits to counteract scurvy was known as early as in 1535 (Captain Jacques Cartier, France), this fact is not mentioned in the regulations of the Royal Marine in 1872. On the other hand, the regulation does recommend an increase in vinegar rations per sailor. Furthermore, it recommends the inclusion of live animals on the ship. Both of these are no constructive measures. Interestingly, it was noted at the time that pigs do not become seasick. In fact, pigs seem to be born "seafarers" since the age of Noah.

One may well ask why this is the case. Diamine oxidase (a histamine-degrading enzyme) is extracted from pigs for laboratory experiments. As pigs are omnivorous animals, they have high blood levels of diamine oxidase (DAO) like lions and tigers. Otherwise, they would die from ingesting spoiled meat (which contains a large quantity of histamine). As histamine is the cause of seasickness, it is quite obvious why animals with high DAO levels do not become seasick.

10.3 Symptoms of Seasickness

The initial and usually earliest sign of seasickness, which should be regarded as an early warning sign, is yawning. Further symptoms include pallor of the face, perspiration on the face, dizziness, nausea, vomiting, and even thoughts of suicide.

Salivary flow is negatively correlated with the severity of seasickness. This is remarkable in view of the fact that dryness of the mouth is frequently attributed to the medications used to treat seasickness.

Evidently, almost any person can become seasick – including so-called professional sailors. Only one member of the victorious Volvo ocean race boat *Illbruck* mentioned that he had never been seasick all his life. The previous captain of the German bark *Gorch Fock* recently told me that 80–90 % (!) of cadets become

seasick during their first voyage. Seasickness is an openly discussed subject in the German navy – it is no longer a taboo issue. I am particularly happy about this fact.

The following extracts from the published literature provide data about the frequency of seasickness and its relation to age and gender:

- During 114 voyages on 9 ships, involving 20,029 passengers, 7 % reported vomiting, 4 % felt absolutely miserable, 4 % felt quite ill, and 21 % reported malaise. In all 36 % of the patients felt unwell.
- Similar figures were reported for 3,256 passengers of tour buses: 1.7 % reported vomiting, 12.8 % experienced nausea, and 28.4 % felt unwell (in all 42.9 %). In fact, three quarters of the passengers had no forward vision.
- In a study comprising 141 pilots who practiced on a Black Hawk flight simulator (Black Hawk is a helicopter), 36 % reported symptoms of motion sickness. Motion sickness in tank simulators occurs twice as often among persons with seasickness in their medical history than among those with no history of seasickness.
- It is widely known that children below the age of 2 years rarely experience seasickness. Children who suffer from migraine become seasick more easily.
- In adults, women are more commonly affected by seasickness than men. An investigation on a sailing vessel with only women on board showed an association between headache or migraine and the occurrence of seasickness in relation to the menstrual cycle. The above-mentioned symptoms occurred less often at the time of ovulation and most frequently at the time of menstruation (Grunfeld et al. 1998).
- Seasickness decreases with advancing age in both genders.

10.4 Causes of Seasickness

Seasickness is attributed to an optokinetic stimulus. The eye, the vestibular system, and the brain appear to play a leading role. The stomach, which is basically an effector organ, is of practically no, or very little, significance as a cause of seasickness.

In the following we will discuss the significance of the eye and the organ of equilibrium in seasickness. Besides, the association between a rise in histamine levels and a simultaneous fall in vitamin C levels and seasickness will be addressed.

10.4.1 Significance of the Eye

Nausea is known to occur in certain large cinema halls which permit the simulation of motion perceived only by the eyes; the body is exposed to no or very little spatial change. Two theories exist for the occurrence of seasickness. One is the classical sensory mismatch theory, while the other is the subjective vertical conflict model.

A common feature of both is that nausea occurs when the anticipated event does not concur with the actual event. Thus, the cerebellum receives incorrect information (Bles et al. 2001).

Reports that support the thesis of nausea being caused by the eye are the following:

One may become seasick while watching a cinema film. Seasickness occurs less often when there is an artificial horizon or when a passenger views a scene through a window.

Seasickness can be improved by prismatic telescopes (Vente et al. 1998).

Under experimental conditions on a swivel chair, severe nystagmus was correlated with greater sensitivity to seasickness. Nystagmus reactions after "vestibular training for cosmonauts" were 20–30 % below the value registered in control subjects (Clement et al. 2001). Purely optokinetic yaw axis rotations (swivel chair) do not make people seasick, provided they do not move their heads (nystagmus is a measure of the occurrence of seasickness) (Ebenholtz et al. 1994). Yawing is defined as the unintentional and recurrent veering of a boat from its steered course by a pivoting motion around its perpendicular axis (Schult 1998).

A high incidence of seasickness has been reported on rescue vessels of drilling rigs and on life rafts after a shipwreck. It should be noted that persons involved in these circumstances have practically no view of the outside.

The driver of a car or the helmsman at sea is rarely seasick. The likely reason is that the helmsman is the only person who can exactly estimate the ship's direction of motion. Thus, there is no discrepancy between anticipated motion and actual motion (interestingly, car drivers are permitted to drive their car after a trip on a car ferry, whereas pilots are not permitted to fly a plane for several hours after practicing on a simulator).

From these extracts of study data, the eye could be assigned a leading function. However, the fact that even blind people can become seasick modifies the theory of the eye being the trigger of seasickness. Even fish can become seasick. In the experimental setting, the vestibular system was found to play a dominant role in triggering motion sickness in gold fish (Lathers et al. 2001).

> The visual system is secondary.

10.4.2 Significance of the Vestibular System

Persons with a dysfunctional inner ear do not become seasick. When rats are subjected to twice the normal force of gravity of the earth, they become seasick. This is expressed by the ingestion of kaolin (also known as pica or the ingestion of substances with no nutritional value). Under normal circumstances rats would never ingest any substance with no nutritional value. Repeating this experiment in rats whose labyrinth in the inner ear had been destroyed, the investigators registered no rise in histamine levels and no sign of nausea (i.e., no absorption of kaolin) (Takeda et al. 1986).

The production of histamine in the brain may also be inhibited by enzymes. Histidine is transformed into histamine by means of an enzyme (histidine decarboxylase). Obviously, no histamine can be formed in the brain when this enzyme is

inhibited by α-fluoromethylhistidine (α-FMH) (Yamatodani et al. 1990; Watanabe et al. 1990). In cats, the administration of α-FMH suppressed motion-induced vomiting (Lucot and Takeda 1992). α-FMH also reduces the release of histamine in the hypothalamus (brain) and suppresses the ingestion of kaolin in rats (equivalent of nausea).

The third option is to render the histamine released in the brain ineffective by blocking the histamine receptor. The administration of a histamine H3 receptor agonist (e.g., thioperamide) significantly reduces the oculovestibular reflex.

The investigations described here show that the destruction of the labyrinth as well as the suppression of histamine release in the brain and the activation of the H3 receptor in the brain are able to suppress the symptoms of seasickness.

When rats are subjected to twice the force of gravity of the earth, they become adapted to the environment after 4 h, but are not adapted after 2 h. Thus, it may be concluded that rats possess a mechanism to suppress seasickness (Uno et al. 1997). Rats release histamine under stressful conditions and are the only creature capable of synthesizing vitamin C. Synthesized vitamin C is apparently able to degrade histamine. In rats, stress increases histamine levels as well as the activity of histidine decarboxylase in the hypothalamus (brain). Histidine decarboxylase is the enzyme that produces histamine from histidine. This is also followed by a rise in plasma corticosteroid levels.

Commands in the brain are mediated by various neuron systems (chemical conductors). Neurophysiological investigations permit the following classification (Takeda et al. 1989, 2001):

The histaminergic neuron system is included and involved in the systems of motion sickness and emesis (vomiting).

The acetylcholinergic nervous system is involved in the process of habituation.

The catecholaminergic nervous system in the brain stem is not involved in the development of motion sickness.

Thus, the results of animal experiments in the published literature demonstrate that *histamine is the primary cause of seasickness*.

10.4.3 Histamine

Histamine is a biologically potent biogenic enzyme released from mast cells in the body. It arises by means of an enzymatic process – through decarboxylation of the amino acid histidine. Its physiological (normal) function consists of the stimulation of gastric acid secretion and vasodilatation. Histamine serves as a neurotransmitter in the circadian rhythm (sleep–wake cycle). It also controls appetite, learning abilities, and memory. Its prime pathological functions include allergies such as conjunctivitis, allergic rhinitis, bronchial asthma, and histamine intolerance. Histamine levels are high in the presence of mastocytosis (increased numbers of mast cells in the skin), polycythemia vera (a rise in red blood cell count in advanced age), and urticaria (nettle rash). Histamine levels are especially high after allergic shock and during contrast-assisted radiographic investigations. Addictive drugs may also cause histamine to be released.

Thus, histamine is the primary cause of seasickness. In view of the fact that histamine is released during stress, which occurs quite easily on small ships and heavy swells at sea, and considering that vitamin C is needed to degrade histamine, it becomes quite easy to establish an association between a deficiency of vitamin C, high histamine levels, and the fact that seasickness occurs easily in this setting.

Histamine is the cause of seasickness, whereas acetylcholine is responsible for the limited duration of seasickness (even if it spans a period of several days). Persons subjected to persistent rocking motions become habituated to the new environment after a certain period of time. Stress or unphysiological body motions (such as those on ships) cause histamine to be released and presumably consume the body's vitamin C reserves.

These facts permit the conclusion that seasickness can be suppressed if one is able to degrade histamine in the brain or thwart its release or production.

10.5 Drugs and Therapy Options

10.5.1 Drugs to Treat Seasickness

In view of the above-mentioned facts, it is no surprise to note that the majority of drugs used to treat seasickness are antihistamines (Table 10.1).

Notably, scopolamine ranks first (the substances in Table 10.1 are listed according to their efficacy and significance). *Scopolamine* is an addictive drug with no antihistaminic effect. In fact, investigations showed that scopolamine does not suppress a rise in histamine levels during motion sickness. Scopolamine is believed to influence the transmission of stimuli in the brain. Professionals are familiar with its high efficacy. However, it has disadvantages: near vision is impaired and acclimatization to vessel motion (which would occur otherwise) is hindered.

It is remarkable to note that even a cortisone preparation, namely, *dexamethasone*, was found to be effective. By administering 0.5 mg dexamethasone (every 6 h for 2 days), persons were able to withstand 80 % more "stressful motions."

Table 10.1 Drugs to treat seasickness

Active substance	Commercial preparations
Scopolamine	Scopolamine TTS plaster
Cinnarizine	Stutgeron 75 mg capsules
Dimenhydrinate	Travelgum 20 mg
Doxepin	Sinequan 10 mg capsules
Doxylamine	Vicks cough syrup concentrate
Phenytoin	Epilan-D-Gerot tablets
Meclozine	Contravert B (meclozine 25 mg) Diligan tablets (meclozine 25 mg, hydroxyzine 10 mg)
Dexamethasone	
Flunarizine (calcium channel blocker)	Sibelium 10 mg
α-Fluoromethylhistidine (inhibitor of histamine synthesis)	Not commercially available (yet)

Overall, *cinnarizine* appears to be most effective. Among 95 test persons, seasickness on rough seas was improved in 69 % by administering 50 mg cinnarizine. Considering the fact that cinnarizine is dosed much higher in just one capsule of Stugeron (75 mg cinnarizine), it becomes quite clear why cinnarizine has a very strong antiemetic effect. Children who suffer from nausea during car rides respond well to cinnarizine. Of 79 children who were given 15 mg cinnarizine 2 h before starting a trip, the treatment was successful or very successful in 81 %.

Antihypertensive drugs such as calcium and vasopressin antagonists are also effective in persons with seasickness. After consulting the internist, they may well be used as a sensible alternative in hypertensive patients.

Doxylamine and *pyridoxine* (vitamin B6) are given to women who experience vomiting during pregnancy. Doxylamine is contained in concentrated form in Vicks® cough syrup.

The previously described substance *α-FMH* is not commercially available.

Placebo rates for drugs are as high as 30 %.

10.5.2 Drugs That Exacerbate Seasickness

While endogenous opiates control seasickness, morphine antagonists such as naloxone intensify seasickness. The latter is also intensified by an antibiotic, namely, erythromycin. Nausea ranks first and vomiting ranks second in the side effects listed in the instruction leaflet for erythromycin.

10.5.3 Alternative Treatment Measures

Alternative measures are recommended time and again. However, investigations have proven the inefficacy of ginger, the "self-fulfilling prophecy," P6 acupressure, and anxiety as triggers of seasickness. With regard to the supposed effect of alternative measures, one should consider the fact that placebo rates are 30 % for these measures as well.

10.5.4 Sleep

Histamine is responsible for the waking phase of the body. Therefore, histamine levels drop to around zero during sleep. One may utilize this fact by asking persons who start to experience nausea to lie down and sleep. As their histamine levels are reduced, these persons are then quite capable of actively participating in life on the ship once they are awake. Histamine levels drop to about zero during sleep. Therefore, in case of symptoms, one should try to sleep midships.

When a person leaves a ship after a stormy trip and believes he/she has passed the test, he/she is confronted with the unpleasant fact that "seasickness" also exists on the ground. It is known as "mal de debarquement" or ridiculed as the sailor's gait (Seemannsgang) in German. It occurs in 66 % of cases after the first voyage at sea.

A significant positive correlation has been reported between the occurrence of seasickness and subsequent "mal de debarquement."

10.6 Therapeutic Approach

Any disease for which a number of different medications exist (and seasickness must necessarily be regarded as a disease of this type), one may assume that none of these is able to completely control the disease. If any of these *could* control the disease, all others would be withdrawn from the market and just one would remain. The fact is that the above-mentioned drugs do alleviate seasickness and even prevent it in some cases, but none of them can be regarded as a brilliant solution. Therefore, we decided to determine how this situation could be improved.

10.6.1 Optical Stimuli

Optical stimuli do exert a certain effect. As far as possible, one should be seated in the direction of motion and midships. Ideally one should remain standing and balance the rolling and stamping motion of the ship with the legs.

10.6.2 Selection of Food

Sailors commonly ingest preserved foods such as salami, hard cheese, tinned tuna fish, tomatoes, and chocolate. Beverages consist of red and white wine, beer, and the "sundowner" in the evening. All of these foods and beverages contain histamine and other biogenic amines, which foster seasickness.

What does the sailor ingest at sea?
Salami
Hard cheese
Tuna fish (tinned)
Tomatoes

Although histamine in blood does not immediately pass into the brain but is gradually passed on to the brain through the blood-brain barrier, constant ingestion of food containing histamine obviously causes the accumulation of histamine in the brain and makes it easier to trigger seasickness. Therefore, at sea one should try to ingest food devoid of histamine: in other words, all fresh food with the exception of spinach and tomatoes (= ketchup and pizza!), which should also not be ingested in fresh condition.

10.6.3 Vitamin C

Let us return to the story mentioned at the beginning: the main cause of seasickness was a vitamin C deficiency or scurvy. It is no coincidence that scurvy occurred at sea and rarely on the ground. Looking at the rat experiment, which showed that rats

exposed to stress release histamine and then synthesize vitamin C to degrade histamine, it becomes quite clear why histamine is released during a stormy passage that causes stress for sailors. The body's endogenous vitamin C reserves, used to degrade histamine, are consumed very rapidly (Johnston et al. 1992). This would be an additional explanation for the occurrence of scurvy – apart from the consumption of food containing no or very little vitamin C.

Two Examples from Daily Life

One patient told me that Greek fishermen hand out slices of lemon to tourists on a fishing boat when they take them from one island to another in stormy weather.

A doctor from Burgenland (a province in Austria) who went to the Samoa Islands several times while doing scientific research told me that the residents of the region eat mango before they embark on a sea voyage. In terms of weight, a mango contains nearly as much vitamin C as a lemon. However, since a mango is about as heavy as three lemons, one is able to meet one's vitamin C requirements in a very pleasant way.

Following this line of thought logically, vitamin C must be an effective means of treating seasickness. The published literature contains a number of studies that show an inverse relationship between histamine and vitamin C (in other words, high histamine levels are associated with low vitamin C levels), but the authors of some publications found no relationship between histamine and vitamin C.

To investigate the interaction between histamine and vitamin C, we examined the influence of vitamin C on histamine in the in vitro setting, i.e., in the test tube. We found that low-dosed vitamin C had no effect on histamine levels. Very high doses were required to cause a rapid drop in histamine levels (Fig. 10.1).

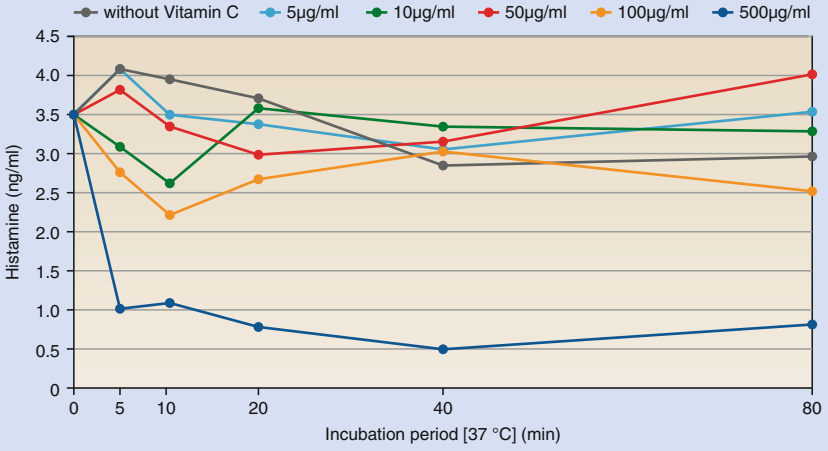


Fig. 10.1 Histamine content of a histamine solution (baseline level 3.5 ng/ml) after the addition of different quantities of vitamin C (co-incubation at 37 °C in the presence of copper)

In view of the fact that laboratory experiments cannot be unconditionally transferred to the human setting, we looked for a human model. Investigations in human subjects on rough seas are difficult to perform for a variety of reasons. We therefore looked for a human model marked by persistently high histamine levels and found this condition in mastocytosis. This disease (looks similar to birthmarks on the skin) is marked by a rise in the patient's mast cell count. Mast cells contain large quantities of histamine and, when faced with a suitable impulse, are liable to release histamine spontaneously. These persons experience skin symptoms such as redness, itching, and wheals, as well as other histamine-related changes like diarrhea and even headache. Besides, they report nausea which may be so severe that women feel as if they were perpetually pregnant. Some of them also lost their joy of living and harbored thoughts of suicide.

Case Report

A 24-year-old woman with mastocytosis had the following clinical symptoms and blood reports (Table 10.2):

- Strong swelling after insect bites
- Intolerance of Chinese food
- Frequent headaches, rarely diarrhea
- Hypotension, occasional arrhythmia
- Dysmenorrhea
- Rarely nausea
- Mild seasickness ("had to give up an airline job")
- High histamine levels
- Low diamine oxidase levels
- Low vitamin C levels

We hypothesized the following:

Assuming that the inverse relationship between high histamine levels and vitamin C – as established in human medicine – is really true, patients with mastocytosis must have low vitamin C levels.

We then investigated the serum of our own patients and that of patients at the General Hospital of Vienna (Allgemeines Krankenhaus der Stadt Wien; AKH), kindly provided by Peter Valent, in respect of vitamin C, and registered significantly low vitamin C levels ($p < 0.02$) (Fig. 10.2).

However, this finding is no real evidence in favor of our hypothesis. Such evidence would be provided if we were able to normalize vitamin C levels by

Table 10.2 Blood reports of a woman with mastocytosis and a propensity for seasickness in her medical history

	Patient's data	Normal values
Plasma histamine	0.5 ng/ml	≤0.4 ng/ml
Serum DAO	4 U/ml	>10 U/ml
Serum vitamin C	3.8 µg/ml	5.2–12.8 µg/ml

DAO diamine oxidase

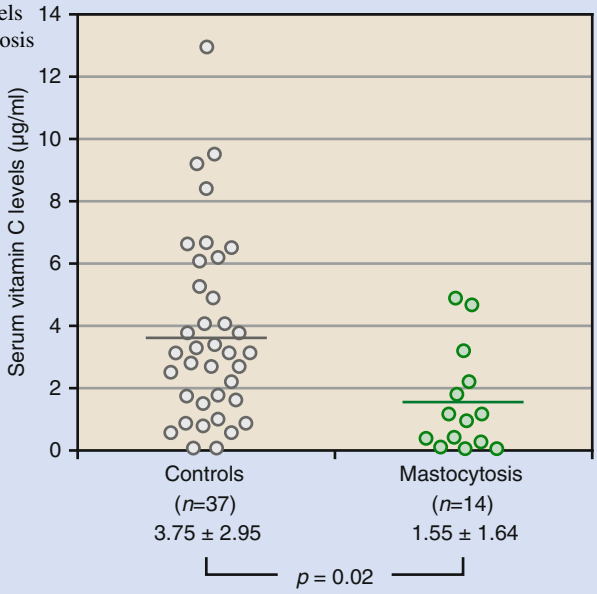


Fig. 10.2 Vitamin C levels in patients with mastocytosis and healthy controls

the administration of vitamin C, reduce histamine levels, and, most of all, eradicate the patients' nausea (which they found most agonizing). In actual fact, vitamin C, administered at a dose of 1–3 g/day, eradicated nausea in the patient with mastocytosis. One of our patients (herself a doctor) is now able to board a plane without becoming "airsick."

Figure 10.3 shows the drop in histamine levels due to the administration of vitamin C in a woman with mastocytosis. It suggests that the efficacy of vitamin C increases in direct proportion to a person's histamine levels. With reference to seasickness, this would mean that the worse a patient feels, the greater is the efficacy of vitamin C. It may be concluded that high-dosed vitamin C may well be able to exert a favorable effect on seasickness. However, the problem in administering vitamin C is that its absorption is subject to a rather slow mechanism of transport in the intestines. Absorption of vitamin C occurs at a specific speed – even when a person takes large quantities of it. Intravenous administration of a drug is always the fastest route, but vitamin C can be administered intravenously only in the infirmaries of large ships. It cannot be given by this route to "ordinary" sailors.

We looked for a solution to the problem. The best means of delivering vitamin C rapidly to the body is undoubtedly through the oral mucosa – in the form of vitamin C chewable tablets.

In our own investigation, after a mere 10 min, we noted a 40 % rise in vitamin C levels following the intake of chewable tablets (500 mg), compared to a 13 % rise after the intake of vitamin C effervescent tablets (1,000 mg).

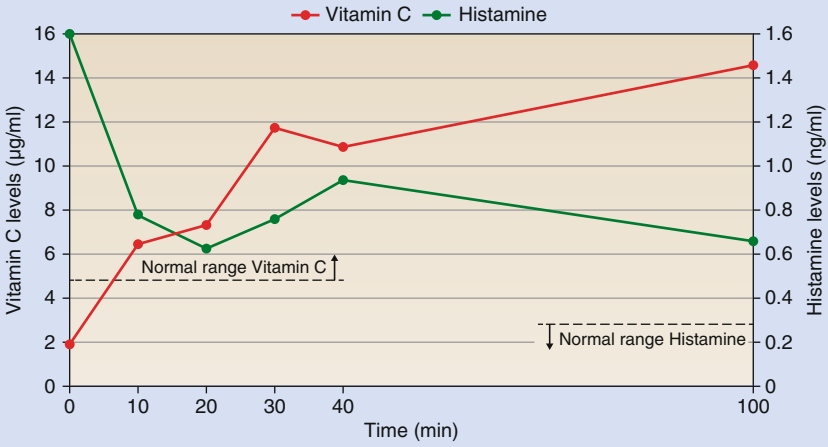


Fig. 10.3 Drop in histamine levels effected by oral administration of vitamin C in a woman with mastocytosis

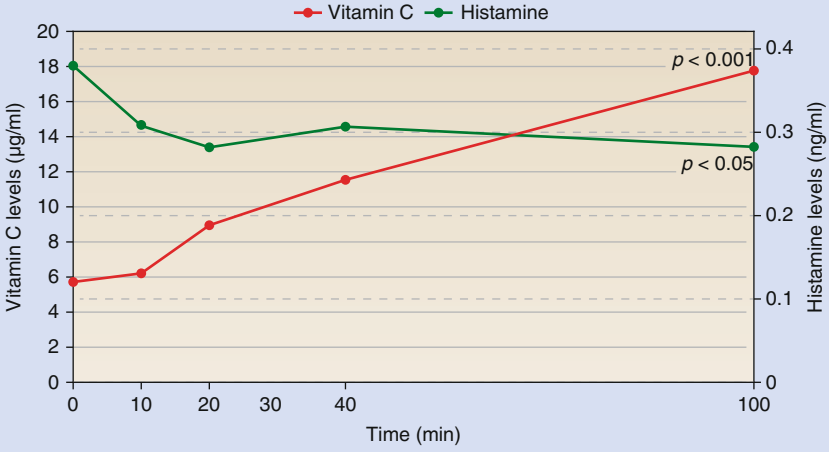


Fig. 10.4 Inverse relationship between histamine and vitamin C levels in 20 patients after oral administration of vitamin C

Figure 10.4 shows, in 20 patients, a rise in vitamin C levels after the intake of four vitamin C chewing tablets (500 mg each) and a simultaneous drop in histamine levels. However, these data reflect changes in blood but not in the brain, where measurements cannot be performed for plausible reasons. The effect in the brain is most likely stronger because vitamin C absorbed by the oral mucosa reaches the brain very rapidly.

Fig. 10.5 Inflatable life raft exposed to one-meter-high waves

10.6.4 Study in the German Navy

After institutional review board approval, the study was performed as a pharmacological trial in Neustadt near Kiel (Germany) (Jarisch et al. 2014). In a double –blind placebo-controlled crossover study two grams of vitamin C or placebo was taken one hour before exposure to one-meter-high waves in an indoor pool (Fig. 10.5). Blood samples were taken one hour before and after exposure to determine histamine, diamin oxidase tryptase and vitamin C levels. Symptom scores were noted on a visual analog scale. On the second day the test persons were asked which day they had felt better.

10.6.4.1 Results

All 70 volunteers were treated according to protocol on 2 days.

Seven (two females, five males) of 70 persons had no symptoms whatsoever on both days and were therefore excluded from the symptom-based analyses.

10.6.4.2 Influence of Vitamin C

Twenty-two of 63 test persons reported more severe symptoms after the intake of vitamin C, whereas 41/63 reported the same after the intake of placebo ($p = 0.008^{*}$).

There was a *gender difference*: women experienced more symptoms after the intake of vitamin C in 4/18 cases, while the same was reported by 14/18 women who were given placebo ($p = 0.049$; Fisher's test). Men had more signs of seasickness in 18/45 cases after the intake of vitamin C while the same was reported by 27/45 after the intake of placebo (n.s.) (Fig. 10.6).

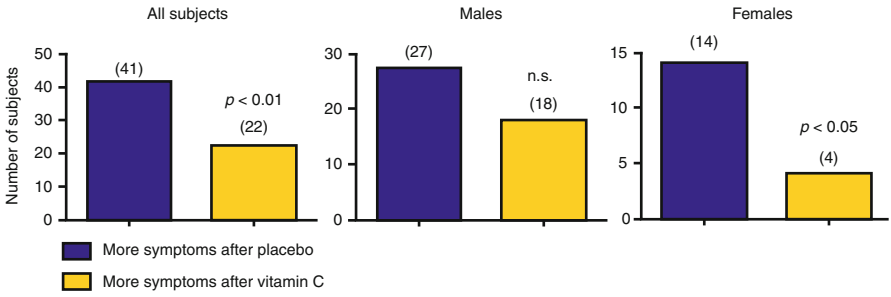
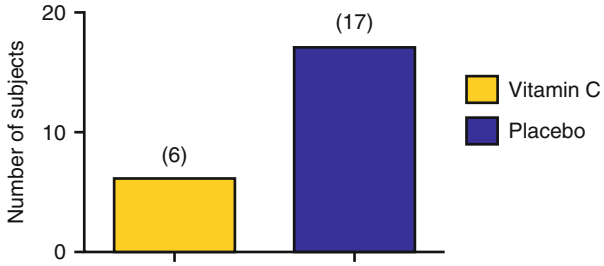


Fig. 10.6 Symptoms of seasickness after placebo vs. vitamin C in all subjects, divided by gender

Fig. 10.7 Number of persons who left the raft earlier than 20 min at least once



No woman was menstruating on the tested days. Seasickness occurs in women more often during menstruation (Grunfeld et al. 1998). Women are less susceptible to seasickness on the day of ovulation and when they take contraceptive pills (Matchock et al. 2008).

10.6.4.3 Comparison of Age Groups Younger or Older Than the Median Age of 27 Years

The median age of all 70 tested persons was 27 years. Three persons were 27 years old. The youngest was assigned to the "younger" group and the remaining persons to the "older" group. The following data refer to 63 symptomatic volunteers.

Twenty-one of 30 test persons (males and females) younger than 27 years of age felt worse with placebo, compared to nine of 30 who were given vitamin C ($p = 0.0169^{*}$; Fisher's test).

Twenty of 33 test persons (males and females) older than 27 years of age felt better with vitamin C, compared to 13/33 who were given placebo (n.s.).

10.6.4.4 Persons in Whom the Treatment Was Discontinued Early

Of 63 volunteers, 23 persons (11 females and 12 males) wished to leave the life raft earlier than the required period of 20 min because of their symptoms. Eight persons left the life raft on both days (six females and two males). Nineteen of 31 persons requested termination of the trip under placebo and 12 under vitamin C. The symptom score after exposure on the visual analog scale (score range 0–10) of those who left the raft earlier than 20 min was 5.45 with vitamin C and 7.57 with placebo. Of those who tolerated the life raft for a shorter period of time than required, 17 had taken placebo and 6 had taken vitamin C (Fig. 10.7).

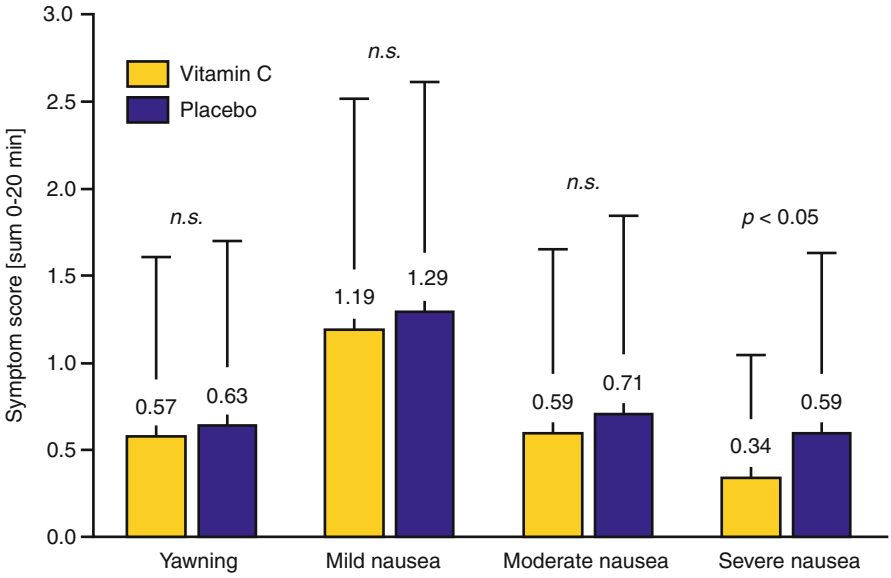


Fig. 10.8 Symptom scores for yawning; mild, moderate, and severe nausea, in relation to the drug taken. Sum of the 5-min intervals for each symptom during exposure to waves (for the specific symptom: 0 = no; 1 = yes), mean ± SD

In this group, the length of stay in the life raft was 16.7 ± 4.4 min after vitamin C compared to 13.6 ± 4.7 min after placebo ($p = 0.035^{*}$).

One woman left the raft with placebo after 7 min but could withstand the entire 20-min period with vitamin C.

10.6.4.5 Severity of Symptoms During and After Exposure

Symptoms during exposure to waves were divided into yawning, mild nausea, moderate nausea, and severe nausea (sensation prior to vomiting). Differences in the symptoms of yawning and mild, moderate, and severe nausea are shown in Fig. 10.8.

Women experienced mild nausea more often with placebo ($p = 0.045$), moderate nausea with placebo ($p = 0.007^{*}$), and severe nausea with placebo ($p = 0.014^{*}$); data not shown.

In persons *younger than 27* years of age, a significant difference was noted only in regard of severe nausea in favor of vitamin C ($p = 0.04$). No difference was registered in persons older than 28 years.

Comparison of symptoms until 180 min after completion of exposure on a visual analog scale showed no difference between vitamin C and placebo, although the symptoms were slightly better after the intake of vitamin C (Table 10.3).

10.6.4.6 Comparison Between the 2 Days of Exposure

A significant difference was noted in the subjects' state of health between days 1 and 2. Day 1 was rated better by 23/63 persons and day 2 by 40/63 ($p = 0.043$, not distinguishing between vitamin C or placebo) (Fig. 10.9).

Table 10.3 Symptom scores on the visual analog scale (0–10) after both exposures to waves ($n=63$)

Time point of rating	0 min	30 min	60 min	120 min	180 min
After vitamin C	3.96 ± 3.44	2.04 ± 2.29	0.97 ± 1.82	0.48 ± 1.5	0.45 ± 1.37
After placebo	4.3 ± 3.29	2.06 ± 2.42	1.05 ± 1.85	0.52 ± 1.15	0.29 ± 0.77
	n.s.	n.s.	n.s.	n.s.	n.s.

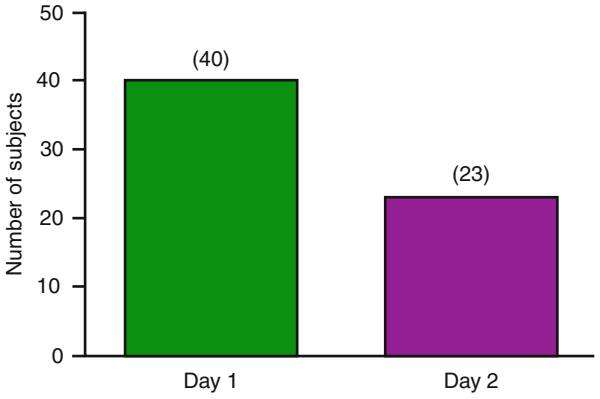


Fig. 10.9 Day with more severe symptoms

Table 10.4 Histamine levels prior to and after exposure to waves, with the intake of 2 g vitamin C or placebo ($n=70$; normal histamine level <0.3 ng/ml)

Histamine levels	Before intake	After exposure	Significance (paired *t*-test)
Vitamin C	0.17 ± 0.1 ng/ml	0.21 ± 0.1 ng/ml	$p=0.003^*$
Placebo	0.25 ± 0.45 ng/ml	0.35 ± 0.82 ng/ml	n.s.

Table 10.5 DAO levels prior and after exposure to waves with the intake of 2 g vitamin C or placebo ($n=70$; normal DAO level >10 U/ml)

DAO levels	Before intake	After exposure	Significance (paired *t*-test)
Vitamin C	16.98 ± 11.37 U/ml	20.39 ± 13.86 U/ml	$p<0.001^*$
Placebo	16.89 ± 12.45 U/ml	18.42 ± 13.46 U/ml	n.s.

10.6.4.7 Serum Parameters

Vitamin C, histamine, and DAO levels prior to and after intake of vitamin C, and prior to and after exposure to waves, are shown in Tables 10.4 and 10.5.

Vitamin C levels increased significantly after the intake of vitamin C (from 12.98 ± 4.57 to 26.03 ± 6.94 mg/l; $p<0.0001$), whereas vitamin C levels remained the same after the intake of placebo.

Histamine levels increased in 79/135 samples, remained the same in 20/135, and decreased in 36/135. Taken together, a significant rise was noted in histamine levels ($p<0.003$) (Table 10.4).

DAO levels increased significantly ($p<0.001$) after the intake of vitamin C and increased slightly after the intake of placebo (n.s.) (Table 10.5).

Two persons had elevated *tryptase* levels (12.4 and 14.9 µg/l) prior to the test and experienced severe symptoms.

10.7 Discussion

The main conclusions derived from the study are the following:

Vitamin C helps to suppress symptoms of seasickness.

A gender difference was noted. Women – who are more prone to seasickness – benefited to a greater extent from the intake of vitamin C than did men younger than 27 years of age. Older persons, who are usually less sensitive, did not benefit as much. The same results were registered by Bos et al. (2005). However, the difference on the visual analog scale in favor of vitamin C was not significant. Significantly more persons given placebo left the raft earlier than 20 min.

The second day of exposure to waves was perceived as a better experience, which concurs with the thesis that habituation occurs over time. The percentage of persons who felt better with placebo was 21.7 % (5/23) on day 1 and 42.5 % (17/40) on day 2. Placebo rates were usually between 20 and 30 %. The rather low placebo rate on day 1 indicates that the test procedure was strenuous. Marine cadets have to be on the life raft for just 5 min during their training. The relatively high rate of success with placebo confirms the fact of habituation.

These data indicate that, to improve the tolerance of a crew, the first day of a voyage on a vessel should cover just a few nautical miles.

On exposure to waves, the majority of persons demonstrate an increase in their blood histamine levels. I would regard this rise in histamine as a stress reaction. An increase was noted in both groups but was not significant in the placebo group. This seems to be due to the much greater variation of data in the placebo group compared to the vitamin C group (Table 10.4). Taken together, a significant increase was noted in both groups ($p < 0.003$). For obvious reasons, histamine cannot be measured in the brain. Potential changes in the brain remain speculative in nature. Animal studies in which histidine decarboxylase was blocked revealed that histamine is the prime cause of seasickness (Lucot and Takeda 1992).

An increase in DAO was noted in both groups but was more significant in the vitamin C group after oral intake of 2 g vitamin C. This fact may be interesting with regard to the treatment of histamine-intolerant persons.

No changes were noted in tryptase levels throughout the study.

Vitamin C is absorbed rather slowly when swallowed and is excreted rather rapidly. In contrast to rats, human beings cannot synthesize this vitamin and must therefore take vitamin C regularly. Dissolved in the mouth, vitamin C tablets increase blood levels faster than do swallowed tablets. Thus, vitamin C must be dissolved in the mouth to achieve a rapid increase in blood levels and effectively counteract seasickness.

None of the medications known thus far helps to counteract seasickness in all cases. The same is true of vitamin C. However, the advantage of vitamin C is that it does not make a person tired and is effective even after the symptoms of seasickness have started to emerge.

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Histamine and Osteoporosis

11

Reinhart Jarisch

Premenopausal women with an allergy experience fractures three times more frequently than do nonallergic women (Ferencz et al. 2006).

Osteoporosis is also related to histamine. Patients with mastocytosis are subject to a higher risk of osteoporosis. It would be quite logical to suspect histamine as the cause of this condition.

In an animal experiment on ovariectomized knockout mice (in whom the transformation of histidine into histamine was blocked by the elimination of histidine decarboxylase) that were given a histamine-free diet, the activity of osteoclasts (which degrade the bone) was suppressed, while the activity of osteoblasts (which form the bone) was stimulated (Fitzpatrick et al. 2003). In persons who received antihistamines with placebo control, the reports in regard of osteoporosis were significantly better [$p < 0.037$] (Kinjo et al. 2008).

Thus, in addition to the previously used therapy, one must consider antihistamines and prescribe a histamine-free diet.

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R. Jarisch, MD
Floridsdorf Allergy Center, Franz-Jonas-Platz 8, Vienna A-1210, Austria
e-mail: jarisch@faz.at

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