

How Histamine Wrecked Four Years of My Life.

(And Is There a Need for a Diagnostic Specialist in the NHS?)

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1. Introduction

I am a fifty-one year old male and I live in the UK.

In the autumn of 2006 I began to experience some health issues that developed over time into a confusing and distressing set of symptoms. I saw numerous doctors, including various specialists, and underwent many investigations and tests.

After around three years with no real diagnosis it began to become clear to me that an important protein in the body called histamine was involved in my problems. However, none of the doctors who were involved in my case at the time believed that histamine might have anything to do with my symptoms.

After a total of four years and further deterioration in my health I was fortunate to discover some more links between my symptoms and histamine. These links spurred me on to more investigation and I eventually found a treatment that resolved all of my symptoms. My diagnosis has since been confirmed by a medical specialist and I now know that the treatment I had started on my own is completely appropriate.

I hope that this story provides some evidence that by being determined, assertive and stubbornly refusing to accept the lack of a proper diagnosis, you may still have a chance to eventually get to the bottom of quite complex health issues. I believe that sometimes a thorough medical investigation needs a bit of 'encouragement'. After all, we are all ultimately responsible for our own health.

I also hope that the information provided in this story might provide ideas or lines of inquiry to some readers who may have one or more of the health issues that I am about to describe.

The remaining sub-sections (1.1 – 1.5) provide a little more in-depth technical information on histamine and related topics.

I have made no attempt to make the following sub-sections complete from a physiological perspective. They are merely there to provide the reader with a very basic understanding of what histamine actually is and enough understanding of histamine, histamine receptors and antihistamines to make the rest of this document very easy to follow.

The technical sub-sections are quite short and it is not important to understand or remember every detail.

1.1 What is Histamine?

Histamine is an important protein in the human body. Histamine is derived from the amino acid histidine. In adults, histidine is a non-essential amino acid, which means that our bodies can manufacture enough of it to avoid the necessity of having it in our diet (infants cannot do this and so for them histidine is an essential amino acid).

Basically, in the presence of an enzyme (histidine decarboxylase) and vitamin B6, histamine may be produced from histidine.

Histamine is a vasoactive amine. Vasoactive means it affects the permeability of blood vessels.

Histamine's name is derived from 'hist' (because it is made from histidine) and 'amine' (because it is a vasoactive amine).

1.2 What Does Histamine Do?

Histamine is involved in local immune responses as well as regulating some functions in the digestive system and acting as a neurotransmitter in the brain.

Histamine is involved in many allergic reactions. Allergies are caused by an immune response to a normally innocuous substance (e.g. nuts, pollen, dust).

As part of an immune response to foreign pathogens, histamine is produced by basophils and by mast cells found in nearby connective tissues. Please see the next section for a little more information on basophils and mast cells. Histamine triggers the inflammatory response and can cause the constriction of smooth muscle.

Histamine can cause inflammation directly as well as indirectly. Upon release of histamine by an antigen-activated mast cell, the permeability of vessels near the site is increased. Thus, blood fluids (including leukocytes, which participate in immune responses) enter the area causing swelling.

Indirectly, histamine contributes to inflammation by affecting the functions of other leukocytes in the area. It has been suggested that histamine release triggers the release of cytokines that in turn increase the inflammatory response.^[1]

Histamine's second type of allergic response is one of the major causes for asthma. In response to an allergen (a substance that triggers an allergic reaction), histamine, along with other chemicals, causes the contraction of smooth muscle.^[2] Consequently, the muscles surrounding the airways constrict causing shortness of breath and possibly complete tracheal-closure, an obviously life-threatening condition.

If the effects of histamine during an allergic reaction are inhibited, the life of an allergic person can be eased (in the case of inflammation) or even saved by preventing or shortening asthma attacks. Thankfully, many effective drugs have been developed to hinder histamine's allergic response activities.

As mentioned above, most histamine in the body is generated in granules in mast cells or in white blood cells called basophils. Mast cells are especially numerous at sites of potential injury - the nose, mouth, and feet, internal body surfaces, and blood vessels.

Non-mast cell histamine is found in several tissues, including the brain, where it functions as a neurotransmitter. Another important site of histamine storage and release is the enterochromaffin-like (ECL) cell of the stomach.

Once formed, histamine is either stored or rapidly inactivated. Histamine is broken down in the body by several different chemical compounds that the body produces e.g. diamine oxidase.

Some forms of food poisoning are due to conversion of histidine into histamine in spoiled food, such as fish.

Histamine occurs in food as a result of microbial enzymes converting the amino acid histidine (present in all proteins) to histamine.

All foods subjected to microbial fermentation in the manufacturing process contain histamine. Included in this category are cheeses, fermented soy products, other fermented foods (e.g. sauerkraut), alcoholic beverages, and vinegars.

Histamine exerts its actions by combining with specific cellular histamine receptors. The four histamine receptors that have been discovered are designated H1 through H4.

1.3 Mast Cells and Basophils

Mast cells and basophils have been mentioned briefly above. It is worth providing a little more background on them.

Mast cells and basophils play a central role in inflammatory and immediate allergic reactions. They are able to release potent inflammatory mediators e.g. histamine, proteases, cytokines etc. that act on the vasculature, smooth muscle, connective tissue, mucous glands and inflammatory cells.

A **mast cell** is part of a group of cells called leucocytes. Leucocytes are white blood cells and are found in the blood plasma with erythrocytes (red blood cells). Mast cells are part of the immune system. They form part of an early warning system. When stimulated, they release chemicals that signal either injury or infection and cause an inflammation in the area.

The chemicals that are produced by a mast cell are called mediators. Two common mediators are histamine and heparin. Histamine, the most important chemical mediator, causes capillary walls to become more permeable. Heparin prevents blood from clotting to allow blood to flow to the area of infection or injury. Mast cells play an important role in allergic reactions because of their ability to produce and release histamine. Mast cells settle in connective tissues and usually do not circulate in the blood stream.

During an immune response, a specific type of antibody, called Immunoglobulin E (or IgE) stimulates a mast cell. Antibodies are grouped into classes based on a chemical chain attached to them. There are five classes of antibodies based on the specific amino acid sequence of the chains, A, D, E, G and M. All antibodies are called immunoglobulins, so they are referred to as IgA, IgD, etc. IgE antibodies attach to the outside of mast cells. All antibodies are specific to particular antigens. The antigen-binding area of the antibodies is left free when they bind to a mast cell. When the mast cell with the antibody attached encounters the specific antigen, the mast cell is stimulated to release histamine.

Histamine is not only released due to encountering a toxic substance, it is also released when mast cells detect injury. It causes nearby blood vessels to dilate allowing more blood to reach the site of the injury or infection. The blood plasma is rich in antibodies and other cells of the immune system. In this way, the mast cells act as an alarm system for the immune cells, attracting them to the required area of infection or injury. The fluid that leaks into the area is what causes swelling during an infection.

Sometimes the body overreacts to foreign substances, which are in fact harmless. Most allergic reactions are due to uncontrolled histamine release when the immune system malfunctions. Symptoms of an allergic reaction are well known, but the underlying cause is less clear. Many of the symptoms of allergies can be attributed to histamine, so it is clear that mast cells are involved.

Basophils are a type of white blood cell. These cells are rare, making up less than one percent of the white blood cells in the body at any given time. They are also not very well understood, although the basic mechanism of basophils and what they do in the body has been studied.

Basophils are part of a family of white blood cells known as granulocytes, named for the distinctive granules of material inside their cell membranes. These granules contain pieces of information relevant to the immune system, and compounds, which the immune system utilizes when it responds to an infection or inflammation. Among other things, basophils can release histamine and heparin to respond to a suspected infection. Release of the granules is known as degranulation.

Basophils originate in the bone marrow, where they are created by stem cells. They circulate throughout the body in the blood stream, with the ability to pass into various

tissues as needed. When an infectious agent is detected by the immune system, basophils respond, along with numerous other types of white blood cells.

Researchers believe that in addition to helping at the site of an infection, these cells also help the body develop immunities by storing information which can be used by the T cells. Normal basophil counts can vary, depending on the patient and the situation. In a healthy person, the count is typically very low. In someone with an active infection or allergic response, the number of basophils in the blood can climb, betraying the presence of an infection. High basophil levels have also been observed in people with asthma, which may be due to the chronic lung inflammations experienced by many asthma sufferers.

Both **mast cells and basophils** contain special granules, which store mediators of inflammation. The extracellular release of the mediators is known as degranulation and may be induced by:

- 1) Physical destruction e.g. high temperature, mechanical trauma etc.
- 2) Chemical substances e.g. toxins, venoms.
- 3) Endogenous mediators, including tissue proteases, cationic proteins derived from eosinophils and neutrophils
- 4) Immune mechanisms

Released histamine from mast cells and basophils acts at histamine receptors on cells and tissues.

The number of basophils and mast cells increase at sites of inflammation. To reach these areas, basophils must migrate from the blood into tissue sites.

The increase in the number of mast cells and basophils, and the enhanced secretion at sites of inflammation, can accelerate the elimination of the cause of tissue injury or, paradoxically, may lead to a chronic inflammatory response. Thus, manipulating mast cell and basophil adhesion may be an important strategy for controlling the outcome of allergic and inflammatory responses.

1.4 The Histamine Receptors

Histamine exerts its actions by combining with specific cellular histamine receptors. The four histamine receptors that have been discovered are designated H1 through H4.

H1 receptors are found on the smooth muscle tissue of the internal organs, the endothelium lining blood vessels, and central nervous system tissue. The interaction of histamine with these receptors is responsible for hives, itching and swelling due to insect bites and similar allergic reactions, and allergic rhinitis, or cold-like symptoms due to allergic reaction.

H2 receptors are located on the parietal cells on the stomach lining and stimulate the secretion of gastric acid when activated by histamine; this process is a normal part of biological function and not a response to pathogens.

H3 receptors are located in the tissue of the central and parietal nervous system and are responsible for the decreased release of neurotransmitters including acetylcholine, histamine, norepinephrine, and serotonin.

H4 receptors are located in the basophils, bone marrow, thymus, small intestine, spleen, and colon. They play a role in chemotaxis, the movement of body cells in reaction to a chemical in their environment.

1.5 Antihistamines

Drugs called antihistamines are frequently used to treat allergies. An allergic reaction is an immune response that should not be occurring because the substance that triggers it should not be dangerous to us. Allowing our immune system to run its course against allergens means living with annoying and potentially dangerous symptoms. The use of antihistamines allows us to live more safely and comfortably by counteracting the body's immunological mistakes.

There is quite a commonly mistaken view that antihistamines actually act directly on histamine to remove it from the human body. This is not the case. Antihistamines are sometimes referred to as histamine receptor antagonists since they are agents that inhibit the action of histamine via histamine receptors. Specifically, antihistamines suppress the histamine-induced response by blocking the binding of histamine to its receptors. So, an H1 receptor antagonist would work by blocking the binding of histamine to H1 receptors. H1 antihistamines are used as treatment for symptoms of allergies such as the runny nose and sneezing associated with hay fever. Examples of H1 antihistamines are cetirizine hydrochloride (e.g. brands Zyrtec, Cetirizine and Citzine), chlorphenamine maleate (e.g. Piriton) and diphenhydramine hydrochloride (e.g. Benadryl).

An allergic reaction, which if severe enough can lead to anaphylaxis, results in excessive release of histamines and other mediators by the body. Other uses of H1 antihistamines help with symptoms of local inflammation that results from various conditions, such as insect stings, even if there is no allergic reaction.

Other commonly used examples of antihistamines include the H2 antagonists e.g. Ranitidine (one brand is Zantac in the UK) which are widely used for the treatment of acid reflux and stomach ulcers as they decrease gastric acid production.

Although there is always some histamine in your body, an insect sting may cause your body to release more histamine, making your skin red and irritated. In extreme cases of allergic reaction, for example in someone who is allergic to peanuts, histamine levels may become so high that it causes anaphylactic shock and possibly death.

In the case of severe allergic reactions antihistamines may not be sufficient to deal with the level of histamine induced. Adrenaline (epinephrine) is the only chemical that quickly eliminates histamine in a person.

2. My Medical History – A Short Summary

Some of my past health issues are relevant to the main subject matter of this document. I will briefly describe the main events in my medical history in chronological order.

2.1 Childhood Illnesses

I had the usual collection of childhood illnesses: chicken pox, measles, german measles.

2.2 Urticaria

When I was aged eleven, I suddenly developed urticaria. Urticaria is also known as hives (especially in the USA). My entire body came up in thick red, itchy swellings, until my entire body, arms, legs, hands, feet and face were covered.

My family doctor said it was urticaria and put me on the antihistamine Piriton (chlorphenamine maleate).

From that moment on, multiple times a week I would randomly have attacks of urticaria. When I had a severe episode the rash would also occur inside my mouth and in my throat so that I could barely breathe. I was typically on 3-4 Piriton per day, but when the

condition was particularly difficult I would need 6-8 Piriton to control it. I was never offered any tests to discover the cause.

Over the next six years the urticaria got gradually less frequent and then stopped for no reason at all.

2.3 Hay Fever

Almost as soon as the urticaria stopped I developed hay fever. It began very severely and I was given Piriton once again. Even on high doses of Piriton the summer months were a nightmare.

I still get hay fever but over the years the symptoms have got less significant, but I still need some antihistamines during the summer months.

2.4 Glandular Fever

When I was twenty-one years old I developed glandular fever (also known as mononucleosis or Epstein Barr virus). When I had the blood test to confirm it, the blood sample was the faintest, pale pink colour. When I saw my doctor for the blood test results he said that it was glandular fever. My doctor also told me that he was surprised that I'd even been conscious at the time of the blood test because I had so few red blood cells relative to the white ones.

I recovered from the worst symptoms after about six weeks but it was a full year until I felt really well again.

2.5 Auto Immune Thyroid Disease

When I was about thirty-two years of age I began to feel unwell. I had put weight on. I was having problems remembering things. I was cold and tired. I had assumed it was stress at work.

I went to my family doctor and a thyroid function test was done. I was diagnosed with very low thyroid function, which in my case was an autoimmune problem (Hashimoto's thyroiditis). Very high levels of autoantibodies were present as well as very low T4, very low T3 and very high thyroid stimulating hormone (TSH).

I was immediately given thyroxine (synthetic T4) and the dose was slowly increased until the TSH fell into the normal range. My symptoms improved a little but not nearly as they should have done.

My thyroid problem is more complex and covers a longer period of time than the medical problem that this article is concerned with.

This section contains a very brief summary of what happened.

The prescribed synthetic thyroxine refused to correct my hypothyroid symptoms regardless of the thyroxine dosage or whatever else it was combined with. The thyroxine did affect my blood levels of TSH, free T4 and free T3, which are the typical thyroid hormones that are checked. These thyroid hormones did respond to the prescribed thyroxine and they were adjusted into the normal ranges. My doctors told me that my thyroid hormones were now normal having been on the T4 replacement therapy.

However, I still had most of the symptoms of hypothyroidism that I walked into my doctor's consultation room with in the first place!

The T4 replacement therapy I had been given had made my blood test results look normal but I still felt dreadfully unwell.

Eventually, other forms of thyroid replacement therapy were tried. These included the use of natural thyroid hormone as well as the use of synthetic T4 combined with different amounts of synthetic T3.

All of these combinations were combined with appropriate vitamin and mineral supplements designed to support the correct biochemical processing of thyroid hormones in the body. I also had tests done which confirmed that my adrenal glands were working.

None of the alternative thyroid hormone replacement therapies worked any better than the poor response I had already experienced with synthetic thyroxine (T4).

After many years, I was given pure synthetic T3 without any T4. The pure T3 worked extremely well almost immediately but it took some time to fine tune the final dosage.

No root cause explanation has ever been given me by any of the medical professionals involved in my thyroid problem. I have now done my own investigations into the problems that I encountered and my findings are included within the above mentioned document.

Anyway, the T3 worked extremely well and I have been happily using it for around ten years.

My atrophic variety of autoimmune thyroiditis has resulted in my thyroid being almost completely destroyed by my autoantibodies. So, I am entirely reliant on taking T3 to keep me well and functioning.

3. The First Signs that I Had Another Problem

In the autumn of 2006 I began to get some indigestion and stomach acidity issues. The symptoms were a minor annoyance for a couple of months before things began to deteriorate.

In December 2006 I had a short episode of gastritis and my family doctor put me on 40 mg/day of omeprazole, which is a stomach acid suppressant, or proton pump inhibitor to give it a more accurate description. I had an endoscopy of my stomach but no stomach ulcer or other problem could be seen.

Having had many years of very difficult issues with my thyroid problem I was very disappointed to have to deal with something else. Little did I know how difficult things were going to get.

I began to refer to this new problem to my family and friends as my 'gastric acid problem'. The name has stuck and I now use it as an overall title for the entire problem.

4. The Omeprazole Withdrawal Incident

In January 2007 my symptoms appeared improved and slowly the omeprazole was reduced.

However, within a day of the last of the omeprazole being stopped my gastric acid levels increased suddenly and dramatically causing extreme pain, sufficient to take me to the accident and emergency department of the nearest hospital. No doctor in the hospital, or the gastroenterologist I saw at the time or my own family doctor knew what had caused the problem.

I was put back on the 40 mg of omeprazole but it no longer controlled the acidity level.

I did some investigation and discovered medical research papers that discuss a situation known as Omeprazole Withdrawal Rebound Hyper-Gastrinaemia.^[3] This basically means that the hormone gastrin (which stimulates gastric acid production) is elevated during the use of omeprazole. This happens because the body attempts to make more acid than the omeprazole will allow. When the omeprazole is removed it is possible to get a sudden

elevation in gastric acid level. This normally avoided by slowly reducing the omeprazole and then stopping it – which we had done.

So, there was a possible explanation but in my case the acid increase was huge.

After a meal my stomach ballooned out visibly in front of me and then suddenly I could hear and feel gurgling. I could then feel a series of large releases of fluid and then my stomach would flatten again. At this point I began to feel a distinct icy cold feeling in my abdomen. This icy cold would then spread, bringing pain with it.

The burning pain was unbearable. I was given a very high dose of codeine to attempt to deal with the pain. This continued for nearly two weeks until the omeprazole dose was increased to 120 mg/day.

Clearly, this was a highly unusual reaction to the withdrawal of the omeprazole. It suggested that something very peculiar indeed was going on.

At 120 mg/day the omeprazole stopped the acidity but I felt dreadfully ill. I had more tests around this time including another endoscopy, blood tests, kidney function and liver function tests.

I asked my family doctor and any other specialist that I saw whether it would be possible to have some basic tests that related directly to the acidity.

I knew that it was possible to test for basal acid output (BAO), maximal acid output (MAO) and gastrin levels. It seemed sensible to me to actually assess the acidity situation itself by looking at the actual acid levels and the level of the gastrin hormone that directly affected gastric acid production. This would have at the very least confirmed precisely what was going on.

However, the doctors I spoke to did not seem familiar with these tests. Instead more specific tests were done aimed at proving or disproving if I had a particular medical condition or not e.g. elevated calcium levels or iron levels. These types of tests for particular conditions were useful to exclude possible causes but it did seem a little odd to be that more basic tests were not being done first.

I still find the above diagnostic process extraordinarily hard to understand. If you are trying to diagnose something that might fundamentally be related to acidity then why not start by measuring gastrin and acid levels (after fasting and after food).

Initially, my high levels of stomach acidity could only be stopped by a total daily dose of omeprazole of 120 mg. I was very concerned because at that sort of dosage I wondered if I might have a serious illness e.g. a pancreatic tumour.

In addition to the above, it became apparent that at the same time that the acidity started I also began to have another issue. I began to be aware that after lunch my heart rate would go up significantly and stay raised for many hours afterwards. I was put on propranolol (a beta blocker) and have subsequently been investigated by a cardiologist.

No cause has been found for my heart rate elevation after food, even though this heart problem started at the same time as the gastric acid problem.

The gastric acid problem continued to be problematic for a while with the worst of the acidity controlled by the very high dose of omeprazole. The main symptoms were:

- 1) A bad pain under my left ribs. The location is well away from where the stomach is.
- 2) Severe burning in the epigastric area (centre of abdomen where stomach is)– no surprises there.
- 3) Digestive disturbances and lower abdominal pain.
- 4) A faster heart rate than normal.
- 5) Occasional flushing of the face, especially when severe epigastric pain was present.
- 6) I was not sleeping because of the above.

I had an abdominal CT scan at the end of February 2007. No causes were found for the gastric acid problem.

Both my kidneys did have slightly enlarged renal pelves. The CT report suggested having a MAG3 kidney scan. I was sent to a kidney specialist but the MAG3 scan was fine – my kidneys were working well within limits.

Eventually, I found the research papers relating to omeprazole withdrawal that I mentioned above and I devised a way of reducing the omeprazole.

In May 2007 I made myself go hypothyroid by drastically cutting down my T3 thyroid medication. I dropped my metabolism down as low as I could and then slowly reduced the omeprazole to 40 mg/day. It took a few weeks but I managed to get the omeprazole dose down without causing the omeprazole withdrawal problem.

I slowly got my dosage of thyroid hormone back up without a major acid problem. It was July 2007 before I was back on normal levels of thyroid hormone with the reduced level of omeprazole.

However, it appeared that I was going to be stuck on omeprazole permanently because I developed severe acid problems as soon as I tried to reduce the omeprazole further.

5. More Tests and Frustration and Time

During the rest of 2007 many more tests were done. On a couple of occasions I also tried the technique of dropping my metabolism by reducing my thyroid medication, as described above, in order to see if I could cope without omeprazole. I discovered that I still had stomach acidity issues that could not be managed without the omeprazole.

As 2007 ended and 2008 began my problems remained the same. My family doctor and I were running out of ideas.

During 2008, more thyroid and adrenal tests were done because it was hard for us to believe that my thyroid was not involved in some way. All of these tests provided no indication of any thyroid or adrenal gland link to my symptoms.

By May 2008 the only way I had found to manage my symptoms was to keep my thyroid hormone dosage at the minimum level that I could live with. So, I was permanently tired due to having too little thyroid hormone but the gastric acid problem was a little bit more comfortable.

I had a few more tests during 2008 but there was nothing to explain what was wrong with me. Clearly, I was incredibly frustrated at this stage. It was hard for me to believe that with the symptoms that I had no diagnosis could be made. I was particularly frustrated that none of the direct measures relating to stomach acid production had been done yet (gastrin, BAO, MAO).

I had hoped to be working with a specialist who would be able to run systematic tests to determine what the acid levels were and then what was causing them i.e. a thorough diagnostic method. This never happened.

Each specialist I saw appeared to only run tests based on their own specialist area. The tests often seemed to be aimed at testing for a specific disease.

I could not perceive an overall diagnostic approach. The impression that was given was a diagnostic approach that was based around a series of tests, with each one aimed at some specific disease or condition.

What I had been hoping for was a diagnostic approach, which was entirely focused on my symptoms and used more analytical thinking to assess what all the possible causes might be before systematically eliminating them. This never happened.

Towards the end of 2008 I began to have periods of depression. I had been making notes throughout my illness in order to keep track of what had been happening. In December 2008 I have one page with just one sentence written on it. It just says: "I am very depressed!".

By the end of 2008, I was very badly depressed and I had suicidal thoughts. I now felt that I was going to get no further help in diagnosing my gastric acid problem.

6. The First Histamine Connection and Frustration and Time

Very little happened during the early part of 2009. I just continued keeping my thyroid medication low and taking low doses of omeprazole.

During 2008 I had begun to think that the medical investigation into my problems was not very systematic and that it lacked a comprehensive approach. So, during 2008 I had begun to seriously research all the possible causes of excess gastric acid.

One of the more unlikely causes of excess gastric acid was due to high levels of histamine. Histamine can also cause facial flushing (which I had when the acid level was very bad) and elevated heart rate.

Histamine was an unlikely cause but I had convinced myself that it was worth investigating.

I suggested to my family doctor that we try anti-histamines even though I thought it was unlikely to reveal anything. My family doctor thought it was very unlikely that histamine had any bearing on my symptoms and that it was a waste of time attempting to use anti-histamines.

I decided to go ahead anyway in order to exclude histamine as a possible cause.

My plan was to try H1 receptor blockers (normal antihistamines like Piriton) first and then to try H2 receptor blockers (antihistamines aimed at reducing gastric acid).

All the above had taken some time, so it was not until June 2009 that I first tried antihistamines.

I was already taking citirizene hydrochloride once a day for hay fever. I simply added 4 Piriton tablets (4 * 4 mg chlorphenamine maleate) spread throughout the day, with the expectation that this would do nothing.

I stopped the omeprazole at the same time and waited for problems to start. I was not on any other form of ant-acids apart from the omeprazole so I fully expected to have problems. If I did get acidity and pain issues then I knew I could drop my thyroid hormone level and resolve them by going back on the omeprazole.

The expected problems did not start! I did not get elevated acid levels or associated epigastric pain and burning.

Amazingly, I felt much better than I had done when taking the omeprazole.

This was so unexpected! It seemed to shed a lot of new light on the gastric acid problem. At least I thought so!

I did not believe that this could be a placebo effect, but to exclude this I have tested this on 3 separate occasions over the past year by reducing or stopping the anti-histamines. Each time the symptoms have returned within 24 hours and brought severe, burning epigastric pain with them.

Now from this last set of experiments I noticed a fixed sequence of events after the stopping of the antihistamines:

- 1) The first thing that happens is that the pain in and up under the left side of my ribs at the front begins to get worse.
- 2) Several hours later after the left side pain, the epigastric burning begins. The burning will begin even if I have not eaten.

My conclusion from all of the above was that the chemical histamine must be involved in my gastric acid problem in some way. How could histamine not be involved? Antihistamines had provided the best relief for my symptoms so far. Surely histamine must be a key aspect of my gastric acid problem?

I tried to get some investigation into histamine levels by explaining what had happened with my antihistamine experiment. I spoke to my family doctor about the situation and asked about blood or urine tests for histamine. I did the same with any specialist that I saw at the time (endocrinologist, gastroenterologist).

No doctor seemed very interested in following this line of investigation. I think that they all thought that it was very unlikely to be related to histamine. This struck me as very strange because I thought it was clear that the clearly positive result with the antihistamines was diagnostic in its own right.

I was encouraged by my doctors to just be glad that there appeared to be a better medication solution. I was surprised and disappointed that the huge breakthrough in understanding that I thought had occurred was not being viewed the same way by the doctors involved in my case. I got little or no interest in following this line of investigation any further.

Simply taking the antihistamines, without really knowing exactly what was going on, felt like putting a large band-aid on something we did not understand.

Over the past year the underlying problem has clearly got very slowly worse. In addition to the antihistamines I began to have to use occasional ant-acids. I have also had some other issues – more on this below.

I also began to wonder whether I had actually been seeing the wrong type of specialist. I was beginning to think that this gastric acid problem might actually be a problem with my immune system. The release of histamine occurs in allergies and naturally I wondered if my immune system might be involved in some way.

All the main health issues in my life have had a fairly high immune system involvement: urticaria, hay fever, glandular fever, and autoimmune thyroid disease. The gastric acid problem began to feel like it might also be connected in some way to my immune system – because of the histamine clue, which only I appeared to have seen as significant.

No real progress was made with my gastric acid problem until 2010, although I did have the joy of a full colonoscopy in 2009 to rule out any disease there. It was clear.

7. The Gift of Depression

My first awareness of being depressed was during December 2008. Prior to that point I had experienced no previous episodes of depression throughout my entire life. My experience in December 2008 was very bad indeed. I had no obvious reasons to be depressed apart from my health issue.

After a few weeks the worst of the depression eased. However, after December 2008 I began to drop into and out of depression for no apparent reason. Then in May 2010 I got depressed again and did not come out of it. Because of my depressive mood, I had 'closed down' and was not communicating well with my family and I was not functioning well generally.

However, it turns out that getting depressed was something of a gift of data.

In the process of looking for information about depression I found several references to a strong link between depression and high histamine levels.^[4] I found some psychiatric research findings that have concluded that statistically significantly abnormal levels of histamine (both high and low levels) have been found in several types of mental illness including depression, phobias, OCD, bi-polar disorder, drug and alcohol addiction, anxiety and even schizophrenia.^[5]

I also found studies that have concluded that improvements have been made in the treatment of some mental illnesses when abnormal histamine levels have also been corrected (alongside more conventional treatment).

In terms of physiology, the highest concentration of H3 receptors is found in the brain. When histamine accesses these H3 receptors in the brain, the result is the reduction in the levels of some of the neurotransmitters including dopamine and serotonin (see section 1.4).

We also know that histamine will, even if only poorly, cross the blood brain barrier. So, it is hypothetically possible for higher than normal levels of histamine to have an effect on brain chemistry and mood in particular.

So there appeared to me to be at least some evidence for a potential relationship between abnormally high histamine levels and depression.

It is important to remember that although I was taking anti-histamines that these do not directly reduce histamine levels. Most antihistamines merely block access of histamine to the H1 receptors, leaving the histamine level unaltered. This is an absolutely crucial point.

So, it was entirely possible that an underlying problem was continuing to produce some histamine even though I was almost completely controlling its affect within my digestive tract using the anti-histamine Piriton. I suspected that a rising level of histamine was now having some serious effect leading to depression.

In addition to all the above I also found studies that concluded that some easily available supplements can be used to lower histamine levels. Vitamin C (ascorbic acid) for instance has a very interesting chemical property. When mixed with histamine, one molecule of vitamin C will destroy one molecule of histamine.^[6] To achieve this in any practical way high levels of vitamin C need to be taken and spread over the day. I'll describe more about this in due course.

I had booked an appointment with my family doctor with the specific intention of discussing my depression and getting started on anti-depressants but before I went to see her I wanted to do another experiment.

8. An Experiment in Histamine Reduction

So, based on all the above, on 17th August 2010 I began experimenting with some of the supplements said to be beneficial in reducing histamine levels (vitamin C, magnesium, calcium, l-methionine primarily).

Having experimented with each of these and in combination I can safely say that it is the vitamin C that has proven to be a wonderfully effective supplement for me. See appendices 2 and 3 for more details on these supplements.

Within 36 hours of using the vitamin C my depression had completely vanished! It did not return. I also felt calmer than I had felt in some time. This may sound unbelievable but it absolutely true.

To achieve this I needed to use several grams of vitamin C taken as smaller doses of 500-1000mg every 3 hours during the day. This may seem like a lot of work but it is a small price to pay for the kind of result that it provided me with. It is also a very cheap and easily bought supplement that is available in different formulations should any digestive upsets appear when using it in high doses. It also has many other beneficial properties that are well documented in various books, including the one referenced above.

The depression I had was severe enough to make me conclude that I needed anti-depressants but I had resisted going to my family doctor for so long because I did not want any more medication. Once on the vitamin C, I also stopped having to top-up with the additional ant-acids.

It became clear to me from this dramatic result that my depression had definitely been linked to elevated histamine levels.

9. My Histamine Hypothesis

By September 2010 I had been living with the gastric acid problem for around 4 years. I had made extensive notes about the problem and had developed a good understanding of the cause and effect relationships between symptoms and medications.

I had spent a lot of time thinking about and investigating what was actually occurring. I firmly believed by now that I had an elevated histamine level and that this was entirely responsible for my symptoms.

I still did not know what was causing the elevated histamine.

Histamine might be raised for 3 major classes of problem:

- 1) **Immune response to allergens** like pollen or nuts – this is the reason that most people are aware of as causing problems and take anti-histamines for. I did not believe I had developed an allergy. The range of symptoms and the way in which the gastric acid problem had progressed seemed to make this highly unlikely.
- 2) **Diseases/Conditions.** Some serious conditions exist (like mastocytomas and carcinoid tumours) that may produce excessive levels of histamine.

Carcinoid tumours are highly life threatening and can secrete one or more hormones, or other chemicals depending on the tumour type – this can include histamine.

Mastocytomas are dense collections of mast cells that can occur in skin or internal organs (like the spleen!). Mastocytomas produce high levels of histamine and can spread and cause a condition known as systemic mastocytosis – which is

manageable but has no cure. Mastocytomas are also linked to late onset, adult leukaemia.

Other less serious conditions are also known to raise histamine levels.

For instance, I have found several fairly recent medical research studies that have been done that are starting to suggest that histamine, and other chemicals like cytokines, may be raised during infection.^[7, 8, 9]

Disease of some kind seemed a possible cause for my histamine problem.

3) **Ingested Food Related Conditions.** This category covers two classes of problems:

a) those caused by the histamine in certain food, and

b) those caused by the digestive system generating histamine (even though the ingested food may have no histamine in it).

Histamine can be ingested in foods, especially fermented foods. Ready meals and fish are two of the worst culprits, as are alcoholic beverages.

It is being currently being suggested that there is a condition known as histamine intolerance, which suggests that some people cannot correctly process the natural levels of histamine found in food.^[10] Some people are proposing that this 'histamine intolerance' may be due to a genetic predisposition to produce insufficient levels of enzymes involved in destroying histamine e.g. diamine oxidase.

However, it is impossible to determine whether any histamine that may be causing symptoms is coming from ingested food or from histamine release within the digestive system i.e. not from the food itself.

Even if reliable tests for genetic conditions leading to the poor processing of histamine in food do exist then this still does not prove that any histamine that is causing problems is arising out of foods or from some other disease or immune system cause.

This last point is to my mind a serious flaw in the entire histamine intolerance idea. Unless the histamine has a label attached to it that indicates that it is coming from food then it is hard to say if a patient's problems are due to histamine intolerance or some other problem associated with elevated histamine levels.

It is made even more complicated because the histamine that is responsible for a patient's symptoms may have originated in the digestive system. There may be several reasons why histamine is raised in the digestive system.

This situation gets even more confuse because for the conditions where food is involved like IBS, food sensitivities and the proposed 'histamine intolerance' the symptoms may be more or less the same.

Take IBS for instance. More research is being done all the time on conditions like IBS and linkages are being found to histamine production from mast cells in some cases.^[11] IBS has very similar symptoms to 'histamine intolerance'. If research is beginning to indicate that IBS can raise histamine levels in the digestive system, it makes a definitive diagnosis of the cause of the symptoms very difficult indeed.

To make matters worse the treatments for all these conditions may be very similar. The choice of treatment that a patient may have is typically either an exclusion diet or medication.

So, I have concluded that trying to distinguish between the different causes of elevated histamine due to foods, in the case where a conventional allergy is not involved, is rather pointless.

The results are more or less the same in terms of the symptoms and so are the treatment options

So, I viewed all the possible causes that fall within this category as the same regardless of how any histamine may have come to be inside the digestive system.

In my case my diet had not changed. I saw no pattern of symptoms with different foods.

I ruled out any specific food related cause.

From the above, admittedly rough, analysis I believed that some form of major or minor disease was the most likely cause of my gastric acid problem.

If a disease was responsible it seemed likely that it was minor because the problem had gone on for four years without developing a great deal.

Excess gastric acid itself causes epigastric pain and burning so this would increase the level of inflammation. The inflammation could easily push histamine levels higher.

Histamine stimulates more gastric acid via the H2 receptors in the stomach.

So, I thought for some reason a vicious circle may have been established with increasing histamine, inflammation, and gastric acid.

This hypothesis suggested that at some point the levels of histamine could cause depression by being high for some histamine to cross the blood brain barrier, reaching the H3 receptors in the brain and so causing lower neurotransmitter levels as a result.

The antihistamine that I was taking was Piriton (a H1 receptor blocker). The histamine receptors in the stomach are H2 receptors and not affected directly by this type of antihistamine.

So, the fact that the antihistamines I was taking actually dramatically reduced my gastric acid level indicated that some condition was being controlled by the antihistamines and only as a result of a lower histamine level was my stomach acid reduced.

This was the weakest point of my hypothesis because I could not be sure what the antihistamines were actually acting upon.

It was only possible to come up with this hypothesis because I had become very depressed and had discovered a link between depression and histamine.

At this stage, in early September 2010, four years after the start of the gastric acid problem, I had my symptoms under control with a combination of antihistamines and supplements (mainly vitamin C in high doses – see Appendix 3 for details).

I considered the management of my symptoms by antihistamines and supplements to be a form of medical band-aid. I also did not know if the band-aid would last since I did not know exactly what it was controlling.

It seemed clear that the next step that was needed was to actually get a proper diagnosis and some actual proof.

So, I went through these ideas with my family doctor.

I suggested that the best course of action would be to see an immunologist who took an interest in the type of problems I had been having and in particular the immune system. My family doctor agreed to try to find an immunologist who was likely to be able to do the necessary diagnostic work.

So, I wrote a letter, which contained most of the ideas that are in this document, and my family doctor used this letter as part of the referral process.

10. The Immunologist Stage

As a preparatory step before my appointment with the immunologist I was asked to stop my medication and supplements 3-5 days beforehand. I expected to be asked to do this because any blood tests would need to test my condition at its worst. There was every chance that my histamine levels were much reduced with the combination of supplements and antihistamines that I was taking.

So, I stopped everything about 3 days prior to the appointment. Then I waited for my symptoms to start again.

I had no problems on the first day without any antihistamines or supplements. It was several months since I had done this experiment last and it usually took around a day for the symptoms to start.

During the second day with no antihistamines I had still not developed any symptoms. I began to be a bit puzzled. I had no noticeable epigastric pain or burning after meals.

The third day with no antihistamines arrived and it was clear now that this time I was not going to develop any symptoms!

I was due to see the immunologist on the evening of the third day. I had expected to go to the appointment with severe symptoms, which would make it easier to get the confirmation of high histamine levels through blood tests.

On three previous occasions of stopping or reducing the antihistamines my symptoms had returned savagely within a day or so. Why was this time different? I did not know!

The only difference that I could see was that I had been taking supplements designed to reduce histamine levels. Most notably these supplements included vitamin C in high dose.

The meeting with the immunologist was very interesting indeed.

10.1 What the Immunologist Told Me

This was a highly valuable meeting. It was clear that I had at last arrived at the consultation room of the right type of specialist for this problem. Immunology was the correct discipline to understand the main health issue that had dogged me for four years.

Here is what I got out of the meeting:

My analysis or hypothesis on what had happened to me over the past four years was partially correct.

The key diagnostic result that antihistamines controlled my symptoms better than omeprazole or anything else was critical and I was right to have identified this. The immunologist would not comment on the lack of interest in this diagnostic result but he was clear that this was the key piece of data.

He fully accepted that when I came off the omeprazole to begin with that it was very likely that I had a large gastric acid surge due to rebound hypergastrinaemia.

However, the epigastric pain and burning since I had eliminated the rebound problem and stopped the omeprazole was almost certainly not due to gastric acid! Hence, 'the gastric acid problem' is NOT a gastric acid problem!

My childhood urticaria, which I had mentioned as part of the detailed written history I had provided prior to the appointment, was very important. Two thirds of people with urticaria have the condition due to an autoantibody. Urticaria is known in some cases to be associated with autoimmune thyroid disease, which I also have.^[12] Patients with urticaria have an increased frequency of Hashimoto thyroiditis with the presence of autoantibodies to thyroglobulin or a microsomal-derived antigen (peroxidase).

Although it is not clear whether the thyroid autoantibodies trigger the urticaria or whether it is some autoantibody or other chemical from the urticaria that triggers the development of autoimmune thyroid disease.

The immunologist said that people that have had urticaria are twice as likely to develop autoimmune thyroid disease than the rest of the population (I do not know how accurate this statistic is).

The immunologist then did an interesting test. He pressed the non-ink end of a pen into the skin on the inside of my forearm and made a cross shape. He repeated this on his own forearm. Ten minutes later we checked both our arms. His was clear. Mine had a couple of clear red lines in a cross shape on it. This was due to pressure on the skin pressing down on sensitised mast cells in the lower layers of the skin. The pressure had made them release histamine. He indicated that my mast cells had a tendency to release histamine.

He then went on to explain that he had seen quite a few patients over the years that had a previous history of urticaria and were now complaining of stomach or digestive problems including epigastric pain. My symptoms fitted right in there with these other patients.

The immunologist believed that the most likely cause of all my symptoms was urticaria in the GI tract. He told me that this was why the antihistamines worked so well. The basic antihistamines (H1 receptor blockers) were working directly on the H1 receptors in the tissues of the GI tract and controlling the urticaria reaction itself. This in turn would tend to damp down the reaction and reduce the histamine levels.

I know believe that the anti-histamines were the most important treatment and the vitamin C was essentially clearing up the remaining histamine in my body and most importantly any histamine that managed to reach my brain.

Antihistamines are the treatment of choice for my condition. I could double or even triple the dose I had been taking if I had to. The medication I had been using was quite benign and without any known side effects. Also, if my symptoms stopped and I could reduce or stop the antihistamines then this was fine also. If I had a relapse then I could go back on them again.

He said I should reduce foods/drinks/drugs that are especially high in histamine or raise histamine. His examples were alcohol and codeine.

He said I should expect flare-ups from time to time. In those situations I should go back on or increase the antihistamines. Only if I could not control the symptoms would I need to see him again.

He said the pain under my left ribs was probably due to a sharing / routing of nerve fibres rather than a different organ i.e. it was coming from the same urticaria problem.

He did need to do some blood tests including measuring tryptase, which is the most abundant marker for mast cell activation. It is released along with histamine and is easier to measure than histamine (which really needs to be measured during an actual attack).

This test was likely not to indicate very much as my symptoms were now under control but at the minimum it would provide a baseline to compare against if the test had to be repeated during a period when I was having a very bad set of symptoms. If there was something very seriously wrong then this test might reveal it.

He said he would send the blood test results and his report to my family doctor and myself in about a week.

After four years and huge frustration I actually felt that I had got somewhere!

I have since also discovered that low levels of thyroid hormones are associated with an increase in the release of chemicals from mast cells, including histamine.^[13] This also illustrates the potential for the connection between low levels of thyroid hormones and the development of sensitivities and allergies.

It is also something to look out for if someone with a potential histamine problem has not been tested for thyroid issues.

10.2 The Immunologist's Final Report

I have the report from the immunologist and there was nothing especially unusual in the blood test results.

I had already developed an appropriate method of managing my symptoms prior to seeing the immunologist, which did not include any special diet or avoidance of certain foods. He confirmed that the treatment regime I was already using was ideal. I could now carry on with the added reassurance that the most likely cause of my symptoms was uncomfortable when it flared-up but not serious.

The immunologist did say in the final report that if the problem returns severely, then the other conditions that may fit my history and symptoms were mastocytosis or eosinophilic gastroenteritis. I would need to see a gastroenterologist to get this confirmed by biopsy if the need arose. If the symptoms did arise again then my family doctor could also check for carcinoid tumours by doing a 5-HIAA urine test.

His most likely view was that my problems have been caused by idiopathic urticaria, which has a habit of coming and going.

11. Is There a Need for a Diagnostic Specialist in the UK?

Without someone piecing this whole puzzle together no one would have realised it was an immunologist I needed to see.

Immediately after the withdrawal of omeprazole at the beginning of this story my symptoms began to be extremely unusual. Almost immediately after this my family doctor was struggling with what the possible cause might be.

Some basic tests were organised (blood counts, kidney function test, liver function test etc.). When these came back normal and I had a normal endoscopy result then my family doctor was struggling. This is not a criticism it is totally expected with a problem like mine.

Family doctors (GPs) have to do the best they can to select an appropriate specialist if they have not managed to diagnose and treat a problem themselves. In my case it was not really clear what was going on. It was not really clear what sort of specialist I needed. I was referred to an endocrinologist and then a gastroenterologist.

This was all rather ad hoc and quite wasteful in terms of money and people. During the four year long process I had: two contrast CT Scans (which I paid for), two endoscopies (the second one was unnecessary); an ultrasound scan of my kidneys and gall bladder; a MAG3 Kidney scan; two 24-hour urinary cortisol tests; a colonoscopy (which did not do any of the biopsies that my immunologist is now saying might exclude mastocytosis or

eosinophilic gastroenteritis); several visits to an endocrinologist; a visit to a surgeon who specialised in GI operations; so many blood tests of various types I will not even list them; inappropriate medication.

It is not reasonable to expect that the medical training of family doctors to cover the topics necessary in order to be optimal in terms of diagnosing a highly complex medical issue. In addition to this, they simply do not have the time to do the type of analysis required when faced with a problem like mine.

It is all very well having specialists in gastroenterology, endocrinology, general surgery, brain surgery, paediatrics, immunology etc. However, when the real issue is simply trying to work out what physiological system within the patient's body is causing the symptoms then these current specialities do not help to do the initial analysis if that analysis happens to be highly complex.

It would have been far better if a diagnostic specialist could have taken over the investigation of my problem. A diagnostic specialist would have had more time to evaluate my history and symptoms and then develop an optimal diagnostic approach. It may then have been possible for a more appropriate, smarter and more cost effective investigation to be performed. I believe that this should have been possible.

A more in depth diagnostic process should have been able to determine that I needed to see an immunologist, after a much more limited set of investigations.

An additional concern is that diagnostic work requires the right diagnostic skill-set and training in alternative diagnostic methods. It may even require a certain sort of mind that is capable of looking at problems in alternative ways. I do believe that these types of skills may be taught. I also believe that having a long list of laboratory tests that may be done is not the way to teach diagnostic skills.

I believe that if family doctors had a patient with a complex and confusing set of symptoms it would be far most cost effective to hand this patient over to a diagnostic specialist. A specialist trained in many diagnostic methods and having a little more time available for each patient may be able to provide either a diagnosis of the patient's problem or at least a confident recommendation on which specialism was required to fully diagnose the patient's problem.

I believe the lack of a diagnostic specialist within the NHS caused the waste of a great deal of money that was spent on inappropriate diagnostic work in my case. In addition, some of the main symptoms that I had were not investigated adequately. Some of the main events that I considered to be diagnostic ('clues') were not understood even when they were pointed out by me.

There must be thousands of cases like mine that are just hard to make sense of. The current process of ad hoc tests must be highly wasteful in terms of money and resources in more patients than me. More importantly there comes a point when the current system begins to fail for the patient.

If a few specialist physicians could be trained to perform creative and effective diagnostic work then I believe that difficult cases would be a lot more elegantly managed and a lot more cost effective.

The reality for me was that I had to try and fill this role myself. This was of course a painfully slow and frustrating process.

12. Vitamin D3 and Other New Ideas

As I conclude the writing of this document I have become aware of some other fascinating pieces of information:

- 1) Vitamin D3 deficiency is common in many Hashimoto's thyroiditis patients. I have heard figures that suggest that 90% of Hashimoto's thyroiditis patients are deficient in vitamin D3.
- 2) Vitamin D3 can be viewed as being a hormone not a straightforward vitamin because it has many regulatory properties in the body.
- 3) In particular, vitamin D3 is a modulator of the immune system because it stimulates regulatory T cells.
- 4) So, insufficiencies of vitamin D3 may lead to inappropriate immune system responses.
- 5) A suggested replacement dose of vitamin D3 for Hashimoto's thyroiditis patients is 5,000 – 10,000 IUs of vitamin D3 per day. These levels of doses do not appear to agree with me so I intend to take 2000 IUs per day.

Now, in one recent book I have read the author suggests that it is the overly active or un-modulated immune system that is responsible for some of the issues that Hashimoto's thyroiditis patients have.^[14] In particular, he suggests that a partial blockade of thyroid receptors by immune system chemicals may be part of the source of issues for Hashimoto's thyroiditis patients.

Whilst the above is not directly relevant to the topic of this document it does raise the possibility that any urticaria within my digestive system may have been partly caused by low levels of vitamin D which have helped to trigger some reaction. This is highly speculative of course.

However, the author of the referenced book also suggests that Hashimoto's thyroiditis patients and low levels of vitamin D3 are also linked to a gluten intolerance issue. He makes no mention of conventional allergies but specifically talks of intolerance.

So, whilst I have no way of proving any of these links I am now intending to supplement with vitamin D3 also, in order to determine if this has any benefit. I have always had seasonal affected disorder and for the first winter in my adult life SAD has not occurred, which also suggests that I may have had a vitamin D issue in the past.

I am also intending to see if I can get a 25-Hydroxy Vitamin D test to ascertain my vitamin D levels. The reference range for this test is typically 50-100 nmol/l, with less than 30 nmol/l indicating an issue.

The supplementation may have multiple benefits. I am hoping that it helps my thyroid condition as well as reduces the risk of any further histamine issues (urticaria).

13. Conclusion

This is a closed episode now as far as I am concerned.

I would like to finish by drawing a few conclusions of my own.

I believe now more than ever that people have to be responsible for their own health and get actively involved when necessary to get the diagnosis and treatment they deserve. This sometimes requires a degree of determination that is likely to cause some conflict with the medical profession at times.

I also believe more strongly than ever that prevention is better than any other course of action. Knowing what I do now, I intend to use a good range of vitamin and mineral supplements as well as a sensible diet and healthy lifestyle to try and limit to chance of any future issues like this!

Finally, we desperately need a better solution for complex diagnostic work in this country. I feel very lucky that my family doctors have been as competent and pleasant to deal with as they have been. However, they have been unable to unravel my complex condition. It is not their fault.

Family doctors do not have the available time to devote to complex diagnostic work, or the additional research that they may be required to do, in order to have a possibility of diagnosing some cases.

I would like to see a better solution put in place that more quickly and cost effectively resolves cases like mine. I would like to see an appropriate solution in the NHS that does not necessitate a patient having to make the level of effort that I have had to make in order to reach a diagnosis. My belief is that the creation of a diagnostic specialist role within the NHS would meet these objectives and be both good for patients and save valuable resources.

Appendix 1 – Histamine and Medical Conditions

Various studies over the past decade have made connections between elevated histamine levels and:

- allergies
- ulcerative colitis
- irritable bowel syndrome
- crohn's disease
- chronic fatigue
- severe fatigue with flu-like symptoms
- fibromyalgia
- M.E. like symptoms
- increased gut permeability
- small intestine bacterial overgrowth (SBO) – also linked to ready meals
- rheumatoid arthritis
- migraines and cluster headaches
- skin diseases
- rashes and flushing
- depression and other mental illnesses
- viruses like Epstein Barr, which remain in the body long after the symptoms have gone
- digestive problems (prolonged diarrhoea or constipation)
- bloating
- stomach pain
- heartburn (caused by excessive gastric acid production)
- belching
- acid reflux
- heart palpitation
- low blood pressure
- urticaria
- eczema
- hay fever
- asthma
-
- this list is probably not exhaustive!

However, I would not like to state that all of these studies have gold plated scientific credentials i.e. some of the studies may be tenuous at best.

I have found several relevant medical research papers that have been done by reputable medical researchers. I will list these briefly to offer some more credibility of the growing body of evidence implicating histamine involvement in a variety of medical conditions:

- 1) Maintz and Novak have suggested that the ingestion of histamine-rich food or of alcohol or drugs that release histamine or block DAO may provoke diarrhoea, headache, rhinoconjunctival symptoms, asthma, hypotension, arrhythmia, urticaria, pruritus, flushing, and other conditions in patients with histamine intolerance.^[10]
- 2) Hosoda et al have done research, which links Rhinovirus to histamine and cytokine production from mast cells and basophils.^[7] This is one piece of research associating elevated histamine and cytokines to a virus.
- 3) Chonmaitree et al did research linking virus and bacterial infection in the middle ear of children to histamine production.^[8]
- 4) Caughey et al have done research linking lung infection with elevated histamine and asthma.^[9]

- 5) Professor Michael Schemann's research team at the TUM Department for Human Biology have done research that suggests a possible cause for irritable bowel syndrome, a complaint that many thousands of people suffer from. They have found that micro-infections are present in the gut mucosa that produce inflammation and many of the associated chemicals of which histamine is one. It is these chemicals that may be responsible for the misery of IBS for many people.^[15]

- 6) Jacob Raber has completed research linking depression and histamine.^[4]

The above was based on a very short investigation. Clearly I did not look for anything on the link between histamine and gastric acid as this is just basic well-understood physiology.

In terms of my own systems, the gastric acid link to histamine is obvious. There are genuinely credible research findings that are beginning to suggest strong links between histamine levels and conditions like depression. This is clearly an area that will continue to have research for many years to come.

Appendix 2 – Vitamin C etc. and Histamine

It is now well accepted that there is good scientific evidence that human beings had a genetic mutation about 5000 years ago and lost the ability to manufacture ascorbic acid (vitamin C). The most likely reason for this genetic mutation was that food was very scarce. Naturally high levels of vitamin C production costs energy and so losing this ability would have offered the mutated human an advantage in times of food shortage.

Many mammals can still manufacture vitamin C themselves (e.g. cats, dogs, rats) and they do this in very large quantities. If we take account of the difference in body weight between some of these animals and humans it would suggest that humans would have produced many grams of vitamin C per day prior to the genetic mutation. These mammals produce even more of their own vitamin C, sometimes a factor of 100 times their normal rate, in times of stress and illness.

Based on the above it is very easy to believe that humans were meant to have ascorbic acid circulating in our blood in far higher quantities than the rather low current RDA would have us believe.

As far as I can tell there has been very little medical research performed by reputable university medical researchers or medical centre researchers into supplements aimed at reducing histamine. There may be one exception to this and that is ascorbic acid, better known as vitamin C.

I have read two books that very clearly, and with extensive reference to experimental data, set out solid scientific case that indicates that the rationale behind the current RDA for vitamin C is flawed. The two books are 1) Vitamin C: The Real Story by Steve Hickey, PhD. and Andrew W. Saul PhD and 2) Ascorbate: The Science of Vitamin C written by Drs. Steve Hickey and Hilary Roberts.^[6, 16] The authors of the latter book are both University of Manchester graduates in pharmacology in England. The book exposes the many flaws involved in the establishment of the Recommended Daily Allowance for vitamin C, and the revelations are alarming.

Doctors Hickey and Robert's develop what they refer to as a Dynamic Flow theory, which they believe, accounts for all known experimental data regarding vitamin C. Their Dynamic Flow theory explains all the factors that affect blood and cellular levels of vitamin C, and it suggests how to actually best take vitamin C as a supplement in health and disease state. One of the main conclusions of their book is that it is far better to take many smaller doses of vitamin C per day than one very large dose. The Hickey/Roberts Dynamic Flow findings indicate that the half-life of vitamin C in the blood stream is 30 minutes, and that doses around 500-1000 mg every few hours keeps the blood at the

highest concentrations all day long. If dynamic flow is achieved then high cellular levels of vitamin C are attained. It is this maintenance of high blood and cellular levels of vitamin C that is instrumental in extracting the benefits of vitamin C that those animals that produce it themselves are able to.

So, the daily dose for a human who is trying to reduce histamine levels using vitamin C is much higher than the RDA and is ideally taken in divided doses.

I found several very specific reasons why people are using vitamin C as a major part of their histamine reduction regime:

- 1) It is a biochemical fact that each molecule of vitamin C destroys one molecule of histamine.^[6]
- 2) It is also a fact that without sufficient vitamin C, humans develop scurvy, which is due to a build up of high levels of histamine in the body.
- 3) I also found several animal based research articles that showed positive results in using vitamin C to treat histamine elevating allergic reactions.^[17]

So, the argument for using vitamin C to help reduce histamine is a compelling one.

I have struggled to find the same level of scientific research that I found for vitamin C for the other supplements that are recommended for the reduction of histamine levels. This does not mean that I believe these other supplements do not work or that I have not tried to use some of these other supplements. Indeed I have experimented with a great many of these other supplements in combination with vitamin C. It just means I have not been able to find the same level of scientifically accepted evidence for these other supplements that I could for vitamin C. This is not terribly surprising since it is only relatively recently that people have begun to realise how non-allergic histamine imbalance can ruin lives.

Some of these other supplements include:

- 1) L-methionine - an amino acid, which many websites suggest detoxifies histamine in the body.
- 2) Calcium, which is supposed to remove histamine from the cells.
- 3) Magnesium - I have seen material on this, which indicates that it stabilises mast cells and supports the use of vitamin C.
- 4) Vitamin B6 important precursor in production of diamine oxidase, which is involved in destruction of ingested histamine in the gut mucosa.

General advice I have seen include:

- 1) Avoiding sugar as it reduces the absorption of vitamin C.
- 2) Avoiding fizzy drinks as they reduce calcium levels due to the phosphates they contain.
- 3) Drink plenty of mineral or tap water to naturally remain hydrated and discourage histamine build up. One of the important functions of natural histamine release in the body is to reduce water loss when you are de-hydrated. By taking on board sufficient water this release of histamine will be avoided.
- 4) Avoid / reduce NSAIDs (drugs like aspirin) as they can raise histamine levels.
- 5) Avoid / reduce codeine as it also can raise histamine levels.

The vitamin C research is probably the most well researched with regard to histamine. The other supplements and their effect on histamine may well prove to be totally scientifically credible. I just failed to find the comparable body of research and factual information on these other supplements that I did for vitamin C (ascorbic acid or a mineral version e.g. sodium ascorbate).

Appendix 3 - My Actual Histamine Reduction Regime

This section includes my anti-histamine medication and all the supplements I have taken to reduce histamine levels.

Firstly, I need to say that my digestive system is very sensitive and that I develop problems if I take doses of vitamin C much above 3000 mg in one go (even if with a meal).

Doctors Hickey and Roberts suggest an optimal method to reach dynamic flow using frequent, small doses. If a single dose or is too high or collectively the dosage is too high then bowel tolerance will be reached. This is also fully explained in the two books Vitamin C: The Real Story and Ascorbate The Science of Vitamin C. In essence once the body has reached its limit of how much vitamin C can be absorbed then the gut will not absorb any more. Consequently, the gut stops absorption including extracting water from food. This results in loose stools. If this occurs then bowel tolerance is reached and you just lower the size or frequency of the vitamin C doses until it corrects. You then know that you are taking a dose, which is very close to dynamic flow, and the maximum that your body can handle. NB this dosage will vary from person to person and is also likely to be significantly higher if you are ill.

The vitamin C dosage I have described here is the dosage I began using to reduce my histamine levels and does not reflect any higher dosage that I might use if I was sick for any other reason. Remember – this dosage is likely to be different from person to person and so I have included it here for completeness and to give any reader an idea of how much vitamin C I was actually using.

My goal was also to use ascorbic acid rather than a mineral ascorbate like sodium ascorbate. The reason for trying to use pure ascorbic acid is that it is the most effective version in the body – again this is explained in the two books already mentioned. However, ascorbic acid is acidic and may produce digestive irritation for some people. In my case since my digestive system is fairly sensitive so I found that I needed to use a mixture of ascorbic acid and sodium ascorbate.

I also wanted to minimise the amount of sodium intake I had. The molecular weight of sodium ascorbate is approx. 198 g/mol. Atomic weight of sodium is about 22 g/mol. So, very roughly the ratio of sodium to sodium ascorbate in terms of atomic weight is approx. 1 : 10. Now, the RDA of sodium is 2500 mg/day. So, for a given daily dose of sodium ascorbate in grams, you can roughly assume that 1/10th of this is sodium, when considering your daily intake i.e. when assessing if you are having too much sodium or not. So, for example for someone taking 5 grams of sodium ascorbate per day, very approximately 500 mg of this would be sodium, and be contributing to your sodium daily intake. This is not huge but it is better if it can be avoided or reduced. If you have any kidney problems then it is important to minimise sodium intake.

I found that my ideal level of vitamin C was six 500mg vitamin C tablets spread over the day. This provided a total of 4 grams of vitamin C per day.

Antihistamines:

Time Taken	Medication and Dosage
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5:20 AM:	10 mg cetirizine hydrochloride (e.g. Zyrtec) One 4 mg Piriton (chlorphenamine maleate) (I take my first thyroid dose of the day at this time – so no problem)
9:00 AM:	One 4 mg Piriton
5:20 PM:	One 4 mg Piriton
9:30 PM:	One 4 mg Piriton

N.B. The immunologist said I could double or even triple these doses if I need to. These antihistamines are quite benign in his opinion. He also said once my symptoms had stopped I could come off them (I only need to start taking them again if I have a relapse of symptoms).

Supplements:

My daily nutritional regime is as follows:

Supplement	Amount	Taken With/When	Comment
Protein drink		Breakfast	Provides slow release energy
Vitamin C	500 mg	Breakfast	Chewable sodium ascorbate. This is part of my histamine reduction regime
Vitamin C	500 mg	Late Morning	
Strong Vitamin B Complex:		Lunch	
B1	50 mg		
B2	50 mg		
Niacin	50 mg		
Pantothenic Acid	50 mg		
Vitamin B6	50 mg		
Vitamin B12	50 mcg		
Folic acid	400 mcg		
Biotin	50 mcg		
Choline Bitartrate	50 mg		
Inositol	50 mg		
PABA	50 mg		
Vitamin C	500 mg	Lunch	
Vitamin B12	100 mcg	Lunch	
Vitamin D3	5000 IUs	Lunch	During October-March (none in months of April to September)
Vitamin E	400 IUs	Lunch	
Calcium+400 IUs D3	500 mg	Lunch	
Multi-Mineral:		Lunch	
Calcium	500 mg		
Iodine	225 mcg		
Iron	5 mg		
Magnesium	125 mg		
Phosphorus	100 mg		
Zinc	5 mg		
Boron	1 mg		
Copper	0.125 mg		
Chromium	10 mcg		
Manganese	5 mg		
Potassium	33 mg		
Selenium	13 mcg		
Selenium	200 mcg	Lunch	Additional to multi-mineral
Zinc	15 mg	Lunch	Additional to multi-mineral
Chromium	200 mcg	Lunch	Additional to multi-mineral
Omega-3 Fish Oil	1000 mg	Lunch	Equivalent to 180 mg EPA, 120 mg DHA
L-Methionine	500 mg	Lunch	Part of my histamine reduction regime, along with vitamin C
Vitamin C	500 mg	Mid Afternoon	
Strong Vitamin B Complex (as above)	As above	Dinner	
Vitamin C	500 mg	Dinner	

Calcium+400 IUs D3	500 mg	Dinner	
Cod Liver Oil	1000 mg	With dinner but only 3 days per week	Equivalent to 2,600 IUs Vitamin A (or 800 mcg or 100% RDA), 200 IUs Vitamin D, 110 mg EPA, 100 mg DHA
L-Methionine	500 mg	Dinner	
Vitamin C	500 mg	Late Evening	

The vitamins are divided into two types:

1) Fat Soluble – they may be taken once a day only and they are available once in the body to be used up on an as needs be basis. These are the A, D and E vitamins. However, even these are absorbed better if in divided doses and with food.

2) Water Soluble – they will be ingested, absorbed into the blood stream and cells but the excess will be excreted quite quickly. To avoid expensive urine take these in smaller doses throughout the day. These are the B vitamins and vitamin C. Take some of these with meals.

The minerals need to be taken with each meal as the body can only absorb what it needs. Look at labels carefully and check level of elemental mineral to get a proper sense of how much is present.

General:

Cut out fizzy drinks. They contain phosphates that cause excess calcium to be leached from our bones and can lead to kidney stones.

Drink less caffeine containing drinks like coffee as they stimulate the adrenals (I drink too much coffee).

Drink plenty of mineral or tap water to naturally remain hydrated and discourage histamine build up. One of the important functions of natural histamine release in the body is to reduce water loss when you are de-hydrated. By taking on board sufficient water this release of histamine will be avoided.

Non-fizzy juices are also a good idea.

Limit use of paracetamol & codeine – put up with back pain more. Codeine is especially bad at raising histamine levels (info from immunologist I saw).

In times of sickness or ill health then my goal would be to try to increase the amount of vitamin C I was using. In this case I aimed to use powdered sodium ascorbate mixed in a large drinking bottle, in order to get regular high doses of vitamin C (perhaps around 1000 mg of vitamin C every hour if I can tolerate it). If I cannot tolerate powdered form then I will take more of the timed release C.

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