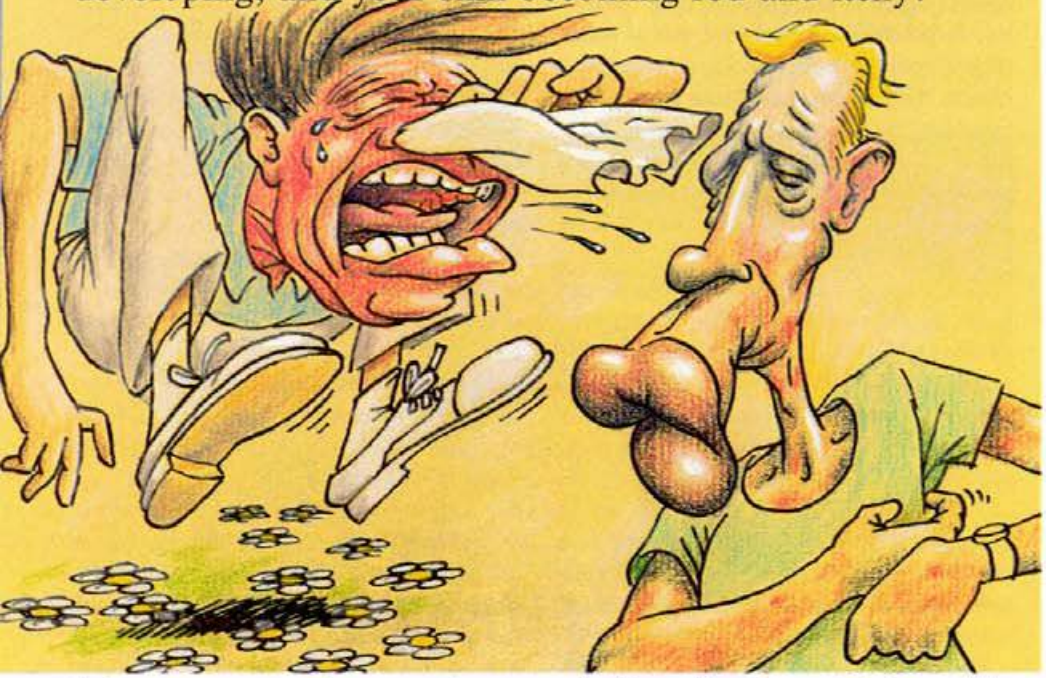
Investigating the causes of allergies

Are you one of those unfortunate people whose walk through a meadow full of grass and flowers is ruined by continuous sneezing and itchy eyes? If you eat strawberries or prawns, do you find your lips swelling, a headache developing, and your skin becoming red and itchy?



Perhaps your nose clogs up and your eyelids swell whenever your cat comes too close, and if you touch it your skin erupts in itchy sores? All these reactions are symptoms of allergy, from which at least 10% of the population suffer.

Similar to allergies in some respects are food intolerances. One of the worst of these is coeliac disease, which affects an estimated 10 000 or so sufferers in Australia alone. People with this condition are unable to eat gluten — an umbrella term for a complex of about 40–50 different proteins found in wheat, rye, barley, and, to a lesser extent, oats. The gluten remains toxic to coeliac sufferers even after cooking. As many wholesome foods contain it (and it is widely used as a thickener and protein supplement), anybody unfortunate enough to have the disease has a severely limited diet.

At CSIRO's Wheat Research Unit, Dr Colin Wrigley, Dr John Skerritt, and their colleagues have been working on coeliac disease as well as allergies involving cereals and closely related plants. Their expertise is the study of cereal proteins, and as it is mainly proteins that are implicated in allergies and intolerances, their work has extended into these fields.

But first, what is allergy? In essence, it is an increased sensitivity of the immune system to certain stimuli, with harmful or unpleasant results. Several different types of allergy or hypersensitivity exist. Being essentially a misplaced immune response, allergy generally involves the production of antibodies, also known as immunoglobulins, which are protein molecules made by a class of white blood cell in response to the presence of foreign material called antigens.

Many molecules can be antigens: for example, the molecules that make up the surfaces of bacteria and viruses, or those found on or in pollen grains. Proteins are among the most effective antigens.

Each type of antigen induces the production of a specific antibody to match it. The antibodies may have several effects.

Each has a region complementary to the chemical 'shape' of its antigen, with which it can therefore form chemical complexes and so render the latter harmless. This is particularly useful if the antigen is, for example, a toxin made by bacteria, or a molecule on the surface of a virus that allows it to gain entry into a cell. Antibodies also attract the scavenger class of white blood cell (phagocytes) and enable them to engulf any object that the antibodies are coating. (If the object proves too large for this, the phagocytes may secrete their digestive enzymes onto its exterior.) Furthermore, antibodies also play a role in the production of a series of substances in the blood important in destroying foreign cells.

So the antibody response to foreign antigens is central to the immune system, which is responsible for defending our bodies against disease and the onslaught of parasites, both large and small. A tribute to its efficiency is the speed with which a dead body — kept at a temperature of 37°C like a living one — succumbs to decomposition by the ever-present bacteria and fungi that live on us and within us, but that, during life, the immune system normally keeps in check.

Allergies seem to be a case of the immune system over-reacting. The trigger can be any antigen — sometimes referred to then as an allergen. A basic principle of immunology, which also applies with allergies, is that the first exposure to an antigen provokes little response. But the immune system 'remembers' and so, upon a subsequent exposure to the same substance, albeit years later, produces the complementary antibody in great quantity.

Various events may flow from this. The occurrence of large numbers of antibody–antigen interactions causes certain changes in the local area, such as increased blood flow (giving rise to redness and a throbbing sensation), a leakiness of the blood vessels that allows fluid to leave them and accumulate in the tissues (swelling results), and the production of various chemicals that cause localised pain.

Bags of chemicals

Repeated exposure to the same antigen will allow a build-up of antibodies against it. Some of these, called immunoglobulin E (or IgE for short), attach to a particular type of cell that occurs widely throughout the tissues. These are mast cells, and they are especially common in the skin and in the epithelia that line the nose, mouth, and respiratory system — probably because it is in these places that the body's defences are most likely to be breached.

Mast cells are essentially bags full of potent biochemicals. Interaction of antigen with the corresponding IgE antibodies on the cells' membranes has a strange effect. It causes the membranes to rupture and the granules of chemicals within the cells to

spill out. One of the most important of the chemicals so released is histamine, and it is this, in the main, that leads to the symptoms experienced by allergy sufferers. It produces the sensation of itching, and through its effect on the permeability of blood vessels creates a local swelling or oedema — the blocked nose familiar to hay fever sufferers.

Temporary relief can be provided by compounds that interfere with histamine's effects on tissues, and such chemicals are therefore called anti-histamines. Another medicament, sodium cromoglycate, stabilises the mast-cell membrane and so prevents release of the active chemicals. But neither of these actually cures the problem — they merely counteract the symptoms.

At present, the only possible cure for an allergy is desensitisation, involving the controlled administration of increasing doses of the responsible allergen. (See the box on page 13 for details on how this is thought to work.) But the procedure varies considerably in its effectiveness.

Allergies in the work-place

Allergies are common occupational diseases. Exposure day after day to a particular substance can induce a hypersensitivity in the immune system. Whether or not it actually does depends greatly on individual factors. Some people are far more prone than others, and this difference may be genetic. The time required for allergies to develop is also very variable; in some cases, a person may undergo regular exposure to a substance for 20 years without any ill effect and then suddenly develop an allergy.

Scientists at the Wheat Research Unit, in their work on allergies to cereal proteins, have studied occupational allergies connected with the baking industry. Foremost among these is the condition of bakers' asthma, a form of allergic asthma caused by the inhalation of cereal flour, which the medical profession has known of for more than 60 years. It's brought about by breathing in tiny (10μm and less) particles of flour and bran during the process of milling or making bread.

Once mast cells carrying the specific IgE antibodies to the allergenic cereal proteins develop in the trachea and bronchi, then further exposure to the allergens will cause the release of the cells' potent chemicals, which, by contracting the muscle of the tubes, cause constriction and difficulty in breathing — an asthma attack.

Flour comprises all sorts of substances, and scientists wanted to discover exactly which components were the allergens. To attempt to do so, researchers made a water-soluble extract of wheat flour, and from it separated out 40 different antigens by a technique called immuno-electrophoresis. To establish which could be the culprits, they added blood from bakers' asthma sufferers. The latter contains IgE that is not attached to mast cells, and that free IgE reacted with 18 of the antigens.

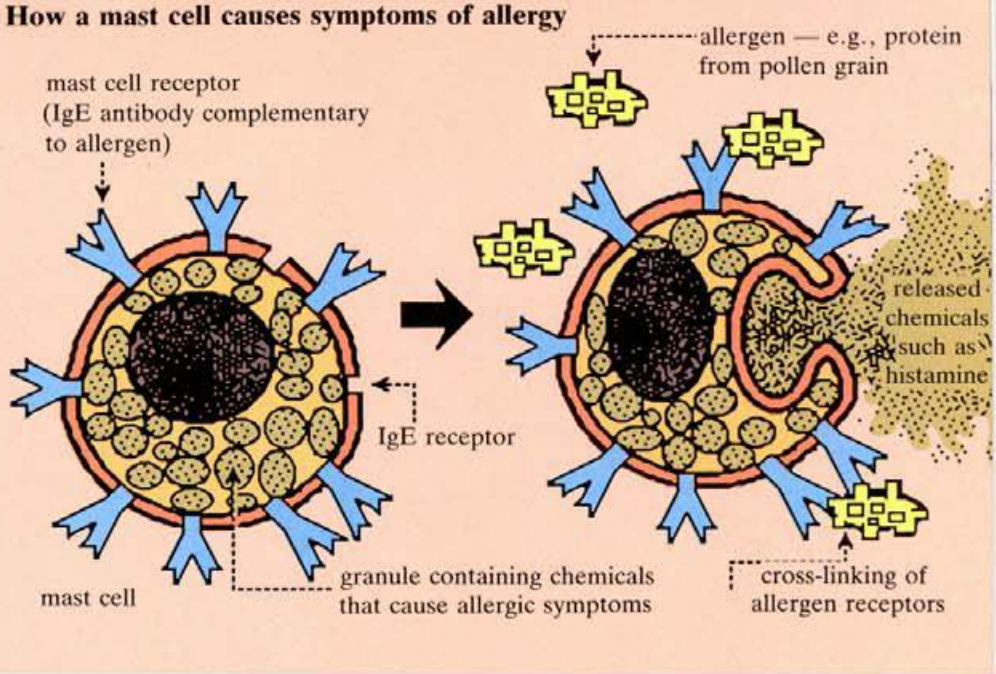
But did this account for all the possible antigens? Dr Wrigley suspected not, and with his colleagues Dr Brian Baldo, Dr Rosemary Sutton, Dr Steve Krilis, and Mr Brad Walsh, he looked for water-insoluble antigens.

He used a technique called the radio-allergosorbent test (RAST), but modified it so that it would work with insoluble antigens, such as the gluten found in wheat flour.

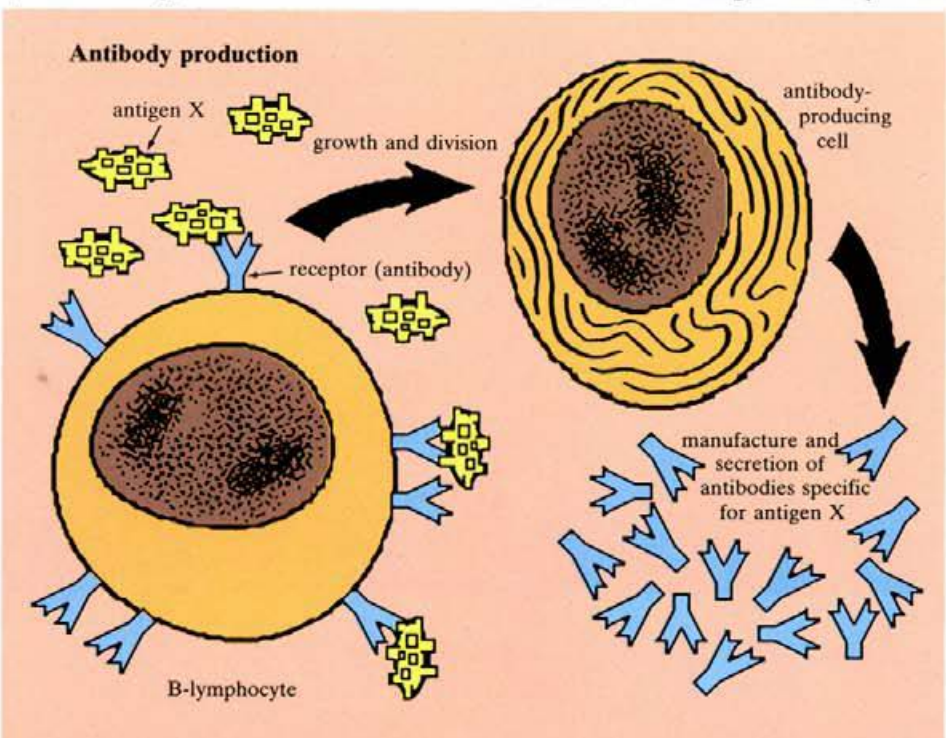
Antibodies to antibodies

To understand the basis of RAST, and of many other immunological tests, one has to realise that an antibody can itself act as an antigen — a foreign protein — when injected into another individual or species. Thus, we can make anti-antibodies that will react only with the class of antibody (say, human IgE) that induced their formation.

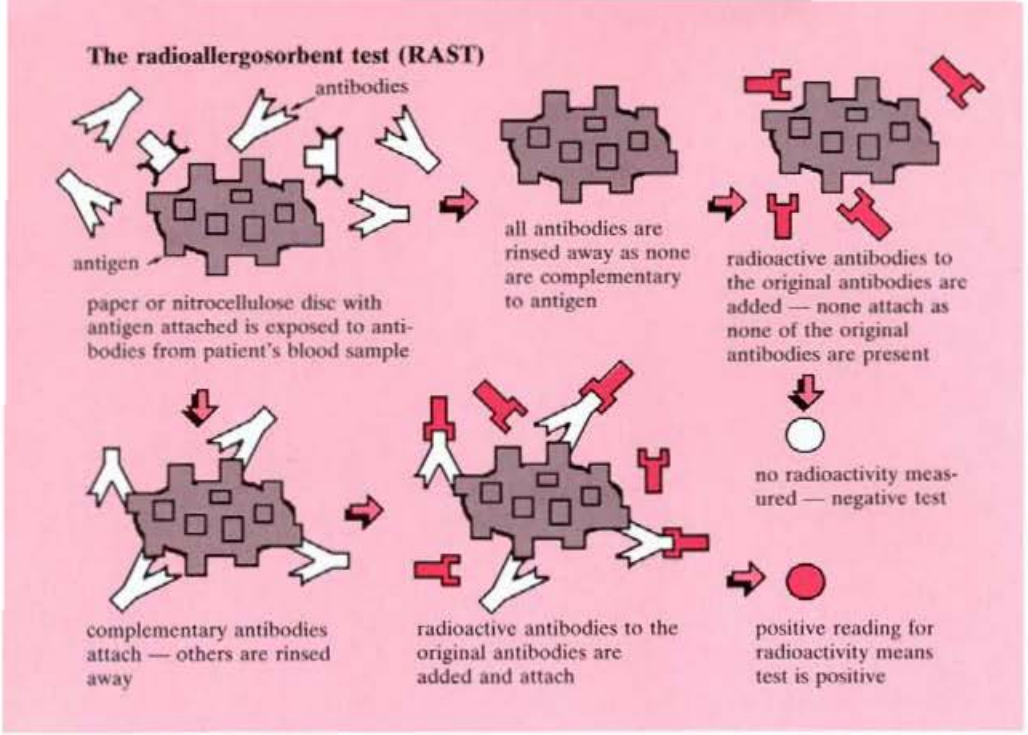
In RAST, a range of allergens to be tested is attached to a paper or nitrocellulose disc. A patient's antibodies — from a blood sample — are placed on the disc. If any of the allergens are the cause



The mast cell contains granules full of potent biochemicals. When complementary allergen molecules link two or more receptors, changes in the cell membrane occur that cause the contents of the granules to spill out. The chemicals so released are responsible for many of the annoying symptoms of allergy.



A B-lymphocyte, a type of white blood cell, changes into an antibody 'factory' following reaction with the antigen (antigen X) complementary to its receptors. The antibodies it now produces are specific to that original antigen and should react only with it, or possibly another very similar antigen (cross-reactivity).



When an allergen-coated nitrocellulose disc is exposed to antibodies from a blood sample, only complementary antibodies (if present) will attach. Whether such attachment occurs is revealed when radioactively labelled antibodies are added. If these attach (measurement of radioactivity shows this) then the test is positive; if not, it is negative.

of the allergy, some of the patient's antibodies will be complementary to them and will attach. Then it is simply a matter of detecting the patient's IgE antibodies and seeing where, and in what quantity, they have attached.

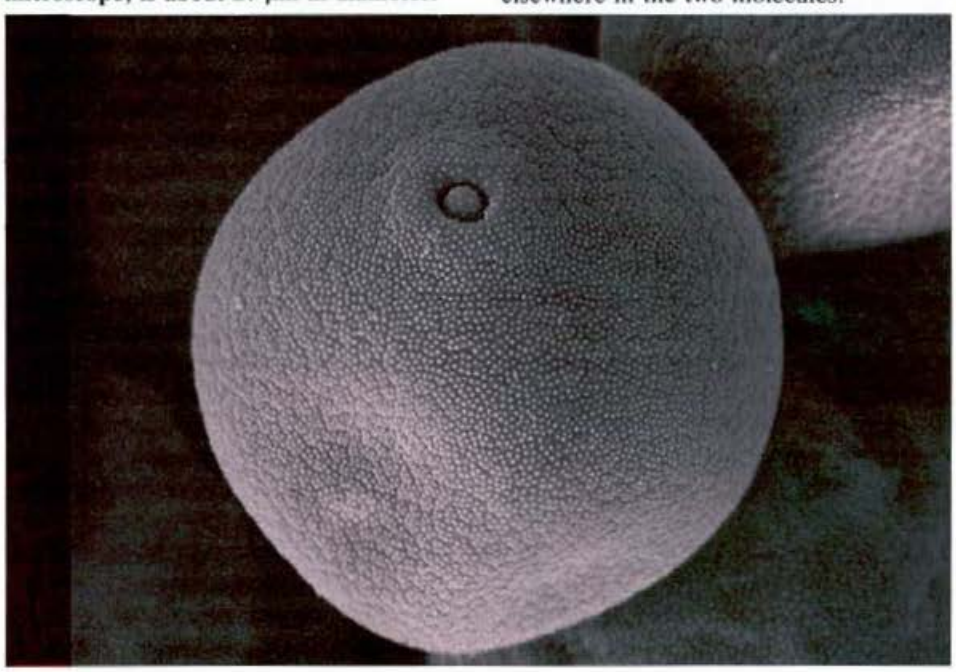
To do this, we can use antibodies specific to human IgE. We can make these by injecting other animals, often rabbits, with human antibodies (which are foreign and therefore act as antigens) and then taking blood from the rabbits and purifiying their antibodies. A radioactive chemical, attached to them, will act as a label. When poured onto the test disc, these rabbit antibodies will attach wherever the human IgE antibody occurs. After the disc is rinsed, only the rabbits' anti-human-IgE antibodies that are bound to their targets remain. They are detected by their radioactivity, which therefore gives a direct measure of the position and quantity of the human antibodies.

The modification of the RAST carried out by Dr Wrigley and his team involved the use of stronger solvents that enabled them to identify hitherto-undetected allergens, such as some of the proteins in gluten. Thus they showed that it was incorrect to state that only the water-soluble part of flour contained the allergen culprits.

In their RASTs, using serum from the blood of 24 allergic bakers, the scientists found a wide variation between individuals. Some proteins could be an important allergen for one person and not for another.

Although the work detected the previously unknown water-insoluble antigens, the water-soluble ones — such as the albumins — were shown to be the main allergens in bakers' asthma. But the existence of the others explained some puzzling anomalies. For example, data given by traditional clinical tests for allergy (exposing scratched skin to a drop of suspected allergen in solution and waiting for a reaction) had sometimes conflicted with other information, such as the occurrence of allergic symptoms, or with the results from RASTs using water-soluble antigens.

Hay fever's commonest cause — pollen. This grain of sorghum pollen, photographed with a scanning electron microscope, is about 20 μm in diameter.



These worries were cleared up with the realisation that water-insoluble antigens also play a part in bakers' asthma.

Dr Wrigley and his team had hoped that by matching the different proteins in flour with patients' differing reactivities to them they might be able to identify a few important proteins that were implicated in every individual's allergic response. In that case, these common proteins, following their identification, could become the target of a selective breeding program to produce a wheat variety without them.

Sadly, it was not that simple. Too many different types of allergen are present in the flour extract, and individuals vary far too much in their sensitivities. Although a few allergens may be involved in the majority of individuals, breeding them out — assuming it were possible — would still leave plenty of other allergens present to cause trouble.

However, the scientists found one water-soluble allergen that reacted with IgE from the sera of 10 allergic bakers. This compound was highly purified, and now Mr Brad Walsh, of the School of Chemistry at Macquarie University, is studying it. He has established the sequence of the amino acids that make it up. The next task is to determine the region within it that binds to IgE.

If the protein causes some reaction in patients whose allergic response is directed at a different antigen (a fairly common phenomenon called cross-reactivity), then we can assume that our protein has something in common with that other antigen — and quite possibly that means a region of similar or identical amino acid sequence despite a total dissimilarity elsewhere in the two molecules.

The hows and whys of an allergy cure

Various means exist for reducing the sensitivity and effectiveness of the immune system. In theory, these would be helpful in the treatment of allergy. However, anything that damps down the immune system also greatly increases the chances of infection, and probably of certain types of cancer.

In transplantation surgery, doctors must give various drugs to the recipient to prevent that person's immune system rejecting the new organ. At the same time, exposure to all infectious agents must be minimised, which makes a normal life difficult. The most trivial problems — such as a cold or an infected fingernail — assume life-threatening dimensions.

Certain unfortunates are born with severely deficient or almost non-existent immune systems. They must remain completely isolated from all micro-organisms by living in a plastic bubble and eating sterilised food. Even so, they rarely survive to adulthood.

Others may acquire deficiencies in their immune systems. Various infectious agents use a strategy of weakening the immunity of their host in order to facilitate their own unhindered multiplication. Currently, the most infamous of these is the virus that causes AIDS, which, of course, stands for Acquired Immune Deficiency Syndrome. In AIDS, death may result from the often bizarre opportunistic infections caused by any of a number of microbes that are relatively harmless to someone with an intact immune system. Also, an otherwise-rare type of cancer often accompanies the disease. Milder virus diseases, such as measles, may also produce a type of immune suppression — but only transitorily.

So, other than disastrously switching off the body's defences, a foolproof cure for allergy doesn't really exist, although plenty of remedies will help alleviate the symptoms. Currently, desensitisation is able to cure the problem some of the time, for some individuals, for a limited number of allergens. It works best for allergies such as hay fever caused by inhalation of the allergen, rather than allergies that follow ingestion.

The aim of the procedure is to cause the immune system to accept the offending antigen without mounting an allergic response. At first sight, the method seems paradoxical: the source of the trouble — the allergen — is given to the patient in small quantities. With time the dose is slowly increased. It may sound like a strange 'hair of the dog that bit you' folk remedy, but it can work.

The precise details of why it works — and why it can fail — are not yet clear. In outline, the procedure relies on the formation of a class of free antibody, called IgG, that in effect works in opposition to the IgE that is attached to mast cells.

To do this, the offending allergen is injected into the patient. It stimulates the production of specific IgG within the blood. Eventually enough IgG antibodies are formed to ensure that, when the allergen enters through the usual route (say, breathed into the nose), complementary IgG antibodies bind to it. The majority of antigen molecules are thus seized before they can interact with the IgE waiting for them on the membranes of the mast cells.

Remember that most of the symptoms of allergy flow from the release of histamine and other chemicals that occurs when the mast cells break up following the attachment of antigens to the IgE antibodies on their surfaces. The IgG antibodies that prevent this by getting to the antigen first are called 'blocking' antibodies. As they are not bound to explosive cells full of potent chemicals, their marriage with antigen causes few untoward effects.

Desensitisation must be carefully monitored. Only small quantities of antigen are given at the beginning because of the danger of anaphylactic shock. This frequently fatal condition can follow from injection of a large dose of an antigen into an already sensitised patient.

For example, if you have received a vaccination against tuberculosis, your immune system is primed to respond vigorously if the antigens associated with the tubercle bacteria enter you. If they come in small amounts, such as following contact with an infected individual, your antibody titre will increase and deal with the offending bacteria, and so you will not suffer the disease. If, however, you receive a sudden, massive dose of the antigen, such as a repeat injection, the resulting antibody–antigen interactions in such large amounts may cause the release of various chemicals that affect the muscle of your blood vessels and respiratory system. The changes in muscle tone can cause death.

That is why, before giving a TB vaccination, doctors first assess the status of the patient by means of a skin test. A small reaction will show that the individual has developed an immunity to the bacterial antigens, and that another injection may provoke anaphylactic shock. Similarly, a sudden massive dose of allergen in an allergic subject may also cause anaphylactic shock, which is why desensitisation must start with small amounts of antigen.

The hunt for sequences in common among all the different antigens may enable us to say that, although each allergic individual has a different 'fingerprint' in his antibody response to the large number of flour antigens, a piece of molecular architecture is common to all those antigens. This particular sequence of amino acids would then be the real culprit.

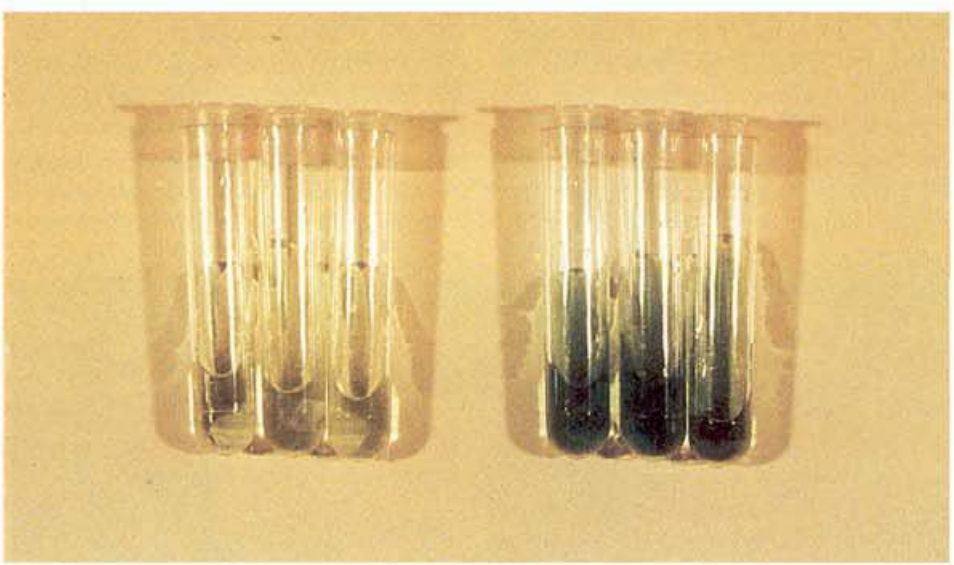
The full identification of all flour allergens may help clinicians in their treatment of patients. Following analysis of a person's particular response pattern to the allergens, the scientists could purify the flour allergens involved. Armed with these, the doctor could then tailor the desensitisation procedure to the individual, using the purified compounds. This contrasts with the present situation, where the particular antigens important for one individual are unknown, and the few used in the treatment may or may not be effective for that patient.

Finding the gluten

In another area of research, the Wheat Unit's Dr John Skerritt has come up with a world first in the form of a simple new test for detecting gluten proteins in foods and estimating their quantity.

Although sufferers of coeliac disease know that they must avoid gluten, that is often easier said than done. Because of its many uses in the food industry, gluten can

An old French cartoon showing that respiratory allergies among bakers is nothing new.



The usual test for gluten involves (top) making an extract of the food...

... and then (centre) soaking nitrocellulose discs in it.

The discs are then put in test tubes (lower) and anti-gluten antibodies, coupled to enzymes, added. A quick rinse removes antibodies not attached to gluten. Finally, adding a colour-producing substrate for the enzyme causes any gluten-containing samples to turn green.

turn up in the most unlikely places: a glass of beer or a milkshake (both use malt); many meat products, such as tinned stew or meatballs (because the gluten binds the meat and aids water and fat retention); gravy (as a thickener); some confectionery; and even pills and tablets, where gluten acts as a binder. More obviously, bread, cakes, biscuits, and many breakfast cereals must also be removed from the diet.

Until fairly recently, detection of cereal proteins in foods mainly depended on biochemical analysis, using a technique called electrophoresis to separate all the complex components found in foodstuffs. However, this becomes less effective if cooking and processing have occurred.

As in so many areas where detection of small quantities of biological material is required, immunology can come to the rescue and replace chemical methods. The idea is simple, and itself is not new: generate antibodies to the substance(s) you wish to detect. The problem has been obtaining the antibodies specific only to certain minor, heat-stable gluten components — and in sufficient quantity. An animal would form these antibodies after an exposure to gluten, but isolating them from all other antibodies in the blood was the difficulty, and the yield of the required antibody was inevitably low.

Then in 1975, at Cambridge, England, Cesar Milstein and his team first produced monoclonal antibodies. Such antibodies are highly specific and pure, and can be formed continuously in great quantity. The secret is to isolate the single white blood cell that produces the antibody you want, and then make that cell immortal so that it will continue to divide forever. Its progeny will all be identical (a clone) and will therefore all produce the same antibody and no other.

To achieve this, scientists make use of a happy fact of design in mammalian immune systems: each of the thousands of different types of specific antibodies an organism can form is made by a different individual cell or its descendants. An antibody-producing cell, or B-lymphocyte, can only make one type of antibody.

All the different types of B-lymphocytes exist in us from birth. If a B-cell comes into contact with its particular antigen (which it may never do during an individual's life), then it divides to produce a clone of identical cells that are all capable of producing antibody specific to that antigen. Next time we come into contact with the antigen, we are prepared. A cohort of the correct B-cells will produce a barrage of antibody and hence neutralise the antigen. This is the basis of 'immunological memory', which ensures that we rarely suffer from the same disease twice. (Exceptions occur in diseases caused by a variety of different microbes, as with the hundreds of different types of cold virus.)

Dr Milstein devised an ingenious procedure for isolating a specific B-lymphocyte and fusing it with a cancer cell, which, of course, can divide forever. The hybrid cell had the potential to produce a vast clone

of identical offspring indefinitely — all making the desired antibody. This cell, or its progeny, can be deep-frozen and kept until required.

Here in Australia, Dr John Skerritt and his colleagues at the Unit, together with Dr Anne Underwood at the Division of Molecular Biology, have succeeded in preparing monoclonal antibodies to two gluten proteins from coeliac-toxic cereals. What's important is that these proteins are unchanged by heat, and so can still be easily detected after cooking.

The Wheat Research Unit now keeps the cell lines that produce these antibodies. To use them for simple gluten detection, the scientists attach an enzyme to them. Then, using a solvent, they extract the material under test and put it in a test tube. Antibodies, each one carrying an enzyme molecule, are added, and will combine only with the appropriate antigens. Simply rinsing the test tube washes off any unbound antibodies, those that remain being firmly attached to the antigen. The final step is to add the molecule for the enzyme to react with (its substrate).

The enzyme–substrate system that Dr Skerritt chose is one that involves a colour change, whose intensity is proportional to the extent of the reaction. In this case, that depends on the amount of enzyme present, which, of course, directly reflects the degree of antibody–antigen binding.

Detection of gluten using monoclonal antibodies promises an important new advance for coeliac sufferers, who cannot always be sure whether a new foodstuff on the market is truly gluten-free. The finding will improve the laboratory testing performed on their behalf, but sufferers themselves would still like to be able to make an immediate decision on a suspect foodstuff. The scientists therefore hope that the current laboratory test may eventually be simplified so that it can be developed as a kit that anybody can use at home.

However, that lies in the future. For the moment, research on the mechanisms underlying coeliac disease carry on apace (see the box on page 16), as do studies into

Entomological allergies

The human body can mount an allergic response to a vast array of organic substances. A source of allergies that at first sight may seem rather unusual is insects — but recent work is suggesting that allergies involving them may be far more common than we imagine.

Work in CSIRO's Division of Entomology obviously involves a great deal of contact with insects. It is perhaps not surprising, therefore, that some laboratory workers develop allergic symptoms. In one case that was studied, the person concerned was rearing sheep blowflies. Neither he nor his family had any history of allergies.

About a year after starting work with the flies, the employee noticed an irritation at the back of the throat while at work. A few months later, sneezing, itchy eyes, blocked nose, and a hot flushed feeling developed. Finally, chest tightness appeared. All these symptoms arose within about half an hour of starting work, and generally improved about an hour after leaving the laboratory.

Dr Tom Bellas, a research scientist with the Division, is interested in these allergies, and together with clinicians Professor Bryan Gandevia and Dr Greg Kaufman, of the Prince of Wales Hospital, and Dr Brian Baldo and Dr Euan Tovey, of the Royal North Shore Hospital, made a study of the problem.

The worker concerned was skin-tested, using antigens from a variety of insects, as well as from local grass, pollens, and the house-dust mite. The subject showed positive reactions to antigens of sheep blowfly larvae and adults, and to those of cockroach, vinegar-fly, and screw-worm fly adults. Locust extract provoked a weak reaction, but all the other insects in the test did not give any reaction, nor did the pollen or the dust-mite extracts.

The study also examined 33 Sydney asthmatics with no occupational exposure to insects. Three gave reactions to blowfly extracts. Their antibodies were then tested with extracts from the screw-worm fly, to which the patients could never have been exposed, as the species is not found in Australia. The antibodies proved highly reactive with the screw-worm fly antigens.

But the story becomes 'curiouser and curiouser'. Blood samples from 50 people in Marseilles in France, all diagnosed as allergic to insects, were sent to the researchers at the Royal North Shore Hospital in Sydney. They tested the samples against extracts of a large number of different insect species, some of which are only found in Australia — such as the Bogong moth — and found strong positive reactions with the French antibodies.

All this suggests that we are witnessing cross-reactivity between the antigens of many insect species — perhaps not surprising in itself, but made more interesting by the fact that the cross-reactivities, as revealed by the antibody responses, do not necessarily parallel the taxonomic distance between the insects. In the future, the team of scientists would like to separate out and purify some of the antigens, and then analyse them chemically to find a molecular basis for the cross-reactivities.

Finally, further recent work found a high level of hypersensitivity to insects in 50 'normal' asthmatics, who had had no particular contact with insects. It seems from this that allergies to inhaled insect 'emanations' — dried excreta, and discarded exoskeletons — may not be rare in Australia.

Asthmatics tested for allergy, and pronounced non-allergic, are often tested only with grass pollen and dust-mite antigens — well-known causes of allergy. Quite possibly, insects should now be added to the list. In many respectable homes, there are beetles that live in the carpets and furniture, dead flies at the bottom of the window, the occasional cockroach under the kitchen sink. Heavy exposure over many years can induce respiratory allergy in many individuals, even those with no previous allergic conditions, such as the CSIRO employee. Susceptible people may become allergic far more easily. So, if you are a hay fever sufferer, or have an allergy of unknown origin, keep insects in mind as potential culprits!

Inhalant allergy following occupational exposure to blowflies. G.L. Kaufman, B.A. Baldo, E.R. Tovey, T.E. Bellas, and B.H. Gandevia. *Clinical Allergy*, 1986, **16**, 65–71.

The work of entomologists brings them close to the insects that they study, which, after long exposure, may induce allergies.

More on coeliac disease

Coeliac disease (also known as gluten-sensitive enteropathy) is an example of dietary intolerance that probably affects up to 10 000 people in Australia. More females have the disease than males, and its incidence may vary in different races.

It is a difficult disease to diagnose: in children it shows as a general failure to thrive, accompanied by frequent diarrhoea — which, of course, can be caused by plenty of other factors. Specific nutritional deficiencies, such as rickets due to insufficient Vitamin D, may also be present. If a child in a developed country has these disorders, yet is being well-fed and looked after, then coeliac disease is a likely suspect. But to prove the existence of the condition it's necessary to carry out a biopsy, where living material is taken from the small intestine. Doctors describe this procedure as invasive and it's certainly none too pleasant for the patient.

Following the biopsy, scientists examine the villi — the small finger-like projections that give the gut's inner surface its velvety appearance. If these have atrophied and are flat, then coeliac disease is probably present.

The patient must go on a strict gluten-free diet, and some months later will undergo a second biopsy. If the villi have improved with this diet, then the doctors can confirm the diagnosis of coeliac disease.

The millions of villi, each 1–2 mm long, provide a vast surface area inside the intestine for the absorption of foodstuffs. If they become flattened, then no matter how much good food is eaten, insufficient is absorbed. The result is diarrhoea and weight loss. Damage to the villi can occur in many conditions, especially intestinal infections with bacteria or large multicellular parasites such as nematode worms; but in coeliac disease no infection is apparent, and the villi will return to their normal state with a gluten-free diet.

The cause of the disease appears to lie in a direct effect that some of the gluten proteins exert on the epithelial cells. This toxicity is most evident in the first part of the small intestine; further down the gut, gluten has less effect, and it is completely harmless in the colon and rectum.

All cells have membrane receptors that are carbohydrate–protein compounds. It may be that those in coeliac sufferers somehow differ — their altered chemistry may permit the binding of some gluten proteins, which would not be able to attach to normal receptors. Scientists know that the binding to cell membranes of certain chemicals (often derived from plants) can cause cell death. Possibly this is an important factor in coeliac disease.

But there's more to it than that: we cannot say that the disease is simply a genetic defect resulting in altered cell receptors, because among identical twins (who are genetically the same, being derived from one cell) one individual may have the disease while the other does not. This suggests an as-yet-unknown environmental trigger. Although more commonly originating in childhood, coeliac disease can start spontaneously at any time of life in people previously free from it.

One thing we do know for sure is that histamine, the bane of allergy sufferers, is not involved. Dr Wrigley and Dr Brian Baldo did not find IgE-type antibodies to gluten in coeliac sufferers. However, in their blood, such individuals may have high levels of antibodies — called IgG and IgA — to gluten components. But many 'normal' people do too, albeit at lower levels.

Dr Skerritt, with collaborators from the University of Adelaide and the Adelaide Children's Hospital, investigated the IgG and IgA antibodies in the blood of both coeliacs and normal controls. All the coeliacs and almost all the 'normals' had antibodies that bound to groups of gluten proteins. Individuals differed as to which proteins they had affinity for. Many of the coeliacs had antibodies that bound to certain groups of a large family of proteins called gliadins. By contrast, the antibodies of 'normal' people tended to bind unrestrictedly to all gliadins. In general, the quantity of antibodies in the 'normals' was lower than that in coeliac sufferers.

These findings may enable scientists to develop a simple blood test for the diagnosis of the disease — a boon for sufferers who must presently undergo several biopsies.

Why do apparently normal people harbour antibodies to gluten proteins? In general, the body can form serum antibodies to many food components if foodstuffs are not absorbed in their fully digested state. This can occur either because of transient tears and small ulcers in the gut wall, or simply because digestion down to the ultimate building blocks is not always efficient. Complete digestion should result in molecules too small to be readily antigenic, such as individual amino acids from proteins. But a group of amino acids still strung together — a peptide — may prove antigenic, as well as possibly having important biochemical effects in its own right.

Dr Skerritt and his colleagues are currently working on an analysis of gluten components to determine which amino acid sequences are responsible for gluten's direct toxicity to intestinal epithelial cells, and which are antigenic — that is, stimulate antibody formation. We don't yet know whether the same sequences are involved in both reactions.

Variation of serum and intestinal antibody specificities in coeliac disease. J.H. Skerritt, R.B. Johnson, P.A.S. Hetzel, J.T. La Brooy, D.J.C. Shearman, and G.P. Davidson. *Clinical and Experimental Immunology*, 1987, **67** (in press.)

the common allergies to cereal proteins, such as the hay fever induced by grass pollen. Meanwhile allergy sufferers can perhaps console themselves with a study that showed that they have a lower incidence of cancer than the general population. Our immune system exists to protect us — and that means against mutated cancer cells as well as foreign organisms. That it may sometimes inconvenience us by being over-zealous is perhaps a small price to pay.

Roger Beckmann

More about the topic

Allergies to cereals. B.A. Baldo and C.W. Wrigley. In 'Advances in Cereal Science and Technology', vol. 6, ed. Y. Pomeranz. (American Association of Cereal Chemists Inc.: St. Paul, Minnesota, 1984.)

Detection and quantitation of cereal protein in foods using specific enzyme-linked monoclonal antibodies. J.H. Skerritt. *Food and Technology in Australia*, 1985, **37**, 570–2.

A comparison of binding of IgE in the sera of patients with bakers' asthma to soluble and insoluble wheat-grain proteins. B.J. Walsh, C.W. Wrigley, A.W. Musk, and B.A Baldo. *The Journal of Allergy and Clinical Immunology*, 1985, **76**, 23–8.

A sensitive monoclonal-antibody-based test for gluten detection: studies with cooked or processed foods. J.H. Skerritt and R.A. Smith. *Journal of the Science of Food and Agriculture*, 1985, **36**, 980–6.