Mucin and chronic bronchitis

In the 1970s I worked for two old Welsh chest physicians in a Derbyshire mining town. What poetry it was to hear them talk of chronic bronchitis, pink puff-ers, blue bloat-ers, emphys-ema, or (the very height of bliss) ten-acious mu-cus. I thought such language had gone out when chronic obstructive pulmonary disease (COPD) came in during the 1980s, but here it is back in a New England Journal of Medicine article called “Airway mucin concentration as a marker of chronic bronchitis.” Mucin is what makes mucus sticky: it has a very ancient Proto-Indo-European pedigree in the root word meug—meaning slippery or slimy. Mucus is usually 98% water but gets its gel-like properties from high molecular weight (>10^7 Da) mucin polymers, predominantly MUC5B and MUC5AC. In days gone by “expectorants” were very popular drugs, and spitting was universal, but this is the first study of mucin and COPD that I can remember reading in the leading journals. It’s an exploratory observational study of the two leading mucins measured by mass spectroscopy in a cohort of 148 patients with COPD. Concentrations are highly related to past and present smoking and related to past and present smoking and are a very plausible reason for infective exacerbations—hence the use of “chronic bronchitis” in this paper. Eventually, as the two Welshmen would sadly conclude, these patients reach the point where they couldn’t blow the skin off a rice pudding.

Treading the marsh of useless information

After about 10 years of reviewing the journals every week, I began to fear that medicine was entering a period of information overload. It’s only a slight consolation that in 1881, the great American surgeon John S Billings made the same complaint in the second volume of The BMJ. But now we really do have a new problem: the ability of modern sequencing techniques to generate genomic information on a scale that defies interpretation. We have to wander into this marshland without knowing if there is terra firma on the other side, with only flickers of marsh gas to guide us. Here’s a study of “Mutation detection in patients with advanced cancer by universal sequencing of cancer-related genes in tumor and normal DNA versus guideline-based germline testing.” Although guarded, I think the conclusion is still over optimistic: “In this referral population with selected advanced cancers, universal sequencing of a broad panel of cancer-related genes in paired germline and tumor DNA samples was associated with increased detection of individuals with potentially clinically significant heritable mutations over the predicted yield of targeted germline testing based on current clinical guidelines. Knowledge of these additional mutations can help guide therapeutic and preventive interventions, but whether all of these interventions would improve outcomes for patients with cancer or their family members requires further study.”

Another good surgical trial

Little trials can have big effects. Bigger, longer trials often cancel these out. That is why underpowered trials are an abuse of human subjects and should be rejected by ethics committees. In surgery especially, they can lead to waves of enthusiasm and early adoption which later prove to be unwarranted or harmful. This article informs us that “short-term outcomes have been found to be better after duodenum-preserving pancreatic head resection than after partial pancreatosoduodenectomy” for chronic pancreatitis. Read these reviews: you will learn something new each week. Anyway, this was a false signal: in a bigger, longer trial “No differences in quality of life after surgery for chronic pancreatitis were seen between the interventions. Results from single centre trials showing superiority for duodenum-preserving pancreatic head resection were not confirmed in the multicentre setting.”

Bivalirudin versus heparin for myocardial infarction

Heparin is a crude cellular extract developed 100 years ago. And yet it remains good stuff: in the VALIDATE-SWEDEHEART trial it proved the equal of bivalirudin, which costs about a hundred times as much. This egregiously named trial compared the two antiocoagulants in 6006 patients undergoing emergency percutaneous intervention for myocardial infarction, with or without ST elevation. Another good surgical trial

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Chronic vertigo: treat with exercise, not drugs

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Change articles aim to alert clinicians to the immediate need for a change in practice to make it consistent with current evidence. The series advisers are Sera Tort, clinical editor, and David Tovey, editor in chief, the Cochrane Library. We welcome any suggestions for future articles (email us at practice@bmj.com).

Chronic vertigo is a challenging problem. Currently patients are usually treated in general practice with betahistine (off-label use), while stronger evidence exists for the effectiveness of vestibular rehabilitation.

Vertigo is the most common type of dizziness. Each year it affects around 1 in 20 people in the general population. About 80% of these people find it severely impairs their daily functioning. Since the symptoms prevent many people from working, as well as resulting in an increase in the risk of falling and a high use of healthcare services, vertigo also represents a substantial economic cost.

Most cases are caused by peripheral vestibular disorders such as vestibular neuronitis, vestibular migraine, benign paroxysmal positional vertigo, and Meniere’s disease. Initial treatment varies, depending on the most likely vestibular disorder. Box 1 provides an overview of specific treatments for the most common disorders.

All peripheral vestibular disorders have a distinct natural course with a substantial chance of developing chronic vertigo: 30-40% of patients with vestibular neuronitis still experience vertigo after six months, and 50% of patients will have experienced recurrence of benign paroxysmal positional vertigo by 3-5 years after initial diagnosis.

Defining vertigo
Vertigo is defined as a false sensation that the body or environment is moving. Acute vertigo concerns well defined, isolated spells with a distinct onset and offset. Chronic vertigo is defined as a continuous sensation or recurrent attacks. Although a clear definition of duration is lacking, chronic vertigo is often defined as symptoms persisting for more than one month (based on the clinical course of vestibular disorders and expert opinion).

Peripheral vestibular disorders induce an innate repair mechanism known as vestibular compensation, which aids functional recovery after damage to the vestibular system. However, there is a large inter-individual variation in the rate and level of recovery. Chronic vertigo occurs when natural vestibular compensation fails.

Vestibular rehabilitation (see box 2) is now considered the preferred treatment for patients with chronic vertigo and is recommended by US, Dutch, and UK practice guidelines. In spite of this, anti-vertigo drugs such as betahistine (see box 3) are commonly prescribed, and vestibular rehabilitation is hardly used. An observational study of patients with vertigo from 13 European countries (4294 participants) found that betahistine was prescribed to more than two thirds of patients with vertigo at first consultation and was still being used six months later. In contrast, surveys of GPs in the Netherlands (n=426) and UK (n=53) found that only 5.8%-6.8% used vestibular rehabilitation. Recent Cochrane reviews showed moderate quality evidence for the effectiveness of vestibular rehabilitation and weak evidence for the effectiveness of betahistine to treat chronic vertigo. There is therefore a need to address the discrepancy between clinical practice and current evidence.

The evidence for change
There is moderate quality evidence, partly from general practice studies, that vestibular rehabilitation is a safe and effective treatment for chronic vertigo. There is low quality evidence, conducted in secondary and tertiary care populations, that patients with chronic vertigo experience a benefit from betahistine treatment compared with placebo (table).
Effectiveness of vestibular rehabilitation

A Cochrane review updated in 2015 (39 randomised controlled trials, 2441 participants) compared vestibular rehabilitation for unilateral peripheral vestibular dysfunction with sham exercises or no intervention. Participants experienced vestibular dysfunction from a variety of causes. Because of heterogeneity in study design, not all studies could be pooled. In a pooled analysis of four studies in which all patients experienced chronic vertigo, patients assigned to vestibular rehabilitation reported higher subjective improvement in vertigo (odds ratio 2.67 (95% confidence interval 1.85 to 3.86), 565 participants). There were no reported adverse effects in any of the 39 randomised controlled trials. Three high quality trials (589 patients) were conducted in a GP population.

We applied the GRADE methodology and judged the overall quality of evidence as moderate. We deemed the risk of bias serious, since over a third of studies in the review were rated as having a high risk of bias. There was no serious inconsistency, indirectness, imprecision, or publication bias. We can summarise that, based on moderate to high quality randomised controlled trials, there is moderate evidence that vestibular rehabilitation is a safe and effective treatment for chronic vertigo.

Effectiveness of betahistine

Betahistine was developed for Meniere’s disease, and early trials were targeted at these patients. A Cochrane review (last updated 2011, 7 randomised controlled trials, 243 patients) that compared betahistine with placebo in patients with Meniere’s disease concluded there was insufficient evidence to say if betahistine has any effect on Meniere’s disease.

Recently, a randomised, placebo controlled trial investigated vertigo symptoms in 211 patients with Meniere’s disease and found no statistically significant benefit for betahistine over placebo.

The effectiveness of betahistine for symptoms of vertigo (including 14 trials with patients with chronic vertigo and 3 trials with a mix of acute and chronic vertigo patients) was examined in a Cochrane review in 2016 (17 randomised controlled trials—including 5 unpublished industry studies, 1025 patients). Participants had varied neurological diagnoses, including Meniere’s disease, benign paroxysmal positional vertigo, and vertigo of unknown origin. In a pooled analysis with patients all experiencing chronic vertigo, a statistically significant improvement was found, indicating that betahistine is an effective treatment for chronic vertigo.
Participants
Low quality
Vertigo symptoms reduced
Results
NNT* vestibular rehabilitation is that they do not know how to give to patients after disease-specific treatment. Evaluate the effect of vestibular rehabilitation, none of these trials was conducted in a general practice population, which limits the applicability of these results for general practice.

Consequences of current clinical practice
Betahistine leads to substantial healthcare costs. Stopping off-label use of betahistine in the UK alone would save over £4 m a year. Since evidence for the most registered indication (Meniere’s disease) is also insufficient, costs could be decreased even further by completely stopping betahistine prescriptions. By choosing betahistine, doctors deny other treatments to patients that have better established evidence of effectiveness. Different causes of peripheral vestibular disease, such as benign paroxysmal positional vertigo and Meniere’s disease, have a specific preferred treatment (see box 1). When chronic vertigo develops after such disease-specific treatments, vestibular rehabilitation should be prescribed by GPs.

Barriers to change
The most important barrier to general practitioners using vestibular rehabilitation is that they do not know how to perform the treatment. Most patients surveyed prefer exercise based treatment over anti-vertigo drugs.

There is limited evidence on the factors that contribute to the current mismatch between scientific evidence and clinical practice in the treatment of chronic vertigo. We conducted a survey among 426 Dutch general practitioners about the use of vestibular rehabilitation. The main reason for not applying vestibular rehabilitation was that general practitioners did not know how to perform the technique (92.4%). Other reasons were that it was too time consuming (7.2%), GPs had doubts about its effectiveness (6.3%), and it was not recommended in national guidelines (4.5%). Perceived patient pressure is a key reason that GPs prescribe drugs, even though this perception often does not match the patients’ real expectations. The Dutch College of General Practitioners conducted a focus group meeting (see Patient Involvement box). Patients preferred exercise based treatment over anti-vertigo drugs, but most were offered only drug therapy by their general practitioner. Since betahistine is generally well tolerated, prescribing this drug could be considered an easy fix for a difficult complaint. Compared with a straightforward prescription of betahistine, vestibular rehabilitation may be seen by general practitioners as a difficult and time consuming treatment.

How should we change our practice?
Offer patients with vertigo disease-specific treatments.

Plan a follow-up consultation if symptoms do not resolve after disease-specific treatment. Evaluate the effect of treatment to ascertain whether the patient has developed chronic vertigo, if symptoms persist for more than a month. Stop all anti-vertigo drugs that the patient is using for acute vertigo (see box 1 for indications) and offer vestibular rehabilitation to all patients with chronic vertigo.

In a recently published trial an online vestibular rehabilitation intervention was shown to be effective and well liked by patients with chronic vertigo. Such newly developed self help methods (internet based or booklet based) help GPs to treat patients with vestibular rehabilitation. For patients who need more support, offer referral to physiotherapists or audiologists for guidance.

Competing interests: None declared.

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**Table** Summary of evidence for the treatment of chronic vertigo

<table>
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<tr>
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<th>Comparator</th>
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<th>Anticipated absolute effects (95% CI)</th>
<th>NNT*</th>
<th>Summary of quality of evidence</th>
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<tr>
<td>Systematic review and meta-analysis (4 randomised controlled trials)†</td>
<td>565 adults with different causes of chronic vertigo (vestibular neuronitis, non-fluctuating Meniere’s disease, benign paroxysmal positional vertigo, undefined vertigo)</td>
<td>Vestibular rehabilitation</td>
<td>Sham or no intervention</td>
<td>Vertigo symptoms reduced with vestibular rehabilitation, odds ratio 2.67 (95% CI 1.85 to 3.86). For every 1000 patients, 225 (135 to 317) more will improve with vestibular rehabilitation than with control</td>
<td>5</td>
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<td></td>
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<tr>
<td>Betahistine</td>
<td>606 adults with different causes of chronic vertigo (Meniere’s disease, benign paroxysmal positional vertigo, undefined vertigo)</td>
<td>Betahistine in varying doses</td>
<td>Placebo</td>
<td>Vertigo symptoms reduced with betahistine, risk ratio 1.30 (95% CI 1.05 to 1.60). For every 1000 patients, 140 (23 to 277) more will improve with betahistine than with control</td>
<td>8</td>
<td>Low quality evidence</td>
<td></td>
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</table>

*Number needed to treat †Evidence judged by GRADE methodology
What it feels like to have a facial disfigurement

Victoria Wright, 38, describes living with an unusual appearance and the lessons she would like to pass on

The first time I realised that I looked different was when a boy called me “fat chin” at primary school. Thirty years later I still remember the burning shame.

I was born with cherubism, a rare genetic condition which is associated with variable degrees of abnormal bony overgrowth of the lower part of the face. I started to show signs of this when I was 4. Before then I looked like every other little girl. But over time my jaw grew bigger, my eyes started to protrude, and the bridge of my nose became flat.

Looking different
Growing up with such an unusual appearance was not easy. I was stared at and called names by other children, and even adults as well.

Medical journals in the 1980s said cherubism regressed after puberty. I remember telling my mum that I didn’t mind looking this way as long as I looked “normal” by the time I started college. Instead my symptoms progressed throughout my teens. The medical literature says cherubism is a painless condition, yet I experienced frequent bouts of pain and discomfort in my sinus and eyes and still do.

Luckily I had a loving and supportive family and once I was diagnosed I was followed up by a fantastic NHS maxillofacial department with regular check-ups for a year, which she recommends as a resource.

Apart from that episode my appearance was not easy. I was accustomed to my (funny) face, but over time I grew used to it and it has been the right choice for me. It can be tiring sometimes to explain why I’ve chosen not to have surgery, especially when that isn’t why I’m there in the first place.

I am not anti-surgery and I know others with cherubism who have had it and it has been the right choice for them. But my facial disfigurement is entwined with my sense of identity. If I do choose to have surgery, and I continue to be followed up in a maxillofacial department, it will be for me, not to meet expectations as to how I should look.

Throughout my life I’ve met people who assume that because of how I look, I must live a depressing, isolated life, but I have a good life. I’m a charity campaigner and public relations professional, and I’m blessed with a daughter who makes me laugh every day. When I was growing up, I had fantastic care for the physical side of my disfigurement. But I lacked support for my emotional needs, and having to cope with staring and cruel remarks, I had to build those tools myself. I now seek to provide such tools to support others with facial disfigurements.

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Correspondence to: @VictoriaMWright

WHAT YOUR PATIENT IS THINKING

What it feels like to have a facial disfigurement

Victoria Wright, 38, describes living with an unusual appearance and the lessons she would like to pass on
Guidance on medicines and excipients for patients with dietary intolerances

Medicinal products contain not only active drugs but also other ingredients included for a variety of purposes and collectively known as excipients. Here, we provide an overview of several dietary conditions and the pharmaceutical issues that need to be considered by healthcare professionals advising on the suitability of a medicine.

How common are food allergies or intolerances?
A food allergy is an adverse immune response and a food intolerance is a non-immunological reaction that can be caused by enzyme deficiencies, pharmacological agents and naturally occurring substances. It is estimated that between 1% and 10% of adults and children have some form of food allergy or intolerance. The reason why a person has intolerance to a certain type of food is often not clear. However, as many as 20% of the population experience reactions to foods that make them believe that they have a food intolerance or hypersensitivity. For children, the most common food allergens include cows’ milk, chicken eggs, shellfish, fish, soy, peanuts, wheat, and tree nuts. The most common type of enzymatic food intolerance is lactose intolerance. Excipients in medicines may not be suitable for some people with a dietary intolerance or allergy.

Dietary intolerances and pharmaceutical considerations

Coeliac disease
Coeliac disease is an autoimmune condition associated with chronic inflammation of the small intestine, which can lead to malabsorption of nutrients. Dietary proteins (glutens), which are present in wheat, barley, and rye activate an abnormal mucosal immune response. The total exposure needed to trigger symptoms is not known and may differ between people. It is suggested that consumption of less than 10 mg of gluten a day is highly unlikely to trigger disease activity. Pharmacological starch, which is extracted from plant sources such as wheat, corn (maize), and potato, is used primarily in oral solid-dose formulations, where it acts as a binder, diluent, and disintegrant. Wheat starch could be problematic for people with coeliac disease. However, the UK Medicines and Healthcare products Regulatory Agency (MHRA) has advised that wheat starch of pharmaceutical quality is highly processed and very low in gluten (containing no more than 100 ppm). If a medicine contains wheat starch, this will be indicated in the product information and in the accompanying patient information leaflet (PIL): “Suitable for people with coeliac disease. Patients with wheat allergy (different from coeliac disease) should not take this medicine.” Where wheat starch has not been used in a medicinal product, the product can be regarded as gluten-free. A search of the MHRA database in 2014 identified only 20 marketing authorisations that mention wheat starch as one of the excipients in the medicinal product, so the vast majority of prescribed medicines are gluten-free.

Lactose intolerance
Lactose is a natural disaccharide present in the milk of most mammals. Symptoms of lactase intolerance arise from its malabsorption resulting from low or absent lactase activity. There is considerable intraindividual and interindividually variability in the severity of gastrointestinal symptoms according to the amount of lactose ingested and the patient’s ability to digest it. It has been suggested that adults and adolescents with a diagnosis of lactose intolerance can ingest up to 12 g of lactose in a single dose (equivalent to the lactose content in a cup of milk) with no or only minor symptoms. The onset of such symptoms after ingestion of a lactose-containing drug in lactose maldigesters has been described only in a limited number of case reports, and population studies are lacking.

WHAT YOU NEED TO KNOW

- A food allergy is an adverse immune response, and a food intolerance is a non-immunological reaction that can be caused by enzyme deficiencies, pharmacological agents, and naturally occurring substances.
- Excipients in medicines may not be suitable for some people with a dietary intolerance or allergy: the total exposure to excipients needed to trigger symptoms may differ between people with different intolerances and allergies.
- Patients known to be allergic to peanuts should not use medicines containing peanut oil.
- The MMR vaccine is cultured in fibroblasts derived from chick embryos so the amount of egg protein is negligible, but children with documented anaphylaxis to the vaccine itself should be assessed by an allergist.
Commercially, lactose is produced from the whey of cows’ milk and is widely used as a filler and diluent in tablets and capsules. As cows’ milk proteins have been filtered in the manufacture of pharmaceutical grade lactose, allergic reactions are considered highly unlikely in most allergic individuals, and thus product information leaflets do not warn of the possibility of allergic reactions to cows’ milk protein in lactose-containing medicines. The dose of lactose in most pharmaceutical products seldom exceeds 2 g/day. It is unlikely that severe gastrointestinal symptoms can be attributed to the lactose in a conventional oral solid drug, especially in adults who have not previously been diagnosed as severely lactose intolerant. In a study of 77 lactose maldigesters with intolerance, the administration of capsules containing 400 mg of lactose did not produce changes in hydrogen breath excretion and gastrointestinal symptoms at 8 hours compared with placebo. The researchers suggest that these results indicate that gastrointestinal symptoms can at times be mistakenly attributed to lactose in drugs, thus influencing medication adherence, and may result in the use of alternative, and possibly less effective, therapeutic approaches. They suggest that lactase deficiency should no longer be considered a contraindication to the use of medications with similar or lower doses of lactose. However, there have been anecdotal reports of drug induced diarrhoea due to lactose intolerance after administration of pharmaceutical preparations containing lactose. The British National Formulary also advises that the lactose content in most medicines is too small to cause problems in most lactose intolerant patients. However, in people with severe lactose intolerance, lactose content should be determined before prescribing.

Peanut allergy
Peanut is a member of the legume (bean) family, which also includes soya beans, lentils and garden peas. Allergy to peanut and tree nuts is estimated to affect 1 in 50 young infants. Peanut (arachis) oil is included in some medicines as a solvent for sustained release intramuscular injections, vitamins and hormones, and as a vehicle for topical preparations. Therapeutically, emulsions containing peanut oil have been used in nutrition regimens, in enemas as a faecal softener, and in otic drops to soften ear wax. Adverse reactions to peanut oil in foods and pharmaceutical formulations have been reported extensively. In 2003, the Committee on the Safety of Medicines (CSM) reviewed allergic reactions associated with medicinal products containing peanut oil. It noted that pharmaceutical grade peanut oil is refined, and, therefore, the peanut protein should be removed during the manufacturing process. However, a study has shown that very small amounts of peanut protein may remain in refined peanut oil.

The CSM advised that there was insufficient evidence to conclude that exposure to medicinal products containing peanut oil leads to sensitisation to peanut protein. However, although the risk of an allergic reaction is low, it advised as a precaution that:

- Patients known to be allergic to peanuts should not use medicines containing peanut oil
- As there is a possible relationship between peanut allergy and soya allergy, patients allergic to soya should also avoid medicinal products containing peanut oil
- All medicines containing peanut oil are required to include an appropriate warning in the labelling.
The summary of product characteristics for medicines advise that patients with soya allergy should avoid products containing arachis oil (such as isotretinoin capsules\textsuperscript{15,19})\textsuperscript{,}\textsuperscript{17} although it is rare for a person with peanut allergy to react to soya or other beans and legumes\textsuperscript{,}\textsuperscript{11} and most people with peanut allergy can eat soya quite safely\textsuperscript{.}\textsuperscript{18}

Information on the arachis oil content of medicines may not be evident for imported medicines as there are currently no legal requirements for drug labelling or providing a leaflet in English. This was highlighted by the MHRA in 2012 with German imports of Dekristol (vitamin D) capsules that provided no information to non-German speakers that they contained arachis oil\textsuperscript{.}\textsuperscript{19} Even product information for imports of certain vitamin D products from English speaking countries did not explicitly state that they contained soya oil\textsuperscript{.}\textsuperscript{20} The MHRA suggests that suitable English language labelling should be provided as a matter of good practice and advised importers that prescribers must be made aware of contraindications\textsuperscript{.}\textsuperscript{19,20}

Egg allergy and vaccines

Egg is a common cause of allergic reactions in infants and young children. It often begins in the child’s first year of life and, in some cases, lasts into the teenage years or even into adulthood for a few people.\textsuperscript{21} The prevalence of egg allergy has been estimated at 1.6% at 2.5 years and 0.1% in the adult population.\textsuperscript{22}

There are three vaccines that are cultured on derivatives of hen’s eggs.

**MMR vaccine**—This is cultured in fibroblasts derived from chick embryos and not on egg, and, therefore, the amount of egg protein is negligible. Studies on large numbers of egg-allergic children show there is no increased risk of severe allergic reactions to the vaccines.\textsuperscript{24} *Immunisation against Infectious Diseases* (the “Green Book”) advises that all children with egg allergy should receive the MMR vaccination as a routine procedure in primary care. It notes that anaphylactic reactions to MMR vaccine are not associated with hypersensitivity to egg antigens but to other components of the vaccine (such as gelatin), and children who have had documented anaphylaxis to the vaccine itself should be assessed by an allergist.\textsuperscript{23}

**Yellow fever vaccine** is cultured in chick embryos and contains measurable amounts of egg protein, so individuals with a confirmed anaphylactic reaction to egg should not receive it.\textsuperscript{22,23}

**Influenza vaccines**—Most are cultured in chick embryos and contain measurable amounts of egg protein. According to the Green Book, people with an egg allergy may be at increased risk of reaction to some influenza vaccines.\textsuperscript{24} The Joint Committee on Vaccination and Immunisation has advised that, except for those with severe anaphylaxis to egg, which has previously required intensive care, children with an egg allergy can be safely vaccinated with the live attenuated influenza vaccine (Fluenz Tetra); those with clinical risk factors that contraindicate Fluenz Tetra should be offered an inactivated influenza vaccine with a very low ovalbumin content (<0.12 μg/mL).\textsuperscript{24} In adults, the ovalbumin-free influenza vaccine (Optaflu), if available, can be used in any setting, regardless of the severity of the egg allergy. Adult patients can also be immunised in any setting using an inactivated influenza vaccine with an ovalbumin content <0.12 μg/mL, except those with severe anaphylaxis to egg that has previously required intensive care.\textsuperscript{24}

Shellfish allergy and glucosamine

Glucosamine supplements are either produced synthetically or derived from shells of shellfish. It has been suggested that non-synthetic glucosamine products may cause allergic reactions in people sensitive to shellfish, though some question this, as the allergy is caused by IgE antibodies to antigens in the flesh of shellfish, and not to the shell.\textsuperscript{25} Nevertheless, the summaries of product characteristics for brands of glucosamine contraindicate the use of glucosamine in patients who are allergic to shellfish.\textsuperscript{26-28} It should be noted that glucosamine products are not recommended by the National Institute for Health and Care Excellence (NICE) for the management of osteoarthritis.\textsuperscript{30}

**E-numbers**

E-numbers are additives that have been approved for use in food across the EU. Blocks of numbers refer to specific groups of additives: for example, colours are in E100 series, preservatives in E200 series, and antioxidants in E300 series.\textsuperscript{31} They may be present in some medicines and are generally listed by their chemical name.\textsuperscript{32} Some colorants used in foods may have an adverse effect on activity and attention in children, and, since they are still used to formulate medicines (such as tartrazine), some parents may wish to avoid them. Adverse reactions have been associated with many pharmaceutical preservatives, including benzalkonium chloride, sodium benzoate, chlorocresol, hydroxybenzoates and benzyl alcohol. Sweeteners (such as aspartame and sorbitol) are used to formulate oral liquid medicines but can pose problems for certain patients. Patients who react adversely to additives in foods might need to avoid medicines that contain them.\textsuperscript{33}

**Conclusion**

People with dietary intolerances or allergies may request a medicine that is free of a particular excipient. However, this may not be necessary in all cases. As excipients in medicines that contain the same active drug may vary depending on the manufacturer, formulation, and strength, a suitable alternative can usually be sourced if needed.

**Competing interests** Competing interests are in line with DfT’s policy on conflicts of interests.

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**Case Review**

**Painful red eyes in a contact lens wearer**

A 21-year-old woman from Singapore presented to the eye hospital with a two-week history of painful red eyes, where the severity of the pain was continuing to worsen. She was shortsighted and wore rigid gas permeable contact lenses on most days and admitted to sometimes sleeping with them in situ. She had last worn contact lenses a week before presentation. She reported that she had been cleaning the lenses with tap water over the past two months, including during a holiday in Thailand. She had not been unwell recently, in close proximity to anyone with conjunctivitis, or been subject to trauma. No previous ophthalmic or medical history was noted.

On examination, the best corrected visual acuity was 6/36 right eye and 6/9 left eye, tested with glasses. The conjunctival vessels were diffusely injected. The corneas stained bilaterally in a punctate fashion with fluorescein over a patchy area of whitish haze within the centre and mid peripheries (figure).

1. **What differential diagnoses need to be considered?**
2. **How would you manage this patient?**
3. **How can patients reduce complications with contact lens wear?**

Submitted by Katherine McVeigh, Kaveh Vadhani, Shokufeh Tavassoli, and Derek Tole

Patient consent obtained.

Cite this as: BMJ 2017;358:j3614

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**SPOT DIAGNOSIS**

**Headache and papilloedema in a 10-year-old**

A 10-year-old girl described intense headaches at the front of her head, which had been coming and going since she banged her head two months earlier. She also described feeling sick with the headaches, and had vomited on several occasions. On examination, she had papilloedema, otherwise neurological examination was normal. She had a computerised tomography scan of the head (fig 1A) followed by magnetic resonance imaging of the brain (fig 1B). What is the relevant finding?

Submitted by Anan Shtaya and Bassam Dabbous

Parental consent obtained.

Cite this as: BMJ 2017;358:j3807

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Submitted by Anan Shtaya and Bassam Dabbous

Parental consent obtained.

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MINERVA A wry look at the world of research

Pitfalls in positron emission tomography

A 66 year old man with Hodgkin's lymphoma underwent 18F-FDG positron emission/computed tomography scanning to assess disease response after three cycles of chemotherapy. Diffuse uptake was seen throughout the axial skeleton and spleen, suspicious for malignant infiltration (figure). Further investigation revealed that he had been administered pegylated granulocyte colony stimulating factors (G-CSF) 10 days earlier, causing physiological marrow proliferation and extramedullary haematopoiesis in the spleen. Traditional G-CSF has a half life of 3-4 hours and can affect positron emission for up to 10 days. Pegylated, long acting G-CSF has a half life of 20-30 hours and remains detectable on positron emission tomography for up to 20 days. Drugs with such metabolic effects should be detailed on the scan request.

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Patient consent obtained.

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Gender differences in rheumatoid arthritis

Why is rheumatoid arthritis two or three times commoner in women than men? A large case-control study from Sweden explores the influence of breast feeding and exposure to oral contraceptives but fails to find much in the way of explanation (Ann Rheum Dis doi: 10.1136/annrheumdis-2017-211620). Women who had used oral contraceptives had a slightly lower risk of zero positive rheumatoid arthritis than women who had never used them, but breast feeding made no difference.

Multiple micronutrients on trial

Multiple supplements of micronutrients are frequently given to children in low- and middle-income settings. This might seem a sensible idea, but a trial from rural Gambia raises doubts about its effectiveness (PloS Med doi:10.1371/journal.pmed.1002377). Among more than 1000 children randomised either to micronutrient enriched supplements or to unfortified supplements, there was no reduction in mortality over the following six months.

Too many frailty scores

Some consider frailty as a phenotype of weakness and impaired performance. Others prefer the idea of an accumulation of deficits. Yet another way to think about it is as a multidimensional deterioration of function in cognitive, physical, and social domains. So perhaps it’s no cause for surprise that a pair-wise comparison of 35 (yes, 35) different frailty scores within the English Longitudinal Study of Ageing showed only modest levels of agreement (Am J Epidemiol doi:10.1093/aje/kwx061).

Frailty as a predictor

Lack of consistency between scores might lead one to ask whether the concept of frailty has much value. However, a prospective study in Australia shows that at least one of these scores is useful prognostically (Age Ageing doi:10.1093/ageing/afx081). Frailty status measured at hospital admission in more than 1000 elderly patients predicted a range of adverse outcomes including length of stay, in-hospital falls, and mortality.

Patient HM

HM, one of the most famous cases in medical literature, was the man whose capacity to form anterograde memories was destroyed forever in 1953 when a neurosurgeon removed tissue from both hippocampuses in an attempt to cure epilepsy. The story is re-told by the neurosurgeon’s grandson in a book discussed in the New York Review of Books. He explores the attitudes and motives that led his grandfather, and other neurosurgeons of that time, to perform experimental operations that often left their patients damaged.

Walking the dog

Forget treadmills, personal trainers, and gym membership. Having a dog is a better way to maintain physical activity. Among the 3000 or so participants in the Norfolk cohort of the European Prospective Investigation into Cancer and Nutrition, two thirds of those who owned a dog walked it at least once a day. Dog walkers were more active on wet days than non-dog owners were when it was fine (J Epidemiol Community Health doi: 10.1136/jech-2017-208987).

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Parents of very low birthweight babies

Understandably enough, parents of children born very preterm or with very low birthweight experience a high level of emotional stress during the early years. However, a longitudinal study from Germany finds that, by the time their offspring have reached adulthood, their quality of life is comparable to that of the parents of individuals born at term (Paediatrics doi:10.1542/peds.2017-1263). Few will quarrel with the investigators who call this finding a testament to parental resilience.

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