Avoidance or exposure to foods in prevention and treatment of food allergy?

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Purpose of review

To caution against premature proposals advocating change before epidemiological and clinical evidence warrants such a paradigm shift.

Recent findings

Until 2007, all allergy societies advocated allergen avoidance for prevention and therapy in food allergy. Since then, new evidence has prompted careful re-evaluation of the literature. In primary prevention, delayed introduction of allergenic foods to prevent food allergy was removed from most recommendations. However, there is currently no evidence that allergenic foods ought to be introduced earlier than is recommended for complementary foods, at 4–6 months of age. Here we uphold the view against an emerging school of thought that early and deliberate exposure to allergenic foods may prevent or delay the onset food allergy. While notions of promoting early oral tolerance may have some merit in theory, in practice research remains inconclusive. Of recent development are treatment advances as regards established food allergy, using food allergens to induce tolerance in highly selected populations of allergic children. However, the investigators themselves strongly warn of significant risks and stress the need to optimize safety and understand longer-term implications before these trials can be applied to routine clinical practice. In this paper we endorse the current recommendation that children with confirmed food allergy should avoid foods implicated in immediate reactions.

Summary

It is currently inappropriate and potentially dangerous to advocate deliberate exposure to foods involved in serious reactions against current recommendations and particularly so among food allergic children until more basic and clinical research become available.

Keywords

complementary feeding, desensitisation, food allergy, oral immunotherapy, tolerance and prevention

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Introduction

All persons having business before this international court of allergists are admonished to draw near and give their attention. The case now before this court is the proposal to alter current clinical practice in the primary prevention and treatment of food allergy. Our brief is to uphold the current approach on the basis of the best evidence and best practice. We shall presently respond to the arguments put forward by our learned colleague Scott Sicherer [1], to modify the current clinical approach, based merely on circumstantial and preliminary evidence.

To prove this, let facts be submitted to a candid world

Ladies and gentlemen of the jury, in recent years we have witnessed a major change in the regard for allergens, with a shift from seeing them as invariable 'culprits' in the development of allergic disease towards their possible role as 'cures' [2]. Although there has been considerable expectation and excitement that exposure to extremely allergenic food such as peanut may play an active role in prevention, and even the cure of established food allergy, without clear evidence, safety studies and long-term data, it is premature to advocate these strategies in routine clinical practice.

Currently, the expert consensus is in a state of 'equipoise', held in balance by the precautionary principle (Fig. 1). While we no longer see allergens as culprits in the allergy epidemic, prudence dictates considerable caution against proposing deliberate exposure for prevention and treatment of disease, at least until more evidence is available. It is generally acknowledged that 'absolute' avoidance of allergens is impossible. Exposure

Figure 1 Equipoise: avoidance and exposure

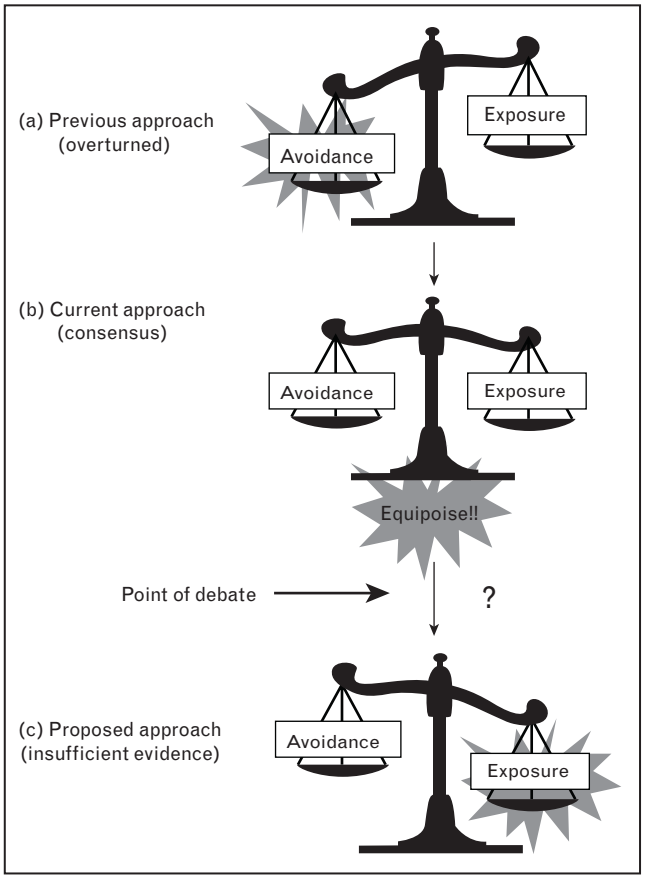


Figure 2 Wrongful conviction: allergens found guilty of allergy epidemic

to trace amounts of common ubiquitous allergens is inevitable even with the most diligent attempts at avoidance. Thus, the focus of current debate now revolves around whether we should be advocating 'deliberate exposure' to allergens or continue the current practice, as outlined in our following submissions to the court.

In the matter of 'food allergens and primary allergy prevention'

Argument of Susan L Prescott, Esq. Counsel for the Defence: Our case is clear and simple. Allergens are not the cause of the allergy epidemic, either by their presence, or their absence. It is most likely that allergens are innocent bystanders and there are other more likely suspects in this case. It is naive and even foolish for us to expect to prevent allergy and reverse this epidemic of immune disease by manipulating allergen exposure.

Given that 'complete' allergen avoidance is impossible, and that international consensus has already established that the current evidence does not justify attempts at allergen avoidance for allergy prevention (Fig. 1a) [3–5] the point of debate also centres on whether to deviate further from the current consensus of 'equipoise' (Fig. 1b) and move to a position of 'deliberate exposure' (Fig. 1c). As we have been invited to take the more conservative stance in this debate, our position is to defend the current consensus. We maintain that although more research is clearly needed in this area, there is currently insufficient evidence to support a move to deliberate early exposure to allergenic foods.

Background of this case: an old vendetta

This is not the first time allergens have stood in the dock. Over 20 years ago, food allergens were first on trial for causing food allergy [6]. They were accused of killing and causing billions of dollars, damage and immeasurable personal and social cost. They were found guilty, convicted largely circumstantial evidence and sent into exile [7] (Fig. 2). Fear and paranoia soon set in. Allergens have become demonised and ostracised, exiled from the diets of small children all around the world. Even now whole populations remain terrified of them, not allowing them near their children (Fig. 3).

Wrongful conviction: allergens liberalised in new guidelines

Recently many of us have called to have this case reopened, to carefully re-weigh the evidence, to call for new evidence and to reconsider the previous verdict [3–5,8–10] (Fig. 4). We recognised that this was a wrongful conviction. The current consensus is that there is no evidence that food allergens caused the allergy epidemic. Instead, focus has shifted away from allergens as culprits.

In general terms the current recommendations are: to breastfeed as long as possible and to feed a child when he is hungry and developmentally ready, generally around

Figure 3 Allergens in exile from diets: families live in fear

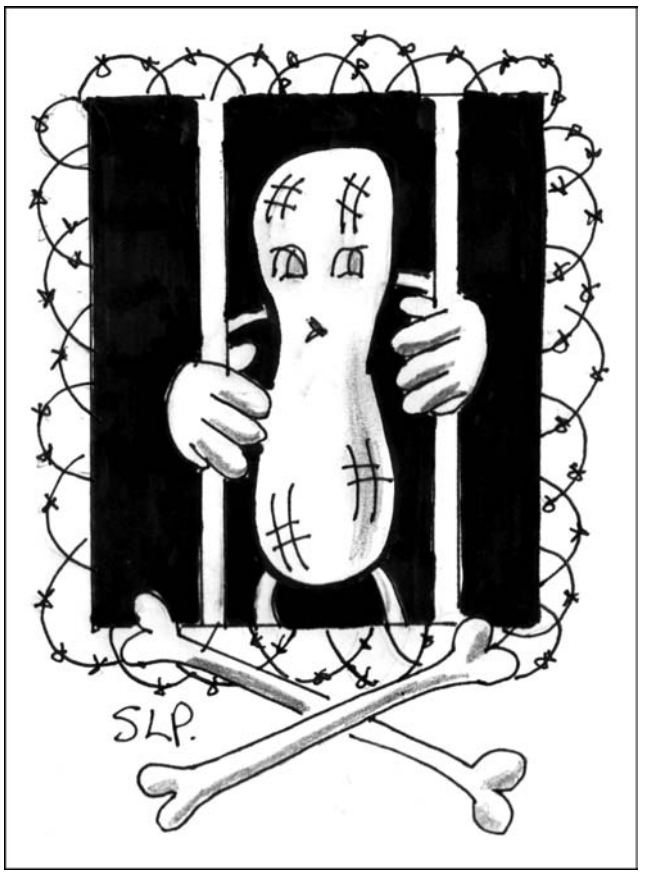


Figure 4 A call for justice: the case is reopened

4–6 months of age. There are no specific recommendations regarding allergenic foods, that is no specific avoidance and no deliberate early feeding [3–5]. This consensus position of equipoise is where the current evidence leaves us (Fig. 1b).

Allergens in the frame again?

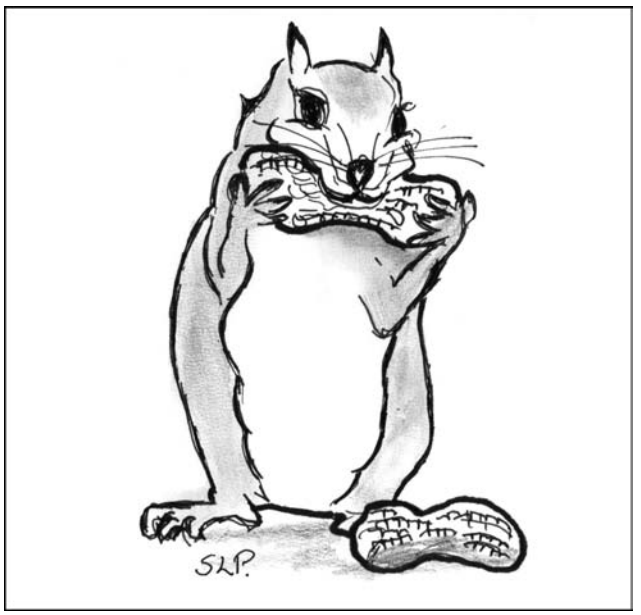
Just when we thought they were in the clear, allergens have once again been thrust into the spotlight, implicated once again in the food allergy epidemic, only this time not by their presence, but by their absence. There is currently a ground swell of support for the notion that attempts to avoid allergens may be in some way implicated in the recent rise of food allergy [3,8,11•], and as discussed by our learned colleague Sicherer in this issue [1]. Some of our most learned colleagues are gathering evidence to support these theories [8]. But we maintain that our colleague [1] and his supporters must wait until the evidence before they serve this indictment and make their case.

The basis for the new case

One key study [12•] that has served to highlight the possibility that early introduction of allergenic foods, such as peanut, in promoting oral tolerance is a study showing significantly lower allergy rates in Israel where peanuts are introduced much earlier than in Britain, which has one of the highest peanut allergy rates in the world. This was based heavily on questionnaire 'here-say' data that can be subject to bias and inaccuracy. It was also not possible to exclude all 'other suspects' or confounding factors that may have explained the difference in allergy rates. It is also possible that there could have been differences in peanut preparations, or 'modus operandi' of allergens, between these two different settings. It is notable, however, that the differences in allergy rates were only seen for peanut and not foods, an observation that does support their case. This is a very interesting 'hypothesis generating' study, but this evidence is largely circumstantial and not conclusive.

A second study, by the same group, has also examined the fascinating effects of cutaneous sensitisation in children who are avoiding exposure via the oral route [11•]. They propose that oral avoidance may increase the risk of peanut allergy in this setting. There have been criticisms that this study was based on questionnaire data from a biased population [13]. The authors have also acknowledged that the exclusion of known peanut allergic families leads to unavoidable bias [14]. Again, we must

Figure 5 New approaches: eating allergens early – a 'leap' of faith?



agree that this is an interesting theory which needs to be tested in further studies, but that it remains circumstantial and not definitive.

Finally, there are epidemiological observations which have been used to support the notion that not only has allergen avoidance been ineffective: that it may indeed be implicated in the rise in food allergy. But most of this evidence is also indirect and inconclusive and cannot support a causal relationship. The rise in food allergy predates the avoidance practices [15]. Studies also suggest that most families do not adhere to avoidance guidelines [16]. Again, many other factors are implicated in this rise in disease and the most likely interpretation is that allergens are not the cause.

Efforts to provide more conclusive evidence

The UK group led by Gideon Lack is one of the main pioneers in this area. Following their observational studies [12•] this group have embarked on the first study, the LEAP Study (www.leapstudy.co.uk) that is attempting to address this issue prospectively in a randomised controlled trial (RCT) (Fig. 5). It should be noted that there is no placebo, and there is possible inclusion bias in that following pretesting only nonsensitised children are enrolled. We are all awaiting the results with great interest, but this will be some years away yet. It would be premature to 'leap' to conclusions, as our learned colleague Sicherer is suggesting in his opposing arguments (this issue) [1] before this evidence has been presented.

We too are involved in this quest to provide clearer evidence on the role of early versus late introduction of allergenic foods. Firstly, Prescott *et al.* are currently enrolling 1512 Australian infants at 'high risk' of allergy based on an immediate family history of allergic disease. In this double-blind RCT children on an 'egg-free' diet are randomised to receive egg protein (powder) or an image-matched placebo from 4–6 months until 10 months of age when all children commence egg normally in their weaning diets. There is no allergy testing at study entry to reduce any population bias. At 12 months of age all children have allergy testing and food challenges to compare the rate of egg allergy in each group. Secondly, in a smaller study we are using a similar study protocol in 250 infants who already have moderate eczema. This group arguably have more permeable skin and more permeable guts and it is entirely possible that the effects of early allergen feeding may vary with phenotype. Whatever the findings, there is very unlikely to be a 'one size fits all' solution.

More complex story: the need to beware of apparently 'simple' solutions

The concepts behind early feeding are tantalising. But it is tantalising because it appears to provide a simple solution: 'Feed early and prevent allergic disease.' But this problem is far from simple. Allergy is a heterogeneous condition. It is the result of complex multifactorial gene–environment interactions. As such, there is unlikely to be a simple solution that will work equally for everyone. Based on what we have learned from our past mistakes in banning allergens, it would be naive to expect anything less.

We have recently reviewed this area, highlighting the uncertainty and the need for more studies [9]. Rather than targeting allergens, we need to optimise other environmental conditions during allergen encounter. In particular we need to understand and optimise colonisation and exposure to dietary immune modulators, including the tolerogenic role of breastfeeding. In other words, we need to understand how to provide more tolerogenic environment.

There has been a rise in many immune diseases. The epidemic of both allergic and autoimmune diseases suggests common mechanisms. Surely we cannot expect to explain this in terms of changes in allergen exposure. Surely we cannot hope to solve this by altering feeding with allergenic foods. No indeed, there are other suspects in this case!

Other suspects: a conspiracy of westernisation

There is little doubt that the modern epidemic of immune disease is multifactorial. This is not the work of one agent, but an organised crime network. Arguments

Figure 6 Another prime suspect: hygiene hypothesis

Figure 7 An organized crime network: the conspiracy of westernisation

over when allergens arrived on the crime scene do not explain the crime, and are distracting us from the real perpetrators. There are other suspects for the same crime, and prime suspect number 1 is the hygiene hypothesis. This suspect has been under surveillance for nearly 20 years (Fig. 6). Although the evidence is much stronger than for allergens, we have so far failed to make a definitive case. There is extensive epidemiological evidence, and extensive forensic 'in-vitro' evidence that changing microbial burden has immune effects, which may be implicated in the rise in allergic disease [17]. Furthermore, the effects are likely to be more wide-ranging effects, implicated in the rise of both allergy and autoimmunity. Do not be fooled by appearances (Fig. 6); this remains a very serious suspect! Other suspects include dietary changes. Here there are many suspicious players, including declining intake of poly-unsaturated fatty acids, vitamin D, vitamin A and other antioxidants [18]. There are even new suspects here, such as dietary folate [19,20••], which has recently been shown to have epigenetic effects promoting the allergic phenotype, even before significant allergen encounter. All of these players have immune effects and epidemiological associations with allergic disease.

This casts more than a shadow of doubt over the role of allergens! We are dealing with some very powerful forces that have had enormous, large-scale effects on our gene expression in a very short time (Fig. 7). These characters are seriously dangerous. And the most frightening thing is that we are not even sure who they are and how they are colluding together! How can we possibly expect allergens to be responsible or to solve this story?

Testimony of an expert witness

Here we finally call on the testimony of an expert witness Wesley Burks who recently reviewed this issue in an Editorial for the Journal of Allergy and Immunology [15]. In his words: '... Although an intriguing proposition, the principle of early feeding to prevent the development of food allergy remains unproven. At this time, there is not enough evidence to put this theory into practice ...'

Summary and implications of the verdict on allergy prevention

It is your duty to base your verdict only on the evidence and beyond any reasonable doubt. To endorse a move from 'equipoise' to 'deliberate exposure' is to indicate that there is enough evidence to advocate another change in our guidelines: to recommend early feeding of specific allergenic foods. But what foods? When? How? Until these questions can be answered this is clearly premature. The only logical choice is to err on the side of caution and maintain the current consensus of 'equipoise' while we gather more evidence, and actively investigate this problem and with a broad focus, not limited to allergens. If any of our learned colleagues propose to change this, the burden of proof lies with them, and they have not produced it!

In the matter of 'food allergens and the treatment of food allergy'

Arguments of Alessandro Fiocchi Esq, Counsel for the Defence of the Precautionary Principle: In my opening statement of the case for the defence, I would like to point out that a major paradox exists in the whole controversy regarding avoidance of allergenic foods. On one hand, there is speculation that 'absolute' avoidance may be detrimental. Yet notwithstanding patients' best efforts, minute-to-low-dose amounts are unavoidably consumed and 'absolute' avoidance can rarely be achieved. We aim for clinically relevant 'avoidance' below a 'threshold for reactivity', but recognise that this threshold varies widely between patients. On the other hand, the proposal that allergen exposure at 'some level' may be required to induce tolerance also implies a threshold level for this effect. So we may speculate that 'thresholds levels for inducing tolerance' may also vary widely between individuals. As yet there are no data to give any indication of such levels, and there is little likelihood that these will be comparable between individuals given the apparent variations between patients.

Background of the case

Avoidance of known allergens is the 'Royal Road' to the treatment of food allergy. Although the gradient and the threshold of exposure necessary to cause/maintain food allergy or, conversely, to ward it off are currently unknown for the individual patient, these could conceivably be used in the future to modify the natural history of the disease if found. Until then, vigilance regarding ingestion remains the only modifiable risk factor affecting all clinical presentations of food-induced allergy, including delayed reactions [21].

Avoidance is the only 'cure' for food allergy

Despite many advances in the field of the dietary management of food allergy, no measure or strategy as direct (yet as difficult to apply) has been proposed as avoidance of offending food allergens in curative interventions [22,23]. The truth of the matter is, members of the jury, that avoidance is actually a product of counterbalancing, a default strategy and a balancing act in the management of food allergy. Its equipoise rests on the precautionary principle. Having to strike a precautionary equilibrium between prohibitive measures against quality-of-life issues, avoidance is a dynamic endpoint that is difficult to assess for efficacy and safety in research settings (it is a negative measure and therefore has no metric) and even more in clinical setting where avoidance measures need to be tailored to the individual's life style and medical requirements.

From the patients' perspective, avoidance means meeting obstacles unshared by one's nonallergic peers, thereby curtailing the quality of life of the individual; whereas, from the physician's outlook, patient education, ensuring compliance and assessing the receptiveness of patients and their family are major concerns. It remains a balancing act, therefore, with the risks which a patient may incur outweighing the permissive approach, although individual benefits may accrue in favour of more stringent measures while keeping the precautionary principle to inform the consensual decision to be made.

The myth of total avoidance

Although 'total' avoidance is (societally, socially) impossible, it is possible to avoid clinically relevant levels of food allergens. Implementing a strict avoidance strategy is a difficult and burdensome task. Children prescribed such a regimen may not comply because of deliberate infractions, incorrect label reading, ambiguous labelling or undeclared ingredients and accidental ingestion [24]. However, from a clinical perspective, many foods are easily avoided without nutritional consequences. Inadvertent ingredients, however, are far more tricky to consistently eliminate from the food chain: wheat, milk, nuts and eggs are the most ubiquitous offenders in that respect. The most acute nutritional problems regard mainly children reacting to milk and egg proteins, for whom good-quality alternative protein sources must be found. To compound the problem, food allergens may come under inhalants as well as contactants, either form being liable to trigger severe reactions [25–27]. Casual exposure is not the only pitfall unfortunately; common antigens and allergens must be frequently consumed with processed foods of industrial origin. No comparative risk assessment study has so far been attempted with the power to make recommendations in that respect. It is not true that we want to shift the responsibility for our knowledge gaps on to the patients, as implied by our learned colleague [1], but we are only applying the principle of precaution in the absence of an incontrovertible indication that exposure shortens or adds to the duration of food allergy.

How 'avoidance' modifies natural history

'Avoidance' has been blamed for longer duration of disease, yet most children who grow on being full-fledged allergic are or have been following an elimination diet. In the context of cow's milk allergy, children prescribed an avoidance diet become tolerant after an average of 1 year [28], whereas in most cases (80%) tolerance is achieved within 3–4 years [29,30,31•].

Some researchers have hypothesized that 'total' avoidance of food allergens could translate into a worsened IgE-mediated response in the long term [32], and a retrospective study has suggested that children with eczema without previous untoward reactions to cow's milk are at risk of developing acute allergic reactions

to cow's milk following long-term elimination from their diet [33]. These case series could be said to reflect the normal course of cow's milk allergy in real life across various populations of infants and children, and may not represent a biological phenomenon *per se*, inasmuch as the majority of children with cow's milk allergy outgrow their condition while on an elimination diet. There is also corroborative evidence from several clinical studies tending to indicate that by not seeing the offending allergen, one's immune system still contrives to achieve tolerance [32,34,35], and perhaps even earlier [36•].

Food allergens may act differently in different phenotypes

Different phenotypes of food allergy have been described. In two cohort studies [37,38], a sub-population of patients expressing an early polysensitisation pattern in association with earlier, persistent and severe symptoms has been described. The same pattern appears to be mirrored among milk-allergic children where a pattern of longer duration of cow's milk allergy evokes the persistent wheezing also found among participants in these two studies [32]. Such studies are still few and far between, and it is only because our ignorance of phenotypic expression of allergic disease is so extensive as regards both natural history and risk factors that we are yet unable to pinpoint which disease phenotype will respond to allergen elimination and in what way. This is not to say, however, that this knowledge gap argues in favour of selective introduction of offending allergens, but it should rather argue in favour of the thesis that utmost caution should be exercised as far as prescribing for the individual patient is concerned [39].

Our learned friend [1] is correct in assuming that 'In practice, we see some children who rapidly outgrow their food allergies without strict avoidance and others who fail to lose their allergies even with the most stringent diet', but this strongly suggests to a candid world that varied phenotypes are at work and does not a recommendation make.

Can 'avoidance' be avoided?

The cases in which avoidance can be avoided (baked forms of milk-containing or egg-containing products are tolerated by children with mild reactions to the unprocessed food) demonstrates that there are gradients and degrees in tolerance as there is in terms of sensitisation and response, and that if the patient ingests food amounts over her individual threshold, this does not influence the course of her disease. However, the same proponents of the 'baked goods' regimen are the first to admit to the scientific press that they would think twice before allowing patients' requests in regard to the re-introduction or prophylactic introduction despite published evidence of the contrary [40]. As far as the avoidance side of the argument is concerned, however, although we are willing to agree that 'the change from a milk avoidance diet to a milk-limited diet could provide a substantial improvement to the quality of life of milk-allergic individuals' [41•], we tend to regard as interesting but as hitherto speculative that 'the frequency of prolonged or permanent milk allergy may be reduced if this type of diet can augment the development of tolerance' [42•].

Lessons from oral immunotherapy studies

At this juncture, we would understand if our learned friend objected that studies on oral immunotherapy confirm his thesis. Such studies have been interpreted as not lending support to the proposal that continued exposure to allergen will increase immunoglobulin E levels or delay the acquisition of tolerance [42•]. However, there are several objections to embracing this approach wholesale. First, the actual mechanisms involved have not reached a satisfactory level of evidence to warrant meta-analysis or systematic review. Secondly, the quality of studies making use of largely subjective outcomes such as quality-of-life enhancement or worsening (which needs validated instruments to measure) is fundamentally not yet ready for community recommendations [43••]. We willingly grant that oral immunotherapy studies (OIT) can improve the quality of life of children with severe milk or egg allergies, but we are still ignorant of the precise immune mechanisms involved. On the basis of a single comparative study [44], we are loath to admit that tolerance depends on continued intakes. Thus, the prosecution thesis that successful OIT disproves avoidance-based approaches does not imply that immunotherapy works for all patients, or that several well defined subsets of patients may not profit from a prohibitionist approach.

Testimony of two expert witnesses

Before closing, I would like to call on the testimony of an expert witness Professor Hugh Sampson, who was interviewed by an editor from the American Association for the Advancement of Science journal. In spite of accruing evidence to some hope on the horizon, he remained sceptic though cautious and stated: 'Asked by worried parents what he would do were the child his own, I'll say, ''I would probably avoid peanut. [...] whatever we are doing is not working [...] because things have only gotten worse'' [41•]. In a more practical register, I would also call of Professor Scott Sicherer who, in a seminal editorial in the Journal of Allergy and Clinical Immunology, advised: 'For now, parents can be told that we do not have proof that they caused their child's allergy through diet selection, and a more expanded risk and benefit discussion about avoidance is justified' [45].

With these, the foremost food allergists' testimonies, members of the jury, I rest my case.

Conclusion

The current approaches for both the prevention and treatment of food allergy are based on the best currently available evidence. The role of our submissions as the defence team has been to uphold these positions against premature proposals for more deliberate allergen exposure, before there is clear evidence available. There is far more than a shadow of doubt surrounding these proposed approaches. There are also dangers, difficulties and dilemmas that have not yet been addressed. Based on the currently available evidence, there can only be one verdict beyond any reasonable doubt: to uphold the current approaches until such time that there is sufficient evidence to indicate that these should be changed. Again, the burden of proof lies with those who are proposing change, and so far clear evidence has not been produced.

Acknowledgements

The illustrations are the work of Susan L. Prescott. Professor Prescott is supported by an NHMRC Practitioner Fellowship.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 270).

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10 Allen CW, Campbell DE, Kemp AS. Food allergy: is strict avoidance the only answer? Pediatr Allergy Immunol 2009; 20:415–422.

11 • Fox AT, Sasieni P, du Toit G, *et al.* Household peanut consumption as a risk factor for the development of peanut allergy. J Allergy Clin Immunol 2009; 123:417–423.

This study examined relationships between household exposure to peanut allergen and the risk of peanut allergy in children who were not eating peanut. Specifically, there was a dose–response relationship between environmental (nonoral) peanut exposure and the development of peanut allergy. They proposed that this could have been owing to cutaneous sensitisation in children who are avoiding exposure via the oral route.

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This study demonstrated significantly lower rates of peanut allergy in Israel than in the United Kingdom, and that peanut products are introduced to the diet at a much earlier age in Israel than the UK. This has been the basis for new studies investigating the role of early introduction of peanut as a means of preventing peanut allergy.

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19 Miller RL. Prenatal maternal diet affects asthma risk in offspring. J Clin Invest 2008; 118:3265–3268.

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In this murine model, maternal supplementation with folate (a dietary methyl donor) leads to hypermethylation and gene silencing of the *Runx3* gene in the offspring. The suppression of this gene, which is normally important for inhibiting airway inflammation, resulted in an increased allergic airway disease, with associated increased production of immunoglobulin E, chemokines and inflammatory cytokines. Moreover, this effect was transmitted to subsequent generations.

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30 García-Ara MC, Boyano-Martínez MT, Díaz-Pena JM, *et al.* Cow's milk-specific immunoglobulin E levels as predictors of clinical reactivity in the follow-up of the cow's milk allergy infants. Clin Exp Allergy 2004; 34:866–870.

31 • Fiocchi A, Terracciano L, Bouygue GR, *et al.* Incremental prognostic factors associated with cow's milk allergy outcomes in infant and child referrals: the Milan Cow's Milk Allergy Cohort study. Ann Allergy Asthma Immunol 2008; 101:166–173.

This is a prospective evaluation of tolerance in a referral cohort of cow's milk-allergic children followed on the Milan Cow's Milk Allergy Cohort. The study indicates the major prognostic factors for a longer duration of the disease. A phenotype characterized by the involvement of two or more organ systems and high intensity of atopic expression (1-mm increment in wheal diameter at skin prick test with cow's milk, low-threshold dose response at DBPCFC with milk, high total immunoglobulin E level, co-sensitisation to both inhalant and ingestant allergens) is associated with longer duration of CMA.

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