

Food allergy diagnosis: are there any missing factors? A theoretical approach

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Summary Actual diagnostic criteria in food allergy frequently show a group of subjects with uncertain diagnosis, i.e., subjects with only occasional reactions to an offending food. These subjects are probably under- or misdiagnosed. It is possible that food itself may be only one of the factors involved in the allergic food reaction, at least in these subjects. In these cases, several factors besides food could modify either the allergenic potential of food or the absorption of allergens and may be relevant for a clinical response to occur. In order to investigate the possible relevance of missing factors, a theoretical model is elaborated by modifying the equation that represents the classical food allergy model: $xAg + (\text{IgE}^*\text{-cell}) \Rightarrow \text{clinical response (mediators release...)}$.

In this classical model, it is assumed that if there is specific IgE against a food ($\text{IgE}^*\text{-cell}$), the only limiting factor will be x (total amount of allergen ingested), being Ag , the allergen supposed to elicit a clinically relevant response. Always that $x \geq a$ (threshold quantity of allergen that elicits a reaction) a reaction should occur. The possible existence of missing factors, i.e., the presence of ‘modified allergens’ (Ag' , Ag'' , ..., Ag^n) induced by modification of the allergenic potential of food, are not considered in the equation, but these factors may have clinical relevance, and these relevance could be related to $x_1, x_2, \dots, x_n$ (relative quantities of ‘modified allergens’). So, a modified formula is proposed:

$$\{x - \Sigma(x_1, x_2, \dots, x_n)]Ag + \Sigma(x_1Ag', x_1Ag'', \dots, x_nAg^n)\} + \text{IgE}^*\text{-cell} \Rightarrow \text{clinical response.}$$

In this formula, depending of the relative amount of the limiting factors: $x_1, x_2, \dots, x_n$ and the relevant allergen ($Ag, Ag', Ag'' \dots$ or Ag^n) to which the subject is sensitized an allergic reaction could or could not be elicited. So, factors other than the food itself and the threshold of sensitivity may be missed in the diagnosis of food allergy. When there are not any factors modifying Ag , the allergic response will depend only on the amount of x (‘classical equation’). But when there is some kind of modification the response will depend on the relevance of the modified allergens and on the relative amount of them. If the factors modifying the allergenicity cannot be controlled, the amount of the clinically relevant allergen cannot be estimated, and the clinical response may be only occasional, explaining the inconsistent findings of some subjects.

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BACKGROUND

Allergic diseases are a growing problem (1). There is scarce information on the prevalence of food allergy in childhood and even less information on the adulthood but about an 8% of the children and 2% of the adults are considered allergic to foods (2). The number of subjects becoming sensitized to foods after infancy is probably growing. In many cases these are subjects sensitized to

other allergens that present minor symptoms (oral allergy syndrome...) with vegetal foods (3).

The current diagnostic criteria of food allergy (clinical history, skin tests and/or in vitro assays like RAST, elimination diets and challenge tests) (4) are useful in many cases of food allergy, especially in infants and children.

Unfortunately all the diagnostic tools have unresolved questions and in some cases there are subjects with food related allergic symptoms in which an accurate diagnosis is hard to achieve; with subjects that in some way do not fit in those criteria.

Important questions about food allergy diagnosis are still trying to be answered:

- Clinical history is often unreliable.
- Food allergenic extracts currently used for in vivo and in vitro tests have poor specificity and sensitivity. Progress in the identification of major food allergens could improve the quality of the food extracts used for diagnosis (5).
- Elimination diets are not a harmless procedure having being described anaphylactic reactions after the reintroduction of food (6,7).
- Challenge tests have been considered the gold standard (8), being a positive double-blind placebo-controlled food challenge (DBPCFC) test the key factor for considering a subject as allergic to a specific food. However, DBPCFC methodology is complicated and is not used in everyday practice and challenge tests are not always feasible. Besides, important questions are still trying to be answered, as the minimum dose of allergen capable of eliciting an allergic response (9) or the role and ways of assessing the false positive responders (10).

But the role of negative results in DBPCFC should be considered with care because of the possibility of not reproducing the factors occurring in the 'natural' reaction (11,12). As DBPCFC is considered the gold standard, subjects with negative challenge tests or in which challenge tests are not feasible are considered as non-allergic or at least are regarded very cautiously and frequently with scepticism by the scientific community.

A group of subjects that reacts only occasionally with a specific food does exist. If it is supposed that these subjects are truly allergic, they will be 'atypical food allergic subjects'. Therefore, these subjects will be under- or misdiagnosed. Some of these subjects could be currently labelled as 'subjects non-allergic to foods' or 'allergic subjects probably related to foods'.

It is well known that in some subjects other factors besides the food are relevant in the development of a clinical response (i.e., exercise (13,14)) and that a specific

food is not always equally allergenic (15). If these factors were not included in the challenge test, the response could be a 'false negative'. Therefore, the possibility exists that other factors, only occasionally described as non-steroidal anti-inflammatory drugs (NSAID) (16), or unidentified yet, could be relevant in some subjects. Factors modifying the reactivity of the subject, either by modifying the allergenic potential of foods (food processing, food storage, cooking...) or the interaction of allergens with the immune system (changes in the absorption of allergens...) could explain some of the negative responses.

So the hypothesis is that there can be several factors affecting the clinical response of subjects with suspected food allergy that if not included in the challenge tests can yield a negative response and a false negative diagnosis of food allergy. Obviously most of the subjects with suspected food allergy should not be affected by these factors and current methods of diagnosis will be able to identify them. In these subjects, who can be labelled as 'classical food allergic subjects', DBPCFC will be an excellent diagnostic tool.

PURPOSE AND LOGICAL FRAMEWORK

If the allergic reaction is expressed as an equation, the effect of several modifications in the formula can be estimated. The variables to be included in the equation are all of them possible, and even more, all are situations previously reported in the literature. But instead of being considered as curiosities or 'case reports', a general equation is proposed, in which all of these cases and factors can be explained as different solutions of the equation.

The null hypothesis (the only factors related with the allergic response are the amount of the allergen and the reactivity of the subject, so DBPCFC is able to reproduce the reaction) is represented by the following equation:

$$xAg + (\text{IgE}^*\text{-cell}) \Rightarrow \text{Clinical response (mediators release...)}$$

In this 'classical equation', x represents the amount of the antigen; Ag , the antigen itself and $\text{IgE}^*\text{-cell}$ the existence of specific IgE against Ag linked to cells. The addition symbol should be *sensu stricto* a multiplication symbol, implying that if one of the two factors is zero, the reaction will not occur, but for clarifying the formula the addition symbol is used.

' xAg ' will represent in some way the 'reactivity' of an allergen in the subject and '($\text{IgE}^*\text{-cell}$)' the 'sensitivity' of the subject to that allergen.

In the animal models, there are strong interactions between the luminal antigens and the intestinal immune system, resulting in increased permeability to allergens and increased responses in some circumstances as reviewed by Heyman and Desjeux (17) and Yu and Perdue (18) for example. All these factors, probably relevant also in humans, may affect the 'reactivity' of the subject, i.e., by increasing the absorption of allergens, but they could also affect the 'sensitivity' of the subject, which depends also on other factors (mast-cell releasability...).

Only factors affecting the 'reactivity' are going to be analysed, and all the factors potentially affecting the 'sensitivity' are going to be considered as a variable with only two possible values: zero (the subject has no specific IgE against that particular allergen so the response will not occur) or one (the subject has specific IgE and if a threshold amount of allergen is reached a response will occur). The threshold value can be different in several subjects and as suggested before, possibly in the same subject in different moments and circumstances, but as expressed above it will be considered as a 0 or 1 response.

The working hypothesis is that the aforementioned formula is true, but that it represents only a particular case in a more general equation, so it will only be true in specific circumstances, when the effect of other relevant factors not included in the formula is negligible. So the equation needs to be reformulated to include/contain other potentially important factors.

The following factors/variables are going to be included in the equation:

Changes in the allergenic potential of food, before food ingestion

Related to natural variability (19), food manipulation (20), conservation (11) or cooking (boiling (21), roasting (15)...). The theoretical idea is that every time that someone eats a specific amount of a specific food, he is not ingesting the same amount of the allergens of that food; and even more, that he can ingest allergens not present in the raw food, or not eating at all allergens present in the raw food. The hypothetical allergens induced under these circumstances are going to be called Ag' and x_1 the total amount of these allergens being present. Of course there can be several different allergens induced under these circumstances but for simplifying the formula all of them are going to be considered as only one (Ag') and are going to be called 'neo-allergens' to express their relationship with the original allergen.

Changes in the allergenic potential of food after food ingestion

Food digestion usually prevents potentially allergenic food of being absorbed. Indeed, food stability to diges-

tion has been considered a valid parameter to distinguish between allergenic and non-allergenic foods (22). However, the allergenicity of easily digested allergens has been established (23). So, there are potentially allergenic foods that are usually digested and poorly absorbed. Variability in food digestion and absorption, induced by several factors such as exercise (24), NSAID (25,26), alcohol (27)... could allow the absorption and passage to the blood of peptides/allergens normally excluded. Also mucosal mast-cells (18) and cytokines (17,28) may enhance the absorption of allergens, at least 'in vitro'. The modified allergens present under these circumstances are going to be collectively called Ag'' and x_2 the total amount of these allergens, and are also going to be considered 'neo-allergens'.

Inclusion of hidden allergens in the food

The possibility of ingestion of hidden allergens is a well-recognized (29) but unresolved problem. Contamination (30), parasite infection (31), undeclared components (spices, additives) (32), transgenic material (33) are all possible sources of hidden allergens. The presence of these allergens cannot be excluded from either the original reaction or the challenge test. These hidden allergens are going to be called: Bg , suggesting they are different in nature from Ag and Ag derived antigens (Ag' and Ag'') and y the total amount of Bg being present.

To simplify, all these neo-allergens and hidden allergens are going to be considered as only one in each group. In addition, the reaction, dynamic in nature is going to be considered static, so the effect of time on the reaction is going to be discarded at this moment.

RESULTS OF LOGICAL ANALYSES

One single neo-allergen

In the simplest case, a reaction occurs after the ingestion of only one food with only one relevant allergen (Ag). As expressed in the equation the reaction depends only on the amount of $Ag(x)$. If a is considered as the minimum amount of food able to cause a clinically relevant reaction (threshold value), then aAg should be the minimum amount of one specific allergen (equivalent in this case to one specific food) that causes a clinically relevant reaction

$$xAg + (\text{IgE}^* \text{-cell}) \Rightarrow \text{Clinical response if } x \geq a.$$

If there were some kind of change in the allergenic potential of the food (Ag), induced by any of the causes suggested above, then Ag will be partially transformed

into a different allergen (Ag'). In this case, the equation should be expressed in the following way:

$$[(x - x_1)Ag + x_1Ag'] + (IgE^* - \text{cell}) \Rightarrow \text{Clinical response.}$$

In this case x_1 is the amount of the neo-allergen (Ag') and $(x - x_1)$, the amount of native allergen remaining. $(x - x_1)$ is going to be called x_0 .

$$(x_0Ag + x_1Ag') + (IgE^* - \text{cell}) \Rightarrow \text{Clinical response.}$$

Under these circumstances, nine situations may occur (Table 1):

1. Ag' is not produced ($x = x_0$; $x_1 = 0$)

In this case the equation is the same than the 'classical equation'.

- A. If the subject is allergic to Ag the response will occur (typical food allergic subject) besides $x(=x_0) \geq a$.
- B. If the subject is equally allergic to both Ag and Ag' , the response will occur ('typical food allergic subject') if $x(=x_0) \geq a$.
- C. If the subject is only allergic to Ag' , the response will not occur ($x_1 = 0$) and the subject could be considered as not allergic to Ag .

2. Ag is completely transformed in Ag' ($x_0 = +0$; $x_1 = x$)

- A. If the subject is only allergic to Ag , as x_0 is zero, the response will not occur but the subject could be considered as not allergic to Ag .
- B. If the subject is equally allergic to both Ag and Ag' the response will occur as in the typical food allergic subject if $x(=x_1) \geq a$.
- C. If the subject is only allergic to Ag' the reaction will occur as in the first formula (typical food allergic subject) if $x(=x_1) \geq a$; because in this case x_0 is zero ($x_0 = 0$; $x_1 = x$) and the equation is 'equivalent' to the classical one but the subject could be considered allergic to Ag , instead of allergic to Ag' .

3. Ag is partially transformed in Ag'

In this case the total amount of either $Ag(0 < x_0 < x)$ or $Ag'(0 < x_1 < x)$ are lower than x but $x_0 + x_1 = x$.

A. If the subject is only sensitized to Ag then: ($0 < x_0 < x$) and ($0 < x_1 < x$); as x_0 is lower than x , the reaction will not occur unless the total amount of food is increased to make x_0 equivalent to x . So the response in this case can be elicited only by increasing the dose. When the amount of Ag is increased from x_0 to x (to achieve a total quantity of Ag identical of that if Ag would not have been transformed) the response will occur. That is, the response can be achieved only when Ag is increased by $n(nx_0 \geq x \geq a)$.

B. If the subject is sensitized both to Ag and to Ag' the equation is still equivalent to the classical one and the reaction will occur if $x(=x_0 + x_1) \geq a$.

C. If the subject is only sensitized to Ag' the reaction depends only on the amount of Ag' , x_1 . Assuming than the threshold value to elicit a response is still a , then the reaction will occur always than x_1 is equal or higher than a ($x_1 \geq a$). In this case, if the amount of Ag' is increased from x_1 to x (to achieve a total quantity of Ag' identical of that if Ag would have been completely transformed into Ag'). That is, the response can be achieved when Ag is increased by $n(nx_1 \geq x \geq a)$.

Obviously if the circumstances than transform Ag into Ag' change, especially in cases 3-A and 3-C, the value of n can be very different. In these cases if the factor transforming Ag in Ag' is manipulated, not only a response can be obtained with different values of n in each case; but the equation can be switched towards cases 1-A or 2-A if the subject is only allergic to Ag and to 1-C or 2-C of the subject is only allergic to Ag' ; depending of the completely enhancement or blockade of the transformation of Ag with the same amount of allergen.

If Ag' had a different threshold of response, then things will be much more complicated, because in the cases in which the relevant allergen is Ag' the threshold value should be b , a value completely independent from a .

The manipulation of the factors that transform Ag in Ag' can greatly affect the response. So the amount of native food required to elicit a response can be different for a identical threshold value a or even the response

Table 1 Solutions of the equation depending on the relevant allergen and the relative modification of the allergens

	Amount of allergen		
	1. Ag' is not produced $x_0 = x$; $x_1 = 0$	2. Ag is completely transformed in Ag' $x_0 = 0$; $x_1 = x$	3. Ag is partially transformed in Ag' $0 < x_0 < x$; $0 < x_1 < x$
Relevant allergen			
A. Only Ag	Response	No response	Variable response
B. Both Ag and Ag'	Response	Response	Response
C. Only Ag'	No response	Response	Variable response

Ag : Ingested allergen towards the subject is supposedly allergic. Ag' : neo-allergen; part of the previous allergen modified by any of the factors suggested in the text. x : total amount of ingested allergen Ag . x_0 : amount of the unmodified allergen Ag remaining. x_1 : amount of the neo-allergen Ag' present.

cannot be achieved whatever the amount of food ingested be, if these factors are completely avoided and Ag is not transformed at all in Ag' . Thus, the reaction will depend only partially of x , the total amount of the allergenic food ingested. In several cases the reaction will depend on the amount of transformed and native food (i.e., the value of x_0 and x_1), values not easily estimated.

If the amount of Ag is increased, or there is any interference with the transformation of Ag to Ag' , manipulating the storage or cooking conditions for example, the reaction may occur or not. Therefore, an erratic reaction may occur in some cases.

In general, the higher is x_1 , the amount of the modified allergen Ag' , the highest will be its influence in the reaction and lowest that of the native food (Ag). If the subject is only sensitized to Ag' and there is a limiting factor blocking its production, the reaction could not happen. If Ag is not transformed at all, then the amount of $Ag'(x_1)$ will be zero and the equation will be identical to the first one. In this case the reaction will only depend on the amount of x . In the case of being sensitized only to Ag' , the manipulation, storage or cooking of the food, depending on the relative influence on the appearance of Ag' , can make the reaction unpredictable. So, in several of these possible situations, an accurate diagnosis cannot be achieved.

Two or more neo-allergens

Two neo-allergens

In case of adding Ag'' (the food allergens elicited after the intake of the food for example) the equation should be expressed as follows:

$$[(x - x_1 - x_2)Ag + x_1Ag' + x_2Ag''] + (\text{IgE}^*\text{-cell}) \\ \Rightarrow \text{Clinical response}$$

If $(x - x_1 - x_2) = x_0$, then

$$: (x_0Ag + x_1Ag' + x_2Ag'') + (\text{IgE}^*\text{-cell}) \\ \Rightarrow \text{Clinical response}$$

In this case, the options expressed before are multiplied depending on the relevant allergens, the amount of each one and the factors modulating its production. So the response is related to the amount of x , x_1 and/or x_2 . As in the previous case if x_1 or x_2 are zero or Ag' and Ag'' are equally allergenic the relevant equation will be the classical one; but if any of these factors is relevant things are much complicated.

Hidden allergens

If hidden allergens (Bg), present in the food, but not related with the first one (Ag) are added to the equation,

things complicate even more and the equation should be expressed as:

$$(x_0Ag + x_1Ag' + x_2Ag'' + yBg) + (\text{IgE}^*\text{-cell}) \\ \Rightarrow \text{Clinical response}$$

In this particular case the amount of Bg is not related to x . Again if these hidden allergens do not exist or the subject is not allergic to them the equation is identical to the previous one.

If the subject is only allergic to Bg , the response is only dependent of y , that is, independent of x . In this case only if the food is 'contaminated' with the hidden allergen the reaction will occur. Only if the subject were allergic to both Bg and Ag or one of its variations a response could be elicited with a lower 'dose' of Ag (i.e., amount of Ag smaller than x).

Several allergens (modified or hidden)

A general equation, including all the potential factors implicated in the response can be expressed as follows:

$$\{[x - \Sigma(x_1, x_2, \dots, x_n)]Ag + \Sigma(x_1Ag', x_2Ag'', \dots, x_nAg'') \\ + yBg\} + (\text{IgE}^*\text{-cell}) \\ \Rightarrow \text{Clinical response},$$

As $[x - \Sigma(x_1, x_2, \dots, x_n)]$ is called x_0 , then:

$$\{\Sigma(x_0Ag, x_1Ag', x_2Ag'', \dots, x_nAg'') + yBg\} \\ + (\text{IgE}^*\text{-cell}) \\ \Rightarrow \text{Clinical response}.$$

Several neo-allergens

If the hidden allergen factor is taken away, and only possible variations of an initial allergen Ag are considered, the allergic equation expressed as follows, can be studied in deep:

$$\Sigma(x_0Ag, x_1Ag', x_2Ag'', \dots, x_nAg'') + (\text{IgE}^*\text{-cell}) \\ \Rightarrow \text{Clinical response}.$$

In the null hypothesis: $x_1, x_2, \dots, x_n$ are all equal to 0. Then $x_0 = x$ and the equation is identical to the initial, so, the clinical response is only related to x (the amount of Ag). In this case DBPCFC is a useful method. The same is true if the modified allergens maintain the same allergenicity (that is, $Ag, Ag', Ag'', \dots, Ag^n$ are equivalent, and all of them can elicit an allergic reaction), then the clinical response is related only to the amount of x too, independently of the relative values of x_1, x_2 or x_n .

If the null hypothesis is wrong, then $x_1, x_2, \dots$ and/or x_n are different from zero.

Therefore if the allergenicity is only related to Ag or if any of the modifications is not allergenic, then Ag, Ag', Ag'' and Ag^n are not equivalent and the amount of un-

modified $Ag(x_0)$ is lower than x , so the response will not happen. Evidently if the value of x is increased (i.e., by multiplying by the factor n), the response can be elicited if: $n[x - \Sigma(x_1, x_2, \dots, x_n)] = a$ or $nx_0 \geq a$.

If the allergenicity is related only to one of the modified allergens (i.e., Ag' , an allergen induced by cooking), the relevant amount of the allergen will be x_1 , so the equation should be reformulated assuming that Ag and ($Ag'', \dots, Ag''$) are irrelevant. Then the equation should be expressed as follows:

$$x_1 Ag' + (IgE^* - \text{cell}) \Rightarrow \text{Clinical response.}$$

Therefore it would not be x the relevant quantity of Ag (needed to elicit a clinical response) but x_1 (the amount of Ag'). By definition x_1 is smaller than x , because: $x = \Sigma(x_0, x_1, x_2, \dots, x_n)$. Then $x_1 = x - x_0 - \Sigma(x_2, \dots, x_n)$.

In this particular case, all factors modifying Ag' , that is the value of x_1 , are relevant. Evidently, one of them is the value of x and of the other variables. But the factors that transform Ag into Ag' can affect in different ways the value of x_1 . Therefore, x_1 depends on x , the total amount of Ag , but also on all the factors that can increase, decrease or modify the 'predigestion' of the native food, and are relevant in the appearance of the neo-antigen Ag' . These factors depend obviously on the nature of the food (Ag) and on the quantity of it (x), but these factors can be 'external' and influenced by the source of the food, preservation methods, storage and cooking (method, time, temperature...) and could affect not only the value of x_1 but the nature of the neo-antigen/s (Ag') produced.

The same is true in the case of x_2 and Ag'' . Factors modifying x_2 can be dependent on Ag , but they can also be *independent* of Ag and dependent on the subject. Therefore, all the independent factors able to modify x_2 should be known in order to solve the equation. Probably in this case the effect of time should be included because the effect of a particular factor in the subject (i.e., exercise, NSAID intake...) could modulate the absorption of allergens in a dynamic way.

Finally is the particular case of yBg . Even if the quantity is a very small one, it represents a different problem: misdiagnosis (allergy to a different food, not to the one suspected or apparently ingested by the subject). If this variable is excluded (variable of unquestionable weight in some cases as peanut contamination of foods or in allergy to *Anisakis simplex*, for example) in order to simplify the equation, the results will be those expressed above.

In conclusion:

$$xAg \equiv \Sigma(x_0 Ag, x_1 Ag', x_2 Ag'', \dots, x_n Ag''') \text{ only if} \\ x_1, x_2, \dots, x_n = 0.$$

Besides, some variables (Ag' , $Ag'' \dots$) are only partially dependent of Ag but others ($\dots Bg$) are independent.

DISCUSSION

In this theoretical approach to the diagnosis of food allergy, a model to understand the possible responses of sensitized subjects when exposed to an allergen is proposed. This model is only a working model, assuming the simplest possibility in every case. As it is showed, a number of inconsistencies between the accepted and the proposed model may exist.

The idea is that in some cases, if Ag , the allergen, is considered as the only variable, an increase in the amount of the ingested food cannot be enough to obtain a response. A non-dose-dependent response can be obtained or even a negative response, when the relevant allergens are modified (Ag' , Ag'') and/or hidden (Bg) allergens do exist, because the relative amount of these allergens ($x_1, x_2, \dots, x_n$ and y) depends only partially and some times in a non-linear way on the total amount of food ingested.

There are factors that can modify the allergenicity of the foods (13,15–21) in a clinically relevant way. Changes in the allergen composition of foods are well known, but they have been considered as particular cases. On the other hand, circumstances in which foods usually tolerated can trigger an allergic reaction are also well known (13–15). In the case of exercise, several hypotheses have been proposed to explain this fact, including changes in intestinal permeability (13). Even more, in some cases only the addition of several factors has been able to provoke a clinical reaction (34,35).

A theoretical model is proposed that tries to integrate the possible role of these modifications in our current understanding of food allergy. Changes in food composition, changes in the intestinal absorption of food and even the presence of hidden allergens are all considered as variables in this model. Therefore, only when these variables are zero or are well known and controlled, our current tools for diagnosing food allergy will be enough to make an accurate diagnosis. In other cases, possibly more frequent in adults and in subjects sensitized via 'incomplete allergens' (23), there can exist an erratic or inconsistent response.

At least in these cases our diagnostic tools should be reassessed, and a negative food allergy diagnosis in the presence of a suggestive clinical history should be considered with care.

The intake of the suspected food after the clinical reaction or in a challenge without clinical symptoms cannot be considered by itself as a negative diagnosis, if all the circumstances suggested above are not considered.

From a practical point of view, probably a 'suggestive food allergy history' should be the one in which the suspected food is always present in the reactions, inde-

pendently of the possible tolerance of the food between episodes. In these cases a detailed clinical history of factors related with the allergic reaction (origin of food, possible contamination, storage, cooking, alcohol, NSAID or other drugs intake, exercise...) can be crucial to identify the inconsistency of the response and the relevant factor or factors implicated.

At the theoretical level, it is impossible in the majority of cases to be sure of the actual allergenic composition of the piece of food to which the subject reacted or that it is being used in the challenge test. But even in the case that purified and standardized allergens could be used, the exact way in which the food should be ingested or if any associated factor needed for the reaction to occur is missing may not be known. The literature suggests that they are specific cases in which these variables are important. As mentioned above, there are well known causes of variability in the allergenic content of a specific food (19–21) and of contamination of a specific food with other possible allergens (29–33). On the other hand, factors as exercise, NSAID and other drugs and alcohol have been described as enhancing factors in the allergic reactions to foods (36), and at least exercise has been related with sensitisation to unusual allergens (13). Even if not well documented, the possibility that other factors favour allergic reactions to unusual allergens, probably not easily absorbed from the gut, cannot be discarded.

A rule with many exceptions is probably not a good rule. Therefore, the rule should be modified in order to fit all the 'exceptions' in it. This model allows us to consider all the exceptions as infrequent solutions to the rule.

While establishing the true significance of these factors, it should probably be kept in mind, that a food allergy diagnosis cannot be easily ruled out in the presence of a suggestive clinical history. On the other hand, the suspicion of missing factors in the diagnostic puzzle of food allergy could show a different perspective to the problem, and will possibly help to find new tools that would enhance the diagnostic skills in food allergy.

CONCLUSION

In the diagnosis of food allergy, factors other than the food itself and the threshold of sensitivity to the food may be missed. The existence of factors that can modify the allergenic composition of the food, or the amount of allergen reaching the immune system should be taken into account. When there are not any modifying factors, the allergic response depends only on the amount of food ('classical equation'). When there is some kind of modification, the response depends on the relevance of the modified allergen and on the relative amount of it. When the factors modifying the allergenicity cannot be controlled or the amount of the clinically relevant al-

lergen cannot be estimated, the clinical response may be inconsistent, explaining the erratic findings or even the negative results in the challenge tests of some subjects with suspected food allergy.

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