

# Allergie ed Allergeni

**Lorenzo M Donini**



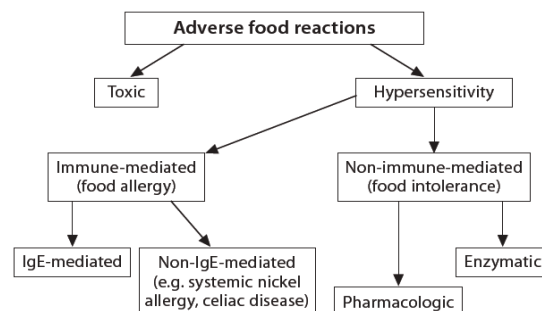
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## **ALLERGIE ALIMENTARI**

- Ogni risposta clinica ad un determinato alimento basata su una reazione immunologica anormale. Comprende reazioni mediate dagli anticorpi di tipo immunoglobuline E (IgE) o di altro tipo.

## **INTOLLERANZE ALIMENTARI**

- Comprendono ogni reazione che segue all'ingestione di un alimento (tossica, metabolica, o farmacologica) e non è di tipo immunologico; per la maggior parte dei casi sono causate da difetti enzimatici (es. intolleranza al lattosio).



- Le **intolleranze** sono reazioni causate da un componente di un alimento (istamina, caffeina, ecc...) o dalla mancanza nel nostro organismo di un enzima che lo metabolizzi.
- La più nota e diffusa è l'intolleranza al lattosio, che può manifestarsi a tutte le età ed è diagnosticabile con certezza solo con il "breath test".

C'è molta confusione:

- intolleranze ad alimenti invece che a componenti
- coinvolgimento di presunte "tossine" o "molecole particolari farmacologicamente attive presenti negli alimenti"

Sono note scientificamente l'intolleranza al glutine (celiachia) e quella al lattosio; alcune allergie vengono scambiate per intolleranze (come quella per il Ni).

Il 90% delle presunte intolleranze sono *intolleranze di secondo livello* o *false intolleranze* (sintomi gastroenterici legati ad altre problematiche)



- Le **allergie** sono causate da un allergene (generalmente una proteina antigene), che entra nel nostro organismo, provocando una reazione (orticaria, eruzione cutanea, gonfiori, asma, crampi addominali, prurito orale o diffuso) che può essere rapida (anche entro un'ora) oppure più lenta (fino a 24 ore dopo).
- Sono pochi gli alimenti responsabili della gran parte delle reazioni allergiche:
  - **nei primi anni di vita:** latte vaccino, uova, grano, soia, arachidi, noci, pesce e crostacei provocano il 90% delle reazioni
  - **nell'adulto:** i casi più frequenti riguardano arachidi e frutta secca, crostacei, molluschi, pesce e uova

Food allergy to preservatives, dyes, or other additives is uncommon to rare (Boden SR: Immunol Rev. 2011)

In common with other forms of allergic disease, food allergy develops in two stages:

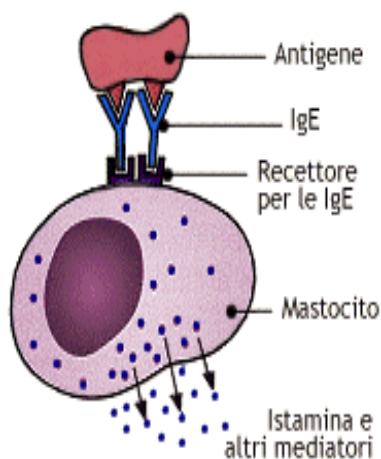
1. exposure to an allergen results in immunological priming and the acquisition of sensitisation.
2. If the sensitised subject is exposed subsequently via the diet to the same inducing allergen, then an allergic reaction may be provoked.

Food allergy can be classified into **IgE-mediated** and **non-IgE-mediated** allergy.

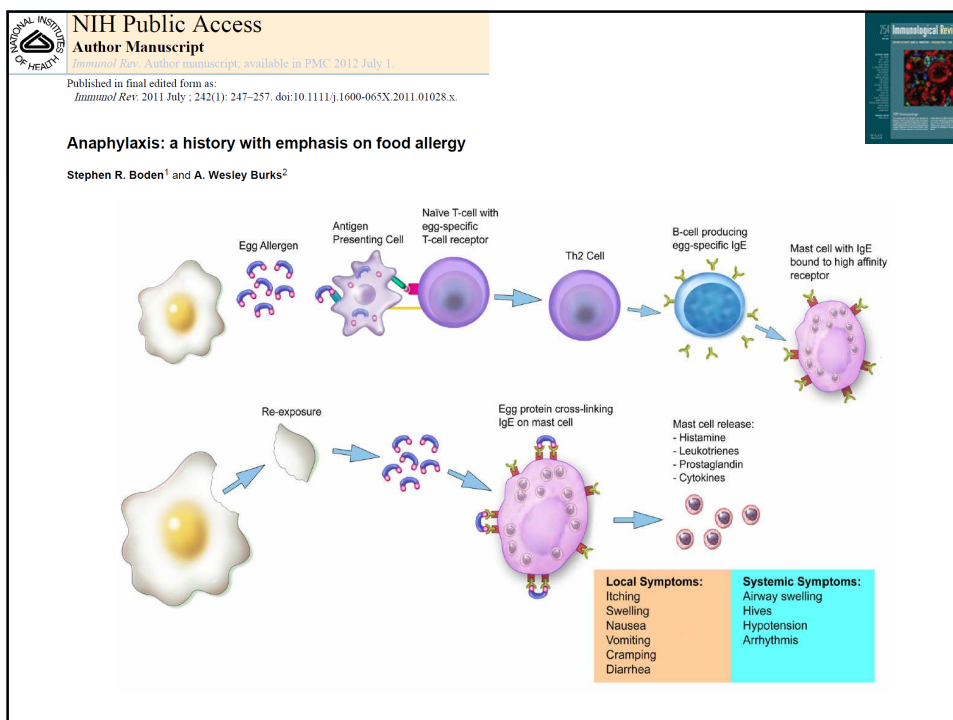
**IgE-mediated** reactions are acute and often have a rapid onset.

**Non-IgE-mediated** reactions are generally characterised by a delayed and non-acute onset.

**Mixed reactions** involve a mixture of both IgE and non-IgE responses.




- The classical model in food allergy states that mast cell bound IgE, which is retained by the high affinity receptor of IgE, FcεRI, recognizes the allergen with its respective specificities.
- Mast cell and/or basophil degranulation in the tissues elicits the typical hypersensitivity type I symptoms.
- Specific IgE can be detected by a skin prick test (SPT) against the eliciting food or it can be measured in serum.



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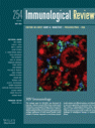
**Anaphylaxis: a history with emphasis on food allergy**  
 Stephen R. Boden<sup>1</sup> and A. Wesley Burks<sup>2</sup>

- Food allergy can vary with **geography**.
  - Sesame allergy is relatively uncommon in the US, yet it continues to be a major allergen in Israel and other parts of the world.
- Surveys that elicit self-reported food allergy indicate a **prevalence** of 3% to 35% of respondents have a food allergy of some type.
- In studies using **oral food challenges** (OFC) the prevalence of food allergy ranges between 1% and 10.8% (Rona RJ et al: J Allergy Clin Immunol 2007)
- Most food allergy reactions occur in early childhood **resolve with age**
  - 80% of children with allergy to milk or egg are able to tolerate ingestion by age 16 years (Savage JH et al: J Allergy Clin Immunol. 2007 ; Sktpak JM et al: J Allergy Clin Immunol 2007)
  - Peanut allergy, traditionally thought life-long, may spontaneously resolve for up to 20% of children by elementary school age (Sicherer SH et al: J Allergy Clin Immunol. 2007 ).
- **Recurrence** of peanut allergy has also been reported following successful OFC without continued exposure in the diet (Sicherer SH et al: J Allergy Clin Immunol. 2007 )



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**Anaphylaxis: a history with emphasis on food allergy**

Stephen R. Boden<sup>1</sup> and A. Wesley Burks<sup>2</sup>


- The **diagnosis** of food allergy is based on
  - skin prick testing and in vitro IgE measurements (information about food sensitization)
  - OFC (oral food challenge to determine tolerance to a food): gradually increasing servings of the suspected food
    - open OFC and single-blind OFC are commonly used to screen for reactions
    - double-blind, placebo control OFC (DBPOFC) remains the gold standard

(Bindslev-Jensen C, et al. *Allergy*. 2004; Bock SA, et al. *J Allergy Clin Immunol*. 1988)



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**Anaphylaxis: a history with emphasis on food allergy**

Stephen R. Boden<sup>1</sup> and A. Wesley Burks<sup>2</sup>

- **Current therapy** for food allergy is not curative
- The primary action is **avoidance of the identified food**
  - Patients, families, and caregivers must be educated to carefully read **food labels** when preparing meals and evaluate the safety of foods obtained from restaurants.
  - Recent changes in food-labeling laws in the United States now require **simple English terms** (e.g. 'milk' instead of 'casein') to indicate the presence of specific foods (the law applies only to milk, egg, wheat, soy, peanut, tree nut, fish, and shellfish)
  - Education should include information about **cross-contamination** of food during preparation (e.g. cutting boards or mixing bowls).
  - Patients and caregivers should be encouraged to obtain **medical identification jewelry**
  - Patients and caregivers must be educated to identify **symptoms of anaphylaxis** and trained to respond when symptoms arise.
  - A personalized, **written action plan** can aid families prepare a response to accidental ingestions




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### Anaphylaxis: a history with emphasis on food allergy

Stephen R. Boden<sup>1</sup> and A. Wesley Burks<sup>2</sup>

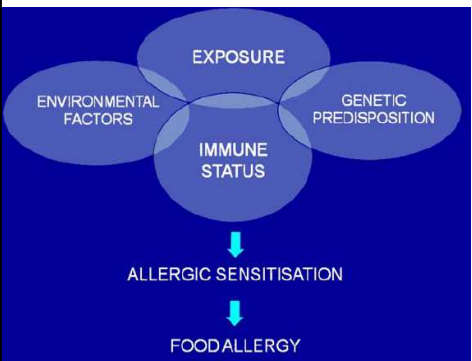
- **current treatment for food allergies significantly impacts ADL and QoL** (Pumphrey RS et al: *J Allergy Clin Immunol.* 2007; Cummings AJ, et al: *Allergy.* 2010).
- **Families report disruption of family social events, school field trips, parties, sleepovers, and play dates with friends.**
- **Children with food allergy also report anxiety** with regard to possible allergen exposure. Shopping, eating out, or birthday parties can be frightening for children who may perceive such activities as life threatening.
- **Because past reactions cannot predict the severity future reactions, patients with food allergy and their families worry that the next exposure may result in mortality**  
(Cummings AJ, et al, *Allergy* 2010; Bollinger ME, et al. *Ann Allergy Asthma Immunol.* 2006; Primeau MN, et al. *Clin Exp Allergy.* 2000; Avery NJ, et al. *Pediatr Allergy Immunol.* 2003)



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Review  
Food allergy – science and policy needs – The UK Food Standards Agency Research Programme  
Joelle Buck<sup>a,\*</sup>, Sue Hattersley<sup>a</sup>, Ian Kimber<sup>b</sup>



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graph TD
    EF([ENVIRONMENTAL FACTORS]) --- EX([EXPOSURE])
    EF --- IS([IMMUNE STATUS])
    EX --- IS
    EX --- GP([GENETIC PREDISPOSITION])
    IS --- GP
    IS --> AS[ALLERGIC SENSITISATION]
    AS --> FA[FOOD ALLERGY]
  
```

*under what circumstances does a dietary protein elicit an IgE antibody response resulting in the acquisition of sensitisation ??*

The development of sensitisation is known to depend upon:

- **nature of the food** and presence of proteins that are potentially able to elicit IgE antibody responses (potentially allergenic proteins)
- **inherent susceptibility of the individual** and possession of an atopic phenotype
- **conditions** (including magnitude, duration, route, timing and context) of exposure

The threshold of exposure for elicitation of a food allergic reaction during challenge of food allergic subjects, and the severity of those reactions, **differ between individuals**, and **vary with time** in the same individual.

Toxicology 278 (2010) 319–325

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TOXICOLOGY

Review

Food allergy – science and policy needs – The UK Food Standards Agency Research Programme

Joelle Buck<sup>a,\*</sup>, Sue Hattersley<sup>a</sup>, Ian Kimber<sup>b</sup>

- **certain foods** are frequently associated with food allergy
- particular foods commonly implicated as allergens are a reflection of the **national diet** and **food preferences**
- the introduction into the diet of **new foods** might be associated with the emergence, over time, of an increasing incidence of sensitisation and potentially allergy to proteins in those foods.
- Kiwi fruit (*Actinidia deliciosa* - *Chinese gooseberry*) is native to Southern China, but was first cultivated commercially in New Zealand.
- Kiwi fruit entered the UK diet gradually from the early 1970s.
- in the 1970s there was very little allergy to kiwi fruit, but reports became more common in the 1980s, predominantly in adults. (similarly to what happened in Finland and France; Mattila et al., 2003; Rance et al., 2005)
- Allergy to kiwi fruit became more evident in children and young adults the 1990s

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- **major kiwi allergen** to which people react in the UK maybe different to that previously described in other studies conducted elsewhere
- people developing kiwi fruit allergy, particularly children, were commonly found to have **other co-existing allergies**; some of these being cross-reactive allergies to fruits, tree pollen or latex, but others were to non-cross-reactive foods such as peanuts, tree nuts, milk, egg and grass pollen
- allergies to new foods introduced into the diet **may not become apparent** immediately after introduction
- if only **mild reactions** are seen initially, this does not necessarily mean that people will not develop severe reactions in future
- the safety of newly introduced foods includes their potential for **cross-reactivity** to known food allergens

## The *Anisakis* allergy debate: does an evolutionary approach help?

Trends in Parasitology, January 2012, Vol. 28, No. 1

Alvaro Daschner<sup>1</sup>, Carmen Cuéllar<sup>2</sup> and Marta Rodero<sup>2</sup>



- In 1990, *A. simplex* allergy was described for the first time in Japan (Kasuya, S. et al. Lancet, 1990)
- Then, a boom of publications and research in the field of *A. simplex* allergy began after a new report from Spain on *A. simplex* induced anaphylaxis in 1995 (Audicana M et al: J Allergy Clin Immunol 1995).
- Patients with acute allergic symptoms after consumption of parasitised fish **displayed specific IgE** against this nematode, and this parasite has from then on been handled as a potential food allergen.

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- Gastroallergic anisakiasis: an acute allergic reaction (urticaria/angioedema or anaphylaxis) which is produced in the context of an acute gastric parasitism by *A. simplex*, when the parasite attempts to penetrate the gastric mucosa
- several critical analyses demonstrated that acute allergic symptoms such as urticaria, angioedema or anaphylaxis are produced **only when the live larvae of *A. simplex* parasitise** the gastrointestinal tract
- Although no study to date has scientifically confirmed that nonviable *Anisakis* material is able to induce acute allergic reactions in humans, the vast majority of all laboratory studies claim their importance from the possibility of this type of allergy.



## The *Anisakis* allergy debate: does an evolutionary approach help?

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Alvaro Daschner<sup>1</sup>, Carmen Cuéllar<sup>2</sup> and Marta Rodero<sup>2</sup>

- several allergens of *A. simplex* have been characterized
- some of them have been claimed major allergens and/or pan-allergens

Table 1. Characterized allergens of *Anisakis simplex*

|                    | MW             | Compartment | Function                      | Positivity <sup>a</sup> | Major allergen? <sup>b</sup> | Pan-allergen? <sup>c</sup> |
|--------------------|----------------|-------------|-------------------------------|-------------------------|------------------------------|----------------------------|
| <i>Ani s 1</i>     | 24 kDa         | ESP         | Kunitz-type trypsin inhibitor | 85%                     | Yes                          |                            |
| <i>Ani s 2</i>     | 97 kDa         | Somatic     | Paramyosin                    | 88%                     | Yes                          | Yes                        |
| <i>Ani s 3</i>     | 41 kDa         | Somatic     | Tropomyosin                   | 4%?                     |                              | Yes                        |
| <i>Ani s 4</i>     | 9 kDa          | ESP         | Cystatin                      | 27%                     |                              |                            |
| <i>Ani s 5</i>     | 15 kDa         | ESP         | SXP/RAL protein               | 25–49%                  |                              |                            |
| <i>Ani s 6</i>     | 7 kDa          | ESP         | Serpin                        | 18%                     |                              |                            |
| <i>Ani s 7</i>     | 139 kDa        | ESP         | Glycoprotein                  | 83–100%                 | Yes                          |                            |
| <i>Ani s 8</i>     | 15 kDa         | ESP         | SXP/RAL protein               | 25%                     |                              |                            |
| <i>Ani s 9</i>     | 14 kDa         | ESP         | SXP/RAL protein               | 13%                     |                              |                            |
| <i>Ani s 10</i>    | 22 kDa         | Somatic?    | ?                             | 39%                     |                              |                            |
| <i>Ani s 11</i>    | 55 kDa         | Somatic?    | ?                             | 47%                     |                              |                            |
| <i>Ani s 11-li</i> | ? <sup>d</sup> | Somatic?    | ?                             | ?                       |                              |                            |
| <i>Ani s 12</i>    | ?              | ?           | ?                             | 57%                     | Yes                          |                            |

Abbreviations: MW, molecular weight; ESP, protein from excretory-secretory products.

<sup>a</sup>Positivity: percentage of IgE reactivity in *A. simplex* sensitized patients.<sup>b</sup>Major allergen: major allergens are recognized by >50% of patients displaying IgE against *A. simplex*.<sup>c</sup>Pan-allergen: highly conserved proteins, which can explain crossreactive antibodies of other food sources.<sup>d</sup>? = unknown.

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### *IgE: link between allergy and parasitology*

- Allergies and the immunologic response against helminth parasites share common pathways.
- Both are typical Th2-activated responses with production of IL-4, IL-13 and IL-9.
- IL-9 has its major effect on mast cells, is responsible for intestinal mastocytosis and sensitizes mast cells for further action of other cytokines or the effect of specific degranulation and mediator release.
- IL-4 and IL-13 have several activities and are paradigmatic of the Th2-deviated immune response, but IL-4 is responsible for the switch to IgE production and has effects on the smooth muscle, epithelial cells and goblet cells of the gastrointestinal tract to produce the 'weep and sweep' response;

**This is an evolutionary maintained response to eliminate larvae or minimize helminth burden**

Biotechnology Advances 30 (2012) 524–540

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Research review paper

**Role of transgenic plants in agriculture and biopharming**

Parvaiz Ahmad <sup>a,\*</sup>, Muhammad Ashraf <sup>b,c,f</sup>, Muhammad Younis <sup>c</sup>, Xiangyang Hu <sup>d</sup>, Ashwani Kumar <sup>e</sup>, Nudrat Aisha Akram <sup>b</sup>, F. Al-Qurainy <sup>f</sup>

- Plant scientists, by employing various genetic engineering techniques, are trying to increase crop production by developing high yielding crops, disease resistant crops (resistant to insects, fungi and bacteria), and crops with high nutritional value and biofuel production

**The safety assessment of transgenic plants is a**

- intersection of many disciplines: ecology, agronomy and molecular biology ⇒ food and environmental safety
- environmental consequences on worms, insects, birds, mammals and other organisms
- Rules and regulations on the “judicious” proper use and disposal of GM plants [Coordinated Framework for Regulation of Biotechnology (since 1986) , National Institutes of Health (NIH), United States Department of Agriculture (USDA), Animal and Plant Health Inspection Service (APHIS), the Environmental Protection Agency (EPA), Food and Drug Administration (FDA), ....]

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- the promoters of GM foods claim that they are environment-friendly, have no risk to human health, profitable for farmers
- many people are still of the firm view that GM foods can be injurious to human and animal health, because they have not been properly tested.

**it is not certain what types of long-term effects GM foods can cause**

1. transferring new genes into a food can alter the chemical composition of that food ⇒ different response to that food ⇒ developing **allergies** or causing long-term **toxicity**
2. several GM crops possess **antibiotic-resistance** genes that could be taken up by bacteria present in the body, thereby increasing bacterial resistance against antibiotics

## Assessment of the safety of foods derived from genetically modified (GM) crops

A. König<sup>a,\*</sup>, A. Cockburn<sup>b</sup>, R.W.R. Crevel<sup>c</sup>, E. Debruyne<sup>d</sup>, R. Grafstroem<sup>e</sup>,  
U. Hammerling<sup>f</sup>, I. Kimber<sup>g</sup>, I. Knudsen<sup>h</sup>, H.A. Kuiper<sup>i</sup>, A.A.C.M. Peijnenburg<sup>j</sup>,  
A.H. Penninks<sup>k</sup>, M. Poulsen<sup>h</sup>, M. Schauzu<sup>h</sup>, J.M. Wal<sup>l</sup>

### Assessment of allergenicity

- Food allergy is an important health issue, which is caused by certain food proteins, including proteins derived from plants.
- There is therefore a need to ensure that the products of novel genes introduced into GM crop are not allergenic and that the process of transformation does not cause unwanted changes in the characteristics and/or levels of expression of endogenous allergenic proteins.

## Assessment of allergenicity of foods from GM crops

- Is the recombinant protein **derived from an allergenic source or a known allergen**?
- Is the recombinant protein **able to induce de novo sensitisation**?
- Is the recombinant protein **cross-reactive with IgE antibodies raised by known allergens**, and therefore potentially capable of eliciting allergic reactions in already sensitised subjects?
- Has transformation itself in some **way altered the allergenic properties of a food derived from a GM crop** (such as, for instance, a change in the level of allergens endogenous to the host plant)?

## Edible Insects in a Food Safety and Nutritional Perspective: A Critical Review

Simone Belluco, Carmen Losasso, Michela Maggioletti, Cristiana C. Alonzi, Maurizio G. Paoletti, and Antonia Ricci

“all over the world monies worth billions of rupees are spent every year to save crops that contain no more than 14% of plant protein by killing another food source (insects) that may contain up to 75% of high-quality animal protein.”

Premalatha M et al: *Renew Sustain Energy Rev* 2011; 15(9): 4357–60.

- Finke and others (1989) reported that the house cricket (*Acheta domesticus*), when fed to weanling rats, was superior to soy protein as a source of amino acids at levels of intake.



Valine 0.84 1.02



fresh weight (silkworm pupae) and common animal foodstuffs fresh weight



|        |       |         |
|--------|-------|---------|
| 160.00 | nd    | 1000 mg |
| 0.80   | nd    | 10 mg   |
| 8.00   | 8.00  | 1000 mg |
| 1.60   | 1.26  | 10 mg   |
| 0.13   | 0.06  | 1.2 mg  |
| 17.0   | 26.00 | nd      |
| nd     | nd    | 1 mg    |

<sup>a</sup>Recommended daily allowances for adults.

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### **Allergy Hazard** (IgE-mediated allergy)

- Carmines dye is a biologically derived colorant obtained from the dried bodies of female cochineal insects (*Dactylopius coccus* Costa/*Coccus cacti* L) used as a food dye (juices, ice cream, yogurt, candy)
- Lentils infested with lentil pests, mainly *Bruchus lentis* (inhalation or ingestion  $\Rightarrow$  sensitization to legume/insect protein) was not clear
- Caterpillars (*Lophocampa caryae*) accidental ingestion  $\Rightarrow$  local and general effects (drooling, difficulty in swallowing, and generalized urticaria)
- Caterpillars (*Imbrasia belina*) and termites (sun-dried after the harvest to obtain a longer shelf-life) are commonly eaten usually sun-dried  $\Rightarrow$  cases of anaphylactic shock
- Silkworm Pupa: each year in China over 1000 patients experience anaphylactic reactions and 50 of them present a severe reaction requiring emergency room admittance



**«Grande è la  
confusione sotto il  
cielo. Quindi, la  
situazione è  
eccellente»**

**Mao Tse-tung**