

# Occupational allergic diseases as a clinical model to approach specific environmental reactivity

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**Abstract.** Hyperreactivity to environmental factors is objectively expressed as respiratory, cutaneous and gastrointestinal disease. Approaching the diagnosis of an occupational disorder, a practical distinction was made between toxicity and allergy. The study of occupational allergic disease included particular procedures that led to standardized models and concepts. The contribution to the improvement of medical knowledge is reviewed according to selected experiences. The diagnostic aspects of asthma, rhinitis, dermatitis and urticaria are considered as regards to methodology of assessment of the occupational etiology with attention to demonstrative examples, which are worthwhile for the general medicine, too. Basic steps of risk agent identification, exposure assessment, threshold dose response measurement, allergen challenges and interaction are the original contribution of the occupational medicine to the diagnosis of allergic disorder. The clinical picture of asthma was clarified by the results of the specific bronchial provocation test, proving the important role of di-isocyanates and metal salts. Occupational rhinitis showed to be connected to asthma with predictive aspects in bakers' disease. Occupational dermatitis was linked to the development of experimental patch tests. Occupational urticaria included the concept of airborne contact allergy or nickel interactive food and occupational sensitivity. Occupational allergic diseases are emerging as a consequence of low environmental exposure, but they were remarkably studied in the past either for pathogenesis or for diagnostic procedures. Methods and acquisition are available also for the general medicine when an individual's specific reactivity is under investigation.

**Key words:** occupational allergy, diagnostic model, bakers' disease, asthma epidemic, allergen challenge, bronchial reactivity patterns, skin allergy, metal salts sensitivity

## Introduction

The man-environment relationship includes several examples of individual hyper-reactivity, and when the immunological system is abnormally activated against environmental factors, we appropriately speak of either allergy or hypersensitivity.

In the occupational sector a sensitized worker may show an alteration of the immunological response which is based on the recognition of self and non-self substances by macrophages and T-lymphocytes of his organism leading to adverse effects caused by agents that are normally well tolerated by other workers. The exposure at work to these possibly sensitizing agents,

either in situ or through indirect pollution, shapes particular study models of the cause-effect relationship in individuals. We have had this experience within the framework of modern occupational medicine especially for diagnostic purposes.

All cases of suspected occupational allergy have three main features: symptoms occurrence after exposure to low doses, individual manifestation in relation to a group of exposed workers and a latency period after starting a health hazardous job. The diseases show the clinical picture of asthma, rhinitis, dermatitis, urticaria, but only a part has been proved to have a typical allergic mechanism mediated by IgE- or lymphocytes, while others still need further experimental in-

vestigation or have a different immunological pathogenesis.

This report is aimed at putting forward some acquired concepts and methods that may be considered a contribution of the occupational medicine to the environmental and general medicine. The reviewed examples come from the author's personal experience as well as from the heritage of the occupational allergy development.

## Procedures and models

### *The march of allergy: baker's rhinitis and asthma*

The baker's disease is the oldest item of occupational pathology, but till the 1970s the cause was ascribed to allergy due to wheat flour contaminant insects, like *Sitophilus granarius*. Now a lot of studies have proved the role of an IgE-mediated allergy to wheat proteins (high molecular weight > 15.000 Dalton) and showed that a repeated long term exposure leads to a natural progressive history of non/symptomatic sensitization, rhinitis and asthma, with an important time-variability according to the type of performed task (1). The whole methodology of the occupational medicine can be applied to the baker's disease and bakeries as follows: (i) identification of the risk agent (wheat flour dust), (ii) measurement of risk (dust concentration, (iii) dust particles diameter, allergenic components), (iv) evaluation of worker's exposure (job activities and personal exposure measurement), (v) early sensitization (detection of specific IgE), (vi) clinical diagnosis, (vii) modification of job organisation and use of protective devices), (viii) preventive care and immunization by allergenic vaccine, (ix) verification of outcome, and (x) re-employment. Nowadays, the baker's allergy march may be stopped without work interruption, and a similar procedure may be transferred to other allergic agents of life-environment such as pollen, mites or moulds. Baker's asthma is one of the few allergic diseases that can be dominated by establishing a global care system avoiding work prohibition and carrying out preventive environmental and individual measures on bakeries and bakers at the work place (2).

### *Asthma epidemic and new agents*

While for natural agents in the occupational settings new allergenic factors may be detected by studying a single abnormal case (sentry event) and so building a basis to recognize other subsequent cases, the documentation of new chemical sensitizer has been often the consequence of an epidemic asthmatic disorders because of particular industrial work technologies. This has been the case of di-isocyanates in the furniture industry, with the use of poliurethanic varnishes since 1968 in Lombardy (3). As far as TDI, HDI and MDI are concerned there has been a lot of literature and an IgE-mediated mechanism could be detected during the former important exposure in spray-painters (4, 5). Presently other immunotoxic mechanisms seem to be activated in the airway inflammation due to low exposure (6). But the case of phenylglycine acid chloride used to be absolutely demonstrative many years ago (7, 8). This small powdered chemical substance is a pharmaceutical intermediate compound which is used during the process of synthesis of ampicillin and cephalexin. It is highly reactive (like di-isocyanates) and irritant, but it is also a strong sensitizer. Facing an epidemic of asthmatic disorder in a factory and investigating the affected subjects and their unaffected co-workers, an intradermal test with protein-conjugate and an IgE-RAST were validated by carefully administering a bronchial provocation test as a gold standard thus making it possible to document the IgE-mediated allergic pathogenesis (9).

This fact led to a renewal of production technologies avoiding the inhalation of the allergic compound. From a medical point of view it was clearly shown how real allergic properties of a small molecule (low molecular weight) linked to and modified the human IgG globulins generating a true allergen inside the human body.

### *Different patterns of bronchial reaction to allergen challenge*

In 1972 in London (10), Pepys was the first to propose a clinical test based on specific challenge in an inhalation chamber with occupational agents. In the

same year and independently in Milan (11) a similar occupational test was performed with asthmatic painters (Fig. 1) In both cases the substance was toluene di-isocyanate of paint and in both cases two different onsets of bronchospasm were documented in different subjects after the same single exposure. This was the starting point of the theory of an early bronchial response, a delayed response, a dual response and a unique prolonged response depending on susceptibility of patients and their individual drug modulation. Such a fourfold model of bronchial reactivity was confirmed for many natural or chemical substances and the procedures of the controlled exposures were standardized first in Italy and later in Europe (12-14) to make a diagnosis by using a predictive tool while new devices for aerosolization of powders or inhalation of vapours were developed for experimental dose-response studies (15).

In our experience (16) with nickel challenges (Fig. 2) the intensity, but not the pattern of the bronchial reaction is influenced by the airborne concentration during exposure. Neither did wheat flour challenges confirm a different prevalence of early or late reaction in subjects exposed to 10 or 100 mg per cubic meter in the inhalation chamber. By this method, besides the cereal flour or di-isocyanates, the

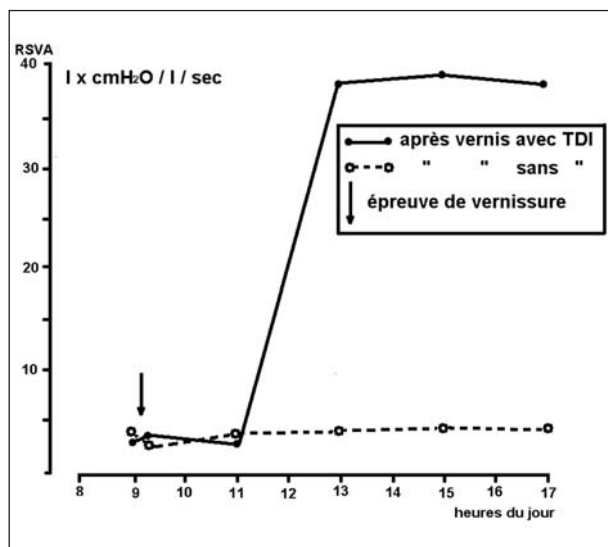


Figure 1. Airways specific resistances variation during the day, after two single challenges with sprayed varnish with and without TDI (From historical quotation #11)

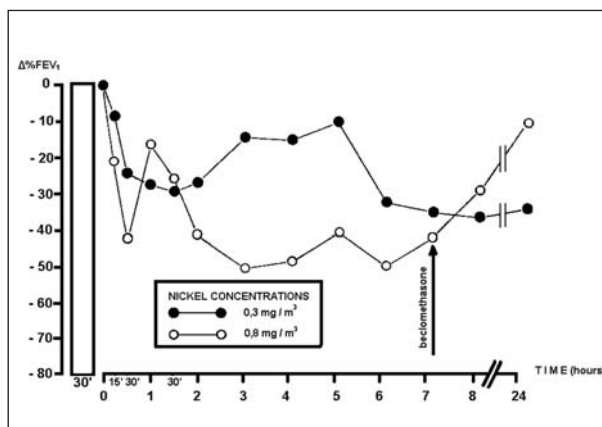


Figure 2. Specific bronchial reactivity to nickel sulphate challenge after two different tentative exposures with different concentration. (From quotation #16)

asthmatic sensitizing property of metal salts were documented for chromium, nickel, cobalt or copper (16), and it was interesting to elicit how steel welders reacted to either nickel or chromium or to various chromium speciation in the same subject (Fig. 3).

The classification of the reactivity has been transferred to nasal response in subjects undergoing challenges by inhaling occupational agents causing either asthma or rhinitis through nose and mouth (17), and generally nasal onset occurred before asthmatic symptoms (18, 19). The occupational model test type has been adopted also for studying pollen exposure reactivity in the Vienna Chamber.

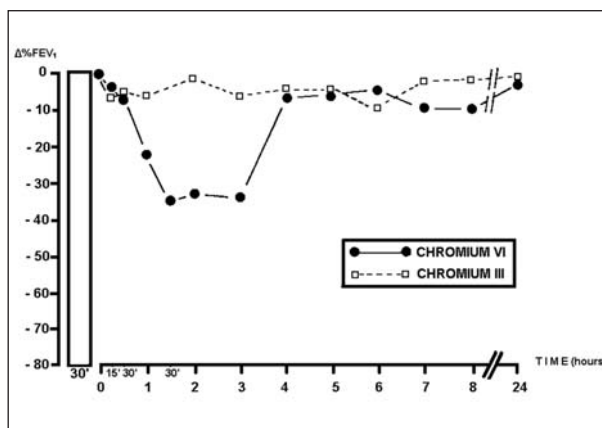


Figure 3. Bronchial responsiveness to chromium VI (0,15 mg/m<sup>3</sup> for 30') and Chromium III (0,26 mg/m<sup>3</sup> for 30') exposure in inhalation chamber (From quotation #16)

### *The case of new contact dermatitis*

Occupational Health Units or Dermatological Health Units have the advantage of collaborating with an industrial hygiene laboratory. Most of the cases of suspected allergic contact dermatitis can be studied through specific patch tests based on freshly made preparation and experimentally controlled evaluation. The continuous development of knowledge from the occupational sector in skin allergy treatment has been promoted considerably by the publication of scientific clinical case studies (20, 21) which is manifest in the occupational patch test series prepared by specialized companies and on-line data base support orienting and dermatologists when performing complicated diagnoses of chemical contact eczemas. Moreover, some occupational teams acquired specific experience in developing patch tests for commercial industrial products which may induce an abnormal irritant or sensitizing skin reactivity. Another important concept introduced by the occupational allergy research is the occurrence of airborne contact dermatitis caused by vapour or aerosole with special occupational activity in the food and metal industry.

### *The interaction between lifestyle and work aspects in allergic disease*

The widespread nickel allergy may cause contact eczema, rhinitis and asthma in skilled workers like welders or metal plating employees as well as urticaria through food allergy. Urticaria may be connected to nickel gastrointestinal intake, but also to occupational airborne absorption. Its manifestation, either associated or not with contact dermatitis is modulated by the nickel concentration in the blood and urine of allergic people (22). This is a typical example of interaction between food habits (nickel is included in several fruits and vegetables) and the occupational risk in nickel exposed workers. Biological monitoring and dieting may prevent the on set of this specific urticarian allergy associated with nickel exposure.

### **Conclusion**

For many years questions were proposed about the importance of toxic versus allergic agents in the

induction of syndromes or specific diseases only in certain subjects as a consequence of their work. Often an agreement about an objective demonstration was missing. Today we can conclude that several clinical manifestations formerly included in the great chapter of intoxication and thus explained by a toxicological mechanism, may be documented as due to an allergic or, more extensively, immunological mechanism. This is the value of occupational allergy as a field of practice and studies, whose models and concepts have been acquired by the general medicine.

For diagnostics and job fitness evaluation, a classification of subjects suspected to be allergic may be appropriately divided into four categories, according to the outcome of documentation of its mechanism: *truly allergic subjects* (IgE-mediated), *sensitized subjects* (IgE-independent, but surely immunologic), *susceptible subjects* (abnormally reactive to low doses of irritants) and *psycho-allergic* (neuro-behavioural responders).

This is the categorization that, coming from an historical review of occupational indoor allergies, is currently also adopted for environmental outdoor and general indoor allergies in the medical practice and for any other allergological investigation.

### **References**

1. Cirila AM. Rinite e asma da farina di frumento. Atti XXI Congr. Naz. S.I.A.I.C. Ed. OIC Incentive, Milano, 1994, 61-6.
2. Cirila AM. Specific immunotherapy in wheat flour induced occupational allergy. Immunological indicators on the effectiveness. Abstract Book 16<sup>th</sup> E.A.A.C.I Congress, Madrid June 1995-Allergy 1995, 50: 87-8.
3. Cirila AM, Sala C, Zedda S. Il problema degli isocianati nell'industria. Dalla patologia al controllo del rischio. *Med Lavoro* 1978; 69: 393-412.
4. Nava C, Arbosti G, Briatico G, Cirila AM, Marchisio M, Zedda S. Pathology produced by isocyanates; methods of immunological investigation. *La ricerca Clin Lab* 1975; 5: 135-45.
5. Zedda S, Cirila AM, Aresini G, Sala C. Occupational type test for the ethiological diagnosis of asthma due to toluene di-isocyanate. *Respiration* 1976; 33: 14-21.
6. Mapp CE, Saetta M, Maestrelli P, et al. Mechanisms and pathology of occupational asthma. *Eur Respir J* 1994; 7: 544-54.
7. Cirila AM, Nava C, Sala C, Zedda S. Occupational allergy due to Phenylglycine Chloride Hydrochloride. *Med Lavoro* 1976; 67: 416-26.

8. Kammermeyer JK, Mathews KP. Asthma due to Phenylglycine acid Chloride. *J All Clin Immunol* 1973; 52: 73-8.
9. Cirla AM, Falagiani P, Achille G, Meregalli G, Nava C. Esperienze di diagnosi con il RAST nella patologia da fenilglicina cloruro cloridrato. *Med Lavoro* 1980; 71: 82-87.
10. Pepys J, Pickering CA, Breslin AB, Terry DJ. Asthma due to inhalation of chemical agents; toluene diisocyanate. *Clin Allergy* 1972; 2: 225-32.
11. Cirla AM, Zedda S, Nava C. Pathologie respiratoire dans l'emploi des vernis aux isocyanates dans l'industrie des meubles. Proceedings First International Symposium of Occupational Medicine in Chemical Industry-MEDICHEM ed, Ludwigshafen 1972, 330-7.
12. Cirla AM, Moscato G. Normalizzazione delle prove di broncoreattività specifica professionali in medicina del lavoro. Gruppo di studio della SIMLII. *G Ital Med Lavoro* 1983; 5: 117-21.
13. Cirla AM, Gherson G, Innocenti A, et al. Diagnosi delle malattie professionali da ipersensibilità. Patologie respiratorie (Position Statement). *Giorn It Allergol Immunol Clin* 1991; 1: 625-53.
14. Maestrelli P, Baur X, Cirla AM, et al. Guidelines for the diagnosis of occupational asthma (Subcommittee on Occupational Allergy of European Academy of Allergy Clinical Immunology). *Clin Experim Allergy* 1992; 22: 103-8.
15. Cloutier Y, Lagier F, Lemieux R, et al. New methodology for specific inhalation challenges with occupational agents in powder form. *Eur Respir J* 1989; 2: 769-77.
16. Cirla AM. Asthma induced by occupational exposure to metal salts. *Folia Allergol Immunol Clin* 1985; 32: 21-8.
17. Desrosiers M, Nguyen B, Ghezzi H, Malo JL. Nasal response in subjects undergoing challenges by inhaling occupational agents causing asthma through the nose and mouth. *Allergy* 1998; 53: 840-8.
18. Palczynski C, Krakowiak A, Ruta U, et al. Nasal response to allergen challenge in patients with immediate asthmatic reaction. *Allergol Immunopathol* 1996; 24: 163-8.
19. Malo JL, Lemièrre C, Desjardins A, Cartier A. Prevalence and intensity of rhinoconjunctivitis in subjects with occupational asthma. *Eur Respir J* 1997; 10: 1513-15.
20. Sertoli A. Dermatologia allergologica professionale ed ambientale. Il Pensiero Scientifico Ed., Roma 1991
21. Crippa M, Baruffini A, Belleri L, et al. Occupational dermatitis in a highly industrialized Italian region: the experience of four occupational health departments. *Sci Tot Envir* 2001; 270: 89-96.
22. Cirla PE, Pisati R, Cirla AM. Dermopatie allergiche e assorbimento di nickel: studio in 128 soggetti sensibilizzati. *G Ital Med Lavoro Erg* 2002; 24: 244.