Eur Respir J, 1994, 7, 761–767
DOI: 10.1183/09031936.94.07040761
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European Respiratory Journal
ISSN 0903 - 1936

SERIES 'OCCUPATIONAL ASTHMA'
Edited by C. Mapp

Prognosis of occupational asthma

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Prognosis of occupational asthma. P.L. Paggiaro, B. Vagaggini, E. Bacci, L. Bancalari, M. Carrara, A. Di Franco, D. Giannini, F.L. Dente, C. Giuntini. ©ERS Journals Ltd 1994.
ABSTRACT: Several studies on the prognosis of occupational asthma have shown that a significant proportion of patients continue to experience asthmatic symptoms and nonspecific bronchial hyperresponsiveness after cessation of work. The determinants of this unfavourable prognosis of asthma are: long duration of exposure before the onset of asthma; long duration of symptoms before diagnosis; baseline airway obstruction; dual response after specific challenge test; and the persistence of markers of airway inflammation in bronchoalveolar lavage fluid and bronchial biopsy. The relevance of immunological markers in the outcome of occupational asthma has not yet been assessed.

Further occupational exposure in sensitized subjects leads to persistence and sometimes to progressive deterioration of asthma, irrespective of the reduction of exposure to the specific sensitizer, and only the use of particular protective devices effectively prevents the progression of the disease. A long-term follow-up study of toluene diisocyanate (TDI)-induced asthma showed that the improvement in bronchial hyperresponsiveness to methacholine occurred in a small percentage of subjects and only a long time after work cessation. Bronchial sensitivity to TDI may disappear, but nonspecific bronchial hyperresponsiveness often persists unchanged, suggesting a permanent deregulation of airway tone. Steroid treatment significantly reduces nonspecific bronchial hyperresponsiveness only when started immediately after diagnosis.
Eur Respir J., 1994, 7, 761–767.

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Keywords: Asthma
bronchial hyperreactivity
occupational exposure
toluene diisocyanate

Received: July 20 1993
Accepted for publication September 12 1993

The outcome of occupational asthma after diagnosis has been studied by several authors. Because occupational asthma is defined as a reversible airway obstruction causally related to exposure in the working environment [1], it could be expected that removal from occupational exposure to the specific sensitizing agent leads to complete recovery from the disease. Unfortunately, this favourable prognosis can be observed in only a small percentage of patients with occupational asthma, whereas, in most of them, symptoms and bronchial hyperresponsiveness persist, although often at a decreased level.

The mechanism of the persistence of occupational asthma after work cessation is unknown. Very few morphological and physiological data are available on this topic. The pathophysiology of this phenomenon may be similar to that underlying the persistence of allergic asthma after cessation of allergen exposure (chronic persistent asthma); thus, studies on the outcome of asthma after diagnosis may provide useful clues to understanding the pathophysiology of asthma [2].

Follow-up of symptoms and nonspecific bronchial hyperresponsiveness (NSBH) after cessation of work

Several authors have reported that cessation of occupational exposure was associated with a decrease in asthma symptoms and an improvement in NSBH in only 50% of asthmatic subjects. On the other hand, the persistence of occupational exposure caused a further impairment of respiratory function and bronchial hyperreactivity. Follow-up studies over a maximum of 4–5 yrs showed that in most cases NSBH persisted indefinitely.

In 1975, ADAMS [3] observed that most patients with toluene diisocyanate (TDI)-induced asthma still complained of respiratory symptoms 2–11 yrs after cessation of exposure. LAM *et al*. [4] reported a significant improvement in NSBH, as shown by an increase in the provocative concentration of methacholine required to induce a 20% fall in forced expiratory volume in one second (FEV_1) (PC_{20}%FEV_1), in patients with occupational asthma several months after the end of occupational exposure. BUTCHER *et al*. [5] reported on a worker exposed to isocyanates who lost airway hyperreactivity to both methacholine and TDI one year after the end of occupational exposure. We studied [6] 27 workers with asthma induced by TDI. Two years after diagnosis, 8 of the 12 patients who had left their job still complained of dyspnoea and wheezing, and only one of the 15 patients with markedly reduced exposure to TDI had recovered from asthma attacks. NSBH persisted or increased in most patients. Similar results have been observed in other models of occupational asthma, such as red cedar asthma [7, 8] or colophony [9], and in recent years these observations have

been confirmed by other studies on asthma induced by TDI [10–19] and by other occupational exposures, such as snow crab processing [14, 15].

Very few prospective studies are available to assess whether NSBH can be induced by the development of occupational asthma and can then improve after cessation of work. Recently, CHAN-YEUNG and DESJARDINS [16] described four workers from a cedar sawmill whose NSBH had been repeatedly measured over several years before and after the development of occupational asthma. NSBH was absent before asthma symptoms, and developed in parallel with the development of asthma, indicating that NSBH is not a predisposing host factor for occupational asthma.

Determinants of the outcome of occupational asthma

The determinants of an unfavourable outcome of occupational asthma after diagnosis can be clinical, immunological or morphological.

Clinical determinants

In 1982, CHAN-YEUNG and co-workers [8] examined the determinants of an unfavourable outcome of occupational asthma due to western red cedar. Asthma induced by Western red cedar (*Thuja plicata*) is similar to other types of asthma due to simple chemicals (*e.g.* isocyanates) as to the pattern of specific airway response and other clinical features [17]. A follow-up study of 232 patients with red cedar asthma showed that the 81 patients who were still symptomatic 4 yrs after cessation of work, had a longer duration of occupational exposure before the onset of symptoms, a longer duration of symptoms before diagnosis and a greater reaction to plicatic acid during specific bronchial provocation test than the 55 subjects who became asymptomatic after cessation of work. Patients who were still symptomatic at follow-up had a lower FEV_1 and forced mid-expiratory flow (FEF_{25-75}) at diagnosis. Patients who became asymptomatic had an improvement in spirometric measurements at follow-up, whereas those who were still symptomatic showed a decline in pulmonary function even after cessation of exposure. PC_{20} methacholine, measured in 102 patients, increased significantly at follow-up only in subjects who became asymptomatic, whereas it did not change in subjects who still complained of respiratory symptoms.

COTÉ *et al*. [18] re-examined 48 of the 68 patients with cedar asthma who were still working in the same plant after a mean follow-up of 6.5 yrs. When changes in asthma symptoms, medication requirement, FEV_1 and PC_{20} methacholine were evaluated, 5 of the 48 patients improved, 25 remained stable, 18 deteriorated, and none recovered. Age, atopy, smoking habits, and the presence of specific immunoglobulin E (IgE) to plicatic acid were not useful in predicting the outcome. Reduction of exposure and the use of an airstream helmet did not prevent deterioration of asthma. Only the use of the twin-cartridge respirator was associated with a favourable outcome.

Immunological determinants

VENABLES and co-workers [19] observed that specific serum IgE against tetrachlorophthalic anhydride-human serum albumin (TCPA-HSA) conjugate decreased in subjects with TCPA-induced asthma after cessation of exposure. When specific serum IgE concentration was plotted against time, a significant correlation was observed in 5 out of 6 subjects with an IgE half-life of 1 yr. Skin reaction to TCPA-HSA also decreased, although there was variation between tests. Because of the persistence of high levels of specific serum IgE and of positive skin reaction after cessation of exposure, the authors hypothesized that the patients may still have some contact with the sensitizing agent without being aware of it. Alternatively, TCPA may be retained in the lungs, either bound to particles of epoxy resin or bound to tissue proteins, thus stimulating IgE production. Also, once started, IgE production might become partly independent of the presence of the antigen/hapten.

In a study on subjects with asthma induced by snow crab processing, MALO *et al*. [20] observed that specific serum IgE decreased significantly over the follow-up period, with a half-life of 20 months.

Thus, in IgE-mediated asthma the persistence of high levels of specific serum IgE even after the end of exposure might explain the persistence of the disease, although in both studies no attempt was made to correlate IgE levels with functional data or symptom score.

Morphological determinants

To evaluate the morphological basis of the difference in outcome of TDI-induced asthma after the end of occupational exposure, we studied 10 patients with bronchial hyperresponsiveness to methacholine and a positive TDI challenge test at diagnosis [21]. After diagnosis, all patients stopped working. Over a 4–40 month follow-up, each patient underwent a methacholine challenge test 3–8 times. Three to 39 months after the end of TDI exposure and in the absence of any acute exacerbation of the disease, the same patients underwent bronchoalveolar lavage (BAL) (table 1). Total cells in BAL fluid were moderately increased in four patients, eosinophils were increased in five and neutrophils in eight of the 10 patients. Eight patients also had mucosal biopsy of main or lobar bronchi: most of them showed epithelial damage and thickening of basement membrane, as well as mild to moderate inflammation in the submucosa, represented mainly by lymphocytes, eosinophils and neutrophils. There was no relationship between cellularity in BAL and responsiveness to methacholine.

Mucosal biopsies from subjects exposed to inorganic dusts showed similar findings, except for the absence of eosinophils in BAL and a lesser degree of basement membrane thickening and of inflammation in the submucosa. Only five out of the 10 patients had a significant improvement in responsiveness to methacholine, as shown by a positive significant linear regression between months of work cessation and $PD_{20}FEV_1$ methacholine. Of these

Table 1. – Results of bronchoalveolar lavage in 10 toluene diisocyanate (TDI) asthmatic patients and in 4 nonasthmatic subjects

Pt	Recovery %	Total cells $\times 10^6$	Macrophages %	Macrophages ($\times 10^6$)	Lymphocytes %	Lymphocytes ($\times 10^3$)	Neutrophils %	Neutrophils ($\times 10^3$)	Eosinophils %	Eosinophils ($\times 10^3$)	Other cells %
TDI asthmatics											
MG	51	13.2	91	(12.0)	6	(778)	2	(290)	<1		-
AL	43	7.0	84	(5.8)	11	(770)	3	(182)	<1		1.3
CE	30	4.2	74	(3.1)	12	(504)	3	(126)	4	(168)	7.0
MR	31	11.5	78	(8.9)	6	(690)	10	(1150)	6	(690)	-
ST	40	4.0	63	(2.5)	17	(680)	11	(44)	1	(40)	8.0
ND	32	6.0	84	(5.0)	4	(240)	1	(60)	11	(660)	-
GG	65	4.8	71	(3.4)	16	(768)	<1		12	(576)	-
LG	50	22.0	81	(17.7)	5	(1078)	14	(3058)	<1		-
AP	44	9.0	89	(8.0)	2	(180)	4	(360)	5	(450)	-
MN	33	4.8	86	(4.1)	7	(336)	6.5	(312)	<1		7.0
Mean	42	8.7	80	(7.1)	9	(602)	5.5	(600)	4.1	(282)	5.8*
SD	11	5.7	9	(4.8)	5	(282)	4.7	921)	4.4	(279)	3.1
Nonasthmatics											
QL	50	14	94	(13.2)	6	(840)		<1	<1		-
NG	55	12	91	(10.9)	8	(960)		<1	<1		-
GG	60	10.6	95	(10.1)	5	(530)		<1	<1		2
TA	55	12	86	(10.3)	9	(1080)	4	(480)	<1		-
Mean	55	12.2	92	(11.1)	7	(852)	1.4	(166)	<1		
SD	4	1.4	4	(1.4)	2	(236)	1.8	(210)	-		
Normal	>40	5–8	93±8		7±1		1		1		-

Absolute values are give in parentheses. In the mean <1 was calculated as 0.5. Other cells: epithelial cells. *: calculated on four patients. (Reprinted from [21] with permission).

five patients, only one had increased eosinophils in BAL, whereas increased eosinophils were observed in all except one of the patients with persistent hyperresponsivess to methacholine. These data suggest that persistent NSBH in TDI asthma after cessation of work may be related to an inflammatory reaction in which eosinophil infiltration seems to be a major determinant.

Recently, SAETTA *et al*. [22] compared the morphological findings observed in TDI asthmatic subjects at diagnosis and 6 months after cessation of exposure to TDI. At diagnosis, epithelial basement membrane was significantly thicker in asthmatic subjects than in control subjects, but 6 months after the end of TDI exposure the basement membrane thickness was significantly reduced and no longer different from that of control subjects. Moreover, inflammatory cell numbers in the lamina propria were significantly higher in asthmatic subjects than in controls, but a significant decrease was observed in only three out of six subjects after the end of occupational exposure. Most eosinophils and mast cells were fully or partially degranulated in the lamina propria of asthmatic subjects, but this finding did not change with the end of TDI exposure. However, no significant correlations were found between morphological and functional data, such as responsiveness to methacholine, either at diagnosis or 6 months after cessation of exposure. In a subsequent study [23], the same authors observed a reduction in the number of submucosal mast cells in patients with TDI asthma 6–18 months after the end of TDI exposure. The number of submucosal mast cells correlated significantly with the thickness of reticular basement membrane, thus suggesting that mast cells may modulate subepithelial collagen deposition.

These data show that airway inflammation is a major feature of TDI asthma. However, the persistence of bronchial hyperresponsiveness to methacholine may depend only partially on the presence of inflammation in the airways.

Time course of changes in NSBH after cessation of work

The time course of changes in NSBH after diagnosis in occupational asthma has not been well characterized.

MALO *et al*. studied 31 workers with occupational asthma caused by snow-crab processing [20]. The follow-up was 64±6.3 months after leaving work and the subjects were examined 1, 2 and 5 yrs after diagnosis. At diagnosis, all 31 subjects required medication for asthma, 11 had a FEV_1 <85% of predicted, and all subjects were hyperreactive to methacholine. A significant improvement in pulmonary function and in the use of medication was observed only at the first follow-up examination, with no further improvement afterwards. A progressive, significant improvement in NSBH was observed up to the second follow-up examination, and a plateau was then reached about 2 yrs after cessation of exposure.

We recently studied the time course of the changes in nonspecific and specific airway reactivity in a small group of subjects sensitized to TDI, who were examined several times over a mean follow-up period of 48 months [24].

Table 2. – Clinical data of 16 subjects with toluene diisocyanate-induced asthma at diagnosis

Pt	Sex	Age yrs	Smoking habit	Exposure duration yrs	Disease duration yrs	FEV_1 %
TG	F	38	NS	21	2	76
BG	F	41	NS	11	6	89
AS	M	54	ES	15	1	69
MB	M	28	ES	13	0.5	88
IC	M	37	NS	18	5	87
AP	M	41	S	6	1	62
MG	M	41	ES	27	3	100
GG	M	46	ES	32	1	67
SP	F	42	NS	18	15	85
CE	F	50	NS	15	3	71
ND	F	44	NS	33	8	89
ST	M	55	NS	17	0.5	83
PA	M	58	ES	31	2	83
MR	M	62	NS	32	10	79
MN	M	51	ES	30	1	70
AL	M	59	S	12	1	109

NS: nonsmokers: ES: ex-smoker; S: smoker; FEV_1: forced expiratory volume in on second. (Reprinted from [24] with permission).

Table 2 shows the clinical data of 16 subjects with TDI-induced asthma. Baseline FEV_1 was 82±12%, the duration of exposure in the furniture industry was 20.7±8.9 yrs, and the duration of symptoms before diagnosis was 3.8±4.1 yrs (range 0.5–15 yrs). Eight out of 16 subjects were nonsmokers, 6 were ex-smokers and two were smokers. After diagnosis, nine subjects completely ceased work. The remaining seven subjects were relocated in a different area of the plant, with no direct exposure to TDI.

Table 3 shows individual values of $PD_{20}FEV_1$ methacholine both at diagnosis and at the end of follow-up, and the correlation coefficients of the linear regression between months of follow-up and $PD_{20}FEV_1$ methacholine. At the end of follow-up examination, only six of the 16 subjects had a $PD_{20}FEV_1$ methacholine >1 mg (which is the cut-off value for a significant bronchial hyperresponsiveness in our laboratory). A significant positive correlation between months of follow-up and PD_{20} FEV_1 methacholine was observed in five out of the 16 subjects: four had ceased and one had reduced TDI exposure.

$PD_{20}FEV_1$ methacholine tended to increase over time, but only after 45 months of follow-up did the increase become significant, and only when subjects were considered all together (fig. 1). When subjects who ceased work and those who reduced TDI exposure were considered separately, $PD_{20}FEV_1$ tended to increase in both groups, but it did not reach statistical significance. At diagnosis, all patients complained of dyspnoea and wheezing. During the follow-up, asthmatic symptoms decreased, without disappearing, in 10 of the 16 subjects; in four of the 10, drug therapy was progressively reduced.

Table 3 shows the pattern of response to specific bronchial provocation test (sBPT) with TDI and $PD_{20}FEV_1$ methacholine of asthmatic subjects at diagnosis and at the end of follow-up. At the end of follow-up, nine of the 16 subjects were no longer responsive to TDI (five had reduced and four had ceased TDI exposure). However, only five of them showed a $PD_{20}FEV_1$ methacholine >1 mg at the time of the last BPT. In subjects still responsive to TDI, the pattern of response to BPT did not change in five subjects, whereas in two subjects dual asthmatic response (DAR) changed into an isolated early asthmatic response (EAR) or late asthmatic response (LAR).

Table 3. – $PD_{20}FEV_1$ methacholine and pattern response to sBPT with TDI, at the first examination (first at diagnosis) and at the end of the follow-up period (last), and correlation coefficients (r) between months of follow-up and $PD_{20}FEV_1$ methacholine, in asthmatic subjects who reduced or completely ceased occupational exposure to TDI

Patient +	Follow-up months	No. obser.	Methacholine $PD_{20}FEV_1$ mg 1st	Last	r	p	Pattern of response to sBPT 1st	Last
Reduction of TDI exposure								
TG	25	8	0.015	0.035	0.05	0.83	Dual	Neg
BG	59	7	0.060	0.065	0.06	0.98	Early	Neg
AS	48	4	0.116	>3.200	0.99	0.008*	Late	Late
MB	54	6	0.589	0.689	0.11	0.99	Early	Neg
IC	24	5	0.303	0.560	0.46	0.42	Late	Late
AP	60	9	0.638	>3.200	0.50	0.20	Dual	Neg
MG	48	4	0.300	1.335	0.22	0.59	Early	Neg
Cessation of TDI exposure								
GG	63	7	0.100	2.333	0.89	0.01*	Dual	Neg
SP	41	6	0.390	0.027	0.87	0.05	Dual	Dual
CE	63	10	0.022	0.019	0.02	0.95	Dual	Early
ND	18	3	0.073	0.231	0.98	0.01*	Dual	Dual
ST	46	9	0.663	0.243	0.05	0.88	Dual	Late
PA	31	3	0.200	3.116	1.00	0.01*	Late	Neg
MR	73	9	0.300	0.063	0.27	0.51	Late	Late
MN	60	10	0.088	>3.200	0.93	0.002*	Late	Neg
Al	60	4	0.300	0.749	0.57	0.30	Late	Neg

*: significant positive correlation between months of follow-up and $PD_{20}FEV_1$; +: patients identified by initials. $PD_{20}FEV_1$: provocation concentration producing a 20% fall in forced expiratory volume in one second; sBPT: specific bronchial provocation test; TDI: toluene diisocyanate. No. obser.: number of methacholine challenge tests during the follow-up. (Reprinted from [24] with permission).

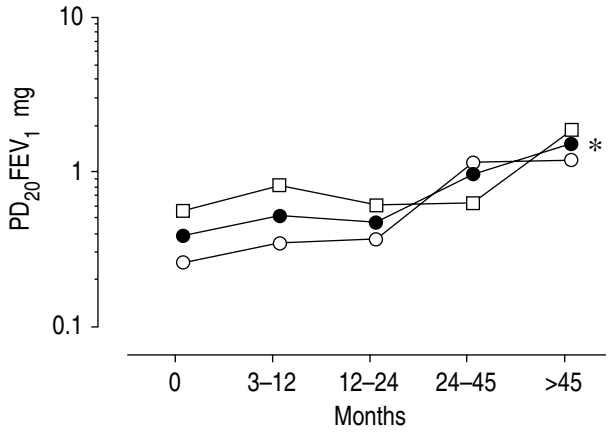

Fig. 1. – Mean values of $PD_{20}FEV_1$ methacholine at different time-points during follow-up examination, in all patients and in those who either stopped or reduced TDI exposure. *: significant difference from baseline value, $p<0.05$. —●— : all patients; —○— : patients who were no longer exposed to TDI; —⊟— : patients with reduced exposure to TDI. $PD_{20}FEV_1$: provocative concentration of methacholine producing a 20% fall in forced expiratory volume in one second; TDI: toluene diisocyanate. (Reprinted from [24] with permission).

Similar results were reported by DI STEFANO *et al*. [23], who observed a significant reduction in the degree of EAR and LAR to TDI, but no significant reduction in NSBH in TDI asthmatic subjects 6–18 months after the end of TDI exposure.

These data confirm that asthma recovery occurs in a small percentage of subjects with TDI asthma, and only after a long period (up to 4 yrs) from the end of occupational exposure. The loss of airway sensitivity to TDI can occur, but it seems only partially related to the improvement in NSBH. Most subjects who were no longer responsive to TDI were still hyperreactive to methacholine, even if symptoms and drug use were reduced. Thus, although NSBH parallels symptoms at their onset [16], when the disease is fully developed NSBH may become independent of symptoms and of sensitivity to the specific agent, suggesting that different mechanisms are involved.

Response to therapy

The effect of drug therapy on the outcome of bronchial hyperresponsiveness in occupational asthma has seldom been evaluated. Some of the patients whose data are reported in table 3 were studied over a longer follow-up period (up to 145 months). Among these patients, we selected six subjects whose NSBH had not changed after a 41–145 month follow-up. At this time, point these subjects were treated with inhaled corticosteroids (beclomethasone dipropionate (BDP), 1.5 mg·day^{-1} for three months), and then a nonspecific bronchial provocation test to methacholine was repeated after one week, one month and three months of treatment. No significant change in $PD_{20}FEV_1$ was observed at any time-point, despite the improvement in FEV_1 and in symptoms (table 4).

By contrast, DE MARZO *et al*. [25] observed that one month treatment with BDP (2 mg·day^{-1}, starting immediately after diagnosis) significantly improved NSBH to methacholine in subjects who had ceased exposure to TDI, whereas such treatment did not affect specific bronchial responsiveness to TDI in the same patients.

The differences in the outcome of NSBH between these two studies may be due to the selection of patients: DE MARZO *et al*. [25] treated all patients immediately after the end of TDI exposure, whereas we chose our patients on the basis of the severity of NSBH, since they showed no spontaneous recovery 41–145 months after the end of occupational exposure

Thus, in subjects recently or currently exposed to the sensitizing agent, inflammation might be an important determinant of NSBH, as shown by the effectiveness of steroid treatment in reducing the severity of NSBH. On the other hand, the persistence of NSBH after long-term cessation of exposure might be due to mechanisms other than inflammation, thus explaining the resistance to further steroid treatment.

Conclusions

Removal from occupational exposure is associated with recovery of asthma in about 50% of subjects, and only several months after work cessation. Factors affecting an unfavourable outcome of asthma are a longer duration of exposure before the onset of symptoms, a longer duration of symptoms before diagnosis, and a greater severity of the disease at diagnosis, expressed by

Table 4. – $PD_{20}FEV_1$ methacholine of TDI asthmatic patients, measured at diagnosis, and before and after 1 week, 1 month, and 3 months of treatment with high dose inhaled steroids

Pt	Months Follow-up	PD_{20} diagnosis	PD_{20} before treatment	PD_{20} 1 week	PD_{20} 1 month	PD_{20} 3 months
SP	41	390	27	196	106	-
ST	63	663	107	-	240	180
MR	85	300	63	83	80	94
AS	61	116	106	193	111	116
CE	88	22	117	24	112	140
BG	145	60	31	56	53	64
Mean		258.5	64.2	84.1	105.9	111.9

For abbreviations see legend to table 3.

a higher degree of baseline airway obstruction and of NSBH, and the presence of a dual response to specific BPT. Such clinical findings, as well as the presence of eosinophils in BAL, are associated with the persistence of asthma even after the end of exposure to the sensitizing agent and possibly with the development of chronic airways obstruction.

In IgE-mediated occupational asthma, allergic sensitivity to the causal agent might be used as a marker of exposure to the sensitizing agent. Studies assessing the relationship between serum IgE levels and other clinical findings, such as symptom score and NSBH, are required.

Specific airway sensitivity to TDI usually decreases after the end of exposure and it can even be lost, but is not always associated with a parallel decrease in NSBH, thus suggesting that the two phenomena may become independent with time. Similarly, NSBH may be independent of the presence of symptoms, as shown by unchanged NSBH in subjects with reduced asthma symptoms. Also, the persistence of NSBH in some subjects even after treatment with high dose inhaled corticosteroids suggests that mechanisms other than inflammation may be involved in the persistence of asthma. These observations suggest that a permanent change in the control of the airway tone could be the consequence of TDI asthma, probably related to some morphological changes in the humoral and neural regulation of the airway reactivity, and not strictly related to the severity of airway inflammation.

It is not known whether continuous exposure to low levels or single exposures to high peaks/spills of the sensitizing agent affect the outcome of asthma differently. As described for reactive airway disease syndrome (RADS), occurring after acute exposure to high levels of irritant gases or fumes [26], acute exposure to high levels of compounds such as TDI may more probably cause chronic persistent damage of the control of airway tone. Also, factors other than the sensitizing agent might affect the outcome of asthma, such as viral infections, exposure to nonspecific irritants, *etc*., but no data are available on this aspect.

In conclusion, the prognosis of occupational asthma after diagnosis is often poor. The only effective measures to prevent the persistence of airway hyperreactivity even after work cessation are early diagnosis and early complete removal from exposure to the sensitizing agent. In subjects who can be immediately removed from a specific job, treatment with high dose inhaled steroids reduces NSBH, although full recovery is observed in only a small number of patients. In subjects who continue to be exposed, only the use of respiratory devices, such as twin-cartridge respirator, effectively prevents further deterioration of asthma. Delay in diagnosis, in the removal from occupational exposure and in drug treatment may result in persistent chronic disregulation of airway tone and in progressive deterioration of lung function. As to legal compensation, persistent NSBH is a sign of chronic damage caused by occupational exposure. Therefore, it should be periodically evaluated to assess the severity of the disability.

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