

## UPDATE ON OCCUPATIONAL ASTHMA

### Occupational asthma in industry

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#### ABSTRACT

Occupational or professional asthma is defined as adult asthma, i.e., an inflammatory respiratory disease characterized by the presence of variable airflow limitation or bronchial hyperreactivity secondary to conditions and causes associated with a given occupational or working environment – not with stimuli found outside the workplace. Depending on the physiopathological mechanism involved, a distinction is made between immune asthma (with or without IgE mediation) and non-immune asthma.

It is difficult to establish the relationship among the symptoms of asthma, the patient's professional activity and the presence or absence of sensitization to certain agents in the working environment. Guided compilation of the case history and measurement of nonspecific bronchial hyperreactivity and bronchial inflammation are currently essential in the diagnostic approach to occupational asthma. Whenever possible, allergists should establish the cause-effect relationship in occupational asthma, as required by the medical-legal and social implications of the disease. Occupational asthma remains a minority diagnosis among occupational diseases in general. Adequate personnel training and the creation of diagnostic centers may help to ensure correct and rapid detection of this disease.

**Key words:** Occupational asthma. Professional asthma. Industry. Epidemiology. Costs.

#### DEFINITION OF PROFESSIONAL ASTHMA

Occupational or professional asthma is defined as adult asthma, i.e., an inflammatory respiratory disease characterized by the existence of variable airflow limitation or bronchial hyper-reactivity secondary to conditions and causes associated with a given occupational or working environment – not with stimuli found outside the workplace<sup>1</sup>.

Non-asthmatic eosinophilic bronchitis (i.e., the presence of eosinophilic bronchial inflammation without bronchial hyper-reactivity) may have an occupational origin<sup>2-6</sup>. Establishing the diagnosis of a disease is always of fundamental importance for the patient. In the case of professional asthma, a correct diagnosis is even more important, since it has not only clinical but also legal, economical and social consequences. The etiological diagnosis of professional asthma is a critical consideration, due to the aforementioned reasons. Whenever possible, a cause-effect relationship must be established between the patient asthma symptoms and professional or occupational exposure. This is essential in order to document the disease in legal courts and in other institutions where the affected patients may seek a declaration of occupational disability and the pertinent economical compensations.

In 1993, Bernstein et al<sup>1</sup> defined professional asthma as "a disease characterized by the existence of variable airflow limitation and/or bronchial hyper-reactivity secondary to conditions and causes associated with a given occupational or working environment, not with stimuli found outside the workplace".

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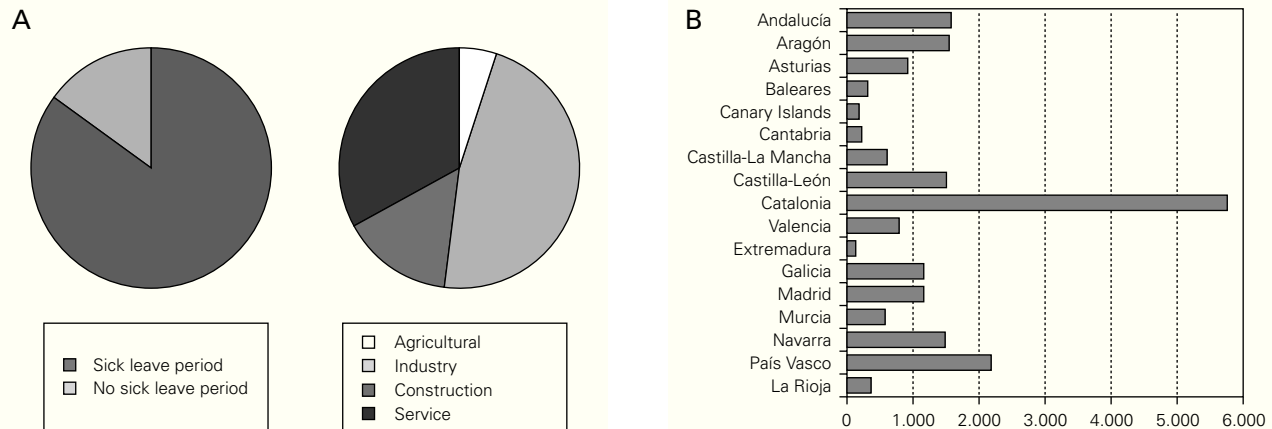


Figure 1.—A) Occupational diseases by severity and sector (January-September 2005). Source: Spanish Ministry of Labor and Social Affairs. B) Occupational diseases by Spanish regions (January-September 2006). Source: Spanish Ministry of Labor and Social Affairs.

The relationship between occupational activities and the appearance of illnesses began to be documented in the XVIII and XIX centuries with the advent of the industrial revolution. As with any major technological advance, victims soon began to be registered. People fell ill and died because of their working activities. In the XVIII and XIX centuries, however, these problems received very little attention.

Two centuries later, legislation in all industrialized countries protects the rights of workers. Nevertheless, a number of things remain to be done in the concrete case of asthma as a professional disease.

## DEFINITION

Spanish Social Security legislation defines professional disease as "an illness contracted as a result of remunerated work done for others (work done on the worker's own account, i.e., on an autonomous basis, being included in this definition on occasion of the last pertinent legal reform), in the context of the activities detailed in the table contemplated by the law and produced by action of the elements or substances specifically related in the mentioned table to each professional disease". This list dates from the year 1978, and at present up to 320 substances capable of causing professional asthma have been identified.

In the period between January and September 2005, a total of 21,858 professional diseases were documented (fig. 1). Of these, 10,642 corresponded to the industrial sector. In the year 2004, a total of 24,047 professional diseases were registered, of which 2910 were caused by chemical agents and 461 resulted from the inhalation of substances not included in the section commented above (fig. 2). In

the period between January and November 2005, a total of 841,135 labor accidents resulting in sick leave were recorded. However, in the last National Survey of Working Conditions, involving 3800 interviewed workers (fig. 2), non-specified respiratory diseases or allergies accounted for only 7.2 % of the total – the most common reason for seeking medical help being back pain (30 %).

## REASONS FOR MEDICAL CONSULTATION IN THE WORKPLACE

These data suggest that the diagnosed cases and registered situations of disability due to professional asthma are probably only the tip of the iceberg. Adequate training of all human resources found between

ILL	CASES	%
Neck disorders	49	9.7
Spine-Back disorders	101	20.1
Upper limb disorders	10	2.0
Lower limb disorders	17	3.4
Tenosynovitis	12	2.4
Sprains and luxations	11	2.2
Fractures	7	1.4
Muscle-skeletal disorders	12	2.4
Accidents	33	6.6
Cardiovascular diseases	11	2.2
Gastrointestinal diseases	32	6.4
Respiratory infections	29	5.8
Others respiratory diseases	11	6.6
Others infections (no respiratory)	9	1.8
Allergy	3	0.6

Figure 2.—Work-related illness. Source: Spanish Ministry of Labor and Social Affairs.

the workers and their workplaces – company physicians, business executives, the workers themselves – and the creation of official reference centers for the specific diagnosis of such diseases should contribute to improve and increase the diagnosis of these problems.

## CLASSIFICATION OF OCCUPATIONAL ASTHMA

Work-related asthma is divided into two major groups:

1. Occupational or professional asthma as such, i.e., caused by specific substances found in the workplace of the patient.
2. Pre-existing asthma exacerbated in the workplace.

In addition, eosinophilic bronchitis without asthma may have an occupational origin<sup>2-6</sup>.

Two groups of asthma are considered, depending on the pathogenic mechanism involved in the development of professional asthma:

### Immunologic asthma

In this form of the disease there is a latency period between occupational exposure and the appearance of asthma. This category comprises all cases in which there is a demonstrable or probable immune mechanism (mediated or not by IgE antibodies), and includes most high molecular weight agents (> 1000 Da) and some low molecular weight agents (< 1000 Da).

### Non-Immunologic asthma

No latency period is observed in this form of the disease, which is represented by reactive airways dysfunction syndrome (RADS) or, more globally, by irritant-induced asthma.

## DIAGNOSIS OF PROFESSIONAL ASTHMA IN THE INDUSTRIAL SETTING

In the year 1975, Jack Pepys wrote: "One of the principal obligations in asthma, as in any other disease, is to establish a precise diagnosis. This is particularly important in the case of allergic disorders, where avoidance of the causal agent determines the course of the disease"<sup>7</sup>. Guided compilation of the

case history and the measurement of nonspecific bronchial hyper-reactivity and airway inflammation (induced sputum study and measurement of exhaled nitric oxide, NO), together with more routine tests, are presently essential considerations in the diagnostic approach to occupational asthma. Identification of the etiology of a case of professional asthma may prove quite straightforward if the causal agent has already been reported elsewhere in the literature, such as for example in painters in the automobile industry sensitized to isocyanates. However, in the industrial setting, this is almost never the case, and investigation of the causal agent may become like searching for a needle in a haystack. Cooperation among company physicians and the labor medical care associations is always desirable to this effect, particularly on taking into account that the expenses derived from the study of any professional disease (including asthma) are covered by such medical care associations – in compliance with applicable Spanish legislation.

The study of the material safety data sheets or summaries of product characteristics of the elements manipulated by the patient in the industrial setting is a first step to guide the study. In most cases the causal agents are low molecular weight substances. The mentioned material safety data sheets may cite components already documented in the literature as being responsible for allergic manifestations (respiratory or otherwise) or respiratory problems in general (pneumonitis, pneumoconiosis, etc.) – alerting us to their possible implication in the asthma of the patient. In other cases this is not so, however. In addition to specifying the physico-chemical characteristics of the product, the formulations, storage conditions, protective measures and safety coding, the material safety data sheets indicate the maximum permissible exposure values, where available (table I). In general, two threshold limit values.

(TLVs) are defined for each substance: the TWA (time-weighted average) and the STEL (short-term exposure limit). The TWA is defined as the mean 8-hour-weighted concentration that must not be exceeded in any period of 8 hours for 40-week working weeks. The STEL is in turn defined as mean concentration for periods of 15 minutes (provided no other time period is specified) that must not be exceeded at any time during the working day.

These are toxicological thresholds, since the sensitization threshold values are always comparatively lower. Nevertheless, they must be known in order to design specific bronchial provocation tests or to conduct environmental studies or provocation tests in the workplace of the patient. As an example, in our routine clinical practice we have had cases of pa-

**Table I**  
**Principales amines used in industry**

Occupational injuries and diseases	Total		Sick leave									
			Total		Mild		Severe		Fatal		No sick leave	
	2003	2004	2003	2004	2003	2004	2003	2004	2003	2004	2003	2004
<b>Total</b>	<b>3.082</b>	<b>2.910</b>	<b>2.683</b>	<b>2.431</b>	<b>2.617</b>	<b>2.376</b>	<b>66</b>	<b>55</b>	<b>-</b>	<b>-</b>	<b>399</b>	<b>479</b>
<i>Occupational diseases due to chemical agents</i>	433	445	367	376	355	369	12	7	-	-	66	69
Lead and its compounds	16	17	16	15	16	15	-	-	-	-	-	2
Mercury and its compounds	11	4	10	2	10	2	-	-	-	-	1	2
Cadmium and its compounds	21	-	21	-	21	-	-	-	-	-	-	-
Manganese and its compounds	2	-	1	-	1	-	-	-	-	-	1	-
Chromium and its compounds	32	45	29	41	27	41	2	-	-	-	3	4
Nickel and its compounds	38	23	35	21	35	21	-	-	-	-	3	2
Phosphor and its compounds	24	60	24	48	23	47	1	1	-	-	-	12
Arsenic and its compounds	7	-	-	-	-	-	-	-	-	-	7	-
Chlorine and its compounds	5	6	4	5	3	5	1	-	-	-	1	1
Bromine and its compounds	2	-	-	-	-	-	-	-	-	-	2	-
Iodine and its inorganic compounds	1	-	1	-	1	-	-	-	-	-	-	-
Sulphur dioxide	1	-	1	-	1	-	-	-	-	-	-	-
Ammonia	1	1	1	-	1	-	-	-	-	-	-	1
Sulphur anhydride	-	1	-	1	-	1	-	-	-	-	-	-
Carbon oxide	1	-	1	-	1	-	-	-	-	-	-	-
Dianhydride acid	1	-	1	-	1	-	-	-	-	-	-	-
Aliphatic hidrocarburos	27	26	21	19	21	19	-	-	-	-	6	7
Alcohols	1	5	1	4	1	4	-	-	-	-	-	1
Ether and its compounds	-	1	-	1	-	1	-	-	-	-	-	-
Ketones	-	2	-	1	-	1	-	-	-	-	-	1
Organic esters	-	1	-	-	-	-	-	-	-	-	-	1
Organic acids	-	2	-	-	-	-	-	-	-	-	-	2
Aldehydes	2	-	2	-	1	-	1	-	-	-	-	-
Benzene, xylene and toluene	3	6	-	5	-	5	-	-	-	-	3	1
Halogens	1	2	1	1	1	1	-	-	-	-	-	1
Phenols	1	1	1	1	1	-	-	1	-	-	-	-
Amines	33	35	29	35	26	35	3	-	-	-	4	-
Isocyanates	12	17	10	14	9	12	1	2	-	-	2	3
Others diseases due to chemical agents	190	190	157	162	154	159	3	3	-	-	33	28
<i>Skin occupational diseases due to agents not mentioned above</i>	2.079	2.004	1.839	1.667	1.816	1.657	23	10	-	-	240	337
<i>Occupational respiratory diseases due to agents not mentioned above</i>	570	461	477	388	446	350	31	38	-	-	93	73
Pneumoconiosis	-	3	-	2	-	2	-	-	-	-	-	1
Silicosis	47	45	39	39	28	26	11	13	-	-	8	6
Asbestosis	9	8	5	8	4	4	1	4	-	-	4	-
Pneumoconiosis due to silicates	11	1	6	1	5	1	1	-	-	-	5	-
Bagassosis	3	-	3	-	2	-	1	-	-	-	-	-
Lung diseases caused by aluminium	1	3	1	2	1	2	-	-	-	-	-	1
Lung diseases caused by talc	7	3	6	2	5	1	1	1	-	-	1	1
Asthma due to substances not mentioned above	283	222	254	194	241	178	13	16	-	-	29	28
Irritative respiratory diseases	192	165	147	131	145	127	2	4	-	-	45	34
Others respiratory diseases	17	11	16	9	15	9	1	-	-	-	1	2

(Continued)

**Table I**  
**Principales aminos used in industry (Cont)**

Occupational injuries and diseases	Total		Sick leave									
			Total		Mild		Severe		Fatal		No sick leave	
	2003	2004	2003	2004	2003	2004	2003	2004	2003	2004	2003	2004
<b>Total</b>	<b>23.775</b>	<b>25.818</b>	<b>21.039</b>	<b>21.616</b>	<b>20.933</b>	<b>21.512</b>	<b>106</b>	<b>102</b>	<b>-</b>	<b>2</b>	<b>2.736</b>	<b>4.202</b>
<i>Infectious and parasitarie occupational diseases</i>	410	463	377	380	343	348	34	32	-	-	33	83
Paludism	21	17	21	16	20	16	1	-	-	-	-	1
Infectious and parasitarie diseases transmitted from animals to humans	28	53	26	52	25	51	1	1	-	-	2	1
Anthrax	2	-	2	-	2	-	-	-	-	-	-	-
Leptospirosis	4	3	4	3	4	2	-	1	-	-	-	-
Brucellosis	124	96	111	84	108	80	3	4	-	-	13	12
Tuberculosis	-	5	-	5	-	5	-	-	-	-	-	-
Infectious and parasitarie diseases in health workers and researchers	187	250	170	182	160	171	10	11	-	-	17	68
Viral hepatitis	44	39	43	38	24	23	19	15	-	-	1	1
<i>Occupational diseases due to physical agents</i>	23.351	25.340	20.649	21.223	20.583	21.156	66	67	-	-	2.702	4.117
Diseases caused by ionizing radiation	3	1	3	1	2	1	1	-	-	-	-	-
Cataract caused by radiation	6	1	4	1	4	1	-	-	-	-	2	-
Hypoacusis and deafness caused by noise	384	490	104	282	94	252	10	30	-	-	280	208
Diseases caused by compressing air	9	9	9	7	9	7	-	-	-	-	-	2
Diseases caused by mechanical vibrations	200	191	179	141	176	139	3	2	-	-	21	50
Bursitis	742	744	684	656	683	656	1	-	-	-	58	88
Tenosinovitis	19.616	21.365	17.519	17.914	17.480	17.885	39	29	-	-	2.097	3.451
Meniscal injuries	289	302	279	289	279	289	-	-	-	-	10	13
Spinal apophysis injuries	4	-	4	-	4	-	-	-	-	-	-	-
Paralysis due to pressure	2.055	2.212	1.824	1.914	1.812	1.908	12	6	-	-	231	298
Others diseases due to fisical agents	43	25	40	18	40	18	-	-	-	-	3	7
<i>Ssytemic diseases</i>	14	15	13	13	7	8	6	3	-	2	1	2
Corneal dystrophy due to vapours	6	9	5	8	5	8	-	-	-	-	1	1
Lung cancer due to asbestos	6	5	6	4	1	-	5	2	-	2	-	1
Cancer due to ionizing radiations	1	1	1	1	1	-	-	1	-	-	-	-
Others systemic diseases not mentioned above	1	-	1	-	-	-	1	-	-	-	-	-

tients with suspected isocyanate-induced asthma in which the corresponding provocation tests proved negative. In these cases it was necessary to visit the workplace of the patient, where isocyanates measured in the working environment were found to far exceed the corresponding TLVs.

The assay of specific IgE may be of help in relation to certain low molecular weight substances (acid anhydrides, platinum salts, reactive dyes, etc.) and in application to most high molecular weight substances (cereal flours, latex, etc.). However, this is not possi-

ble in the case of most industrial low molecular weight agents, either because no underlying IgE-mediated immune mechanism is known for these substances, or because they constitute novel chemical agents. It is therefore necessary to conduct specific bronchial provocation tests in these situations to determine the substance responsible for the professional asthma. The purpose of specific bronchial provocation is to evaluate bronchial reactivity to the agent causing professional asthma in each concrete case. Thus, the test assesses the response of the



specific organ – the airways – to aerosols, powders, vapors or fumes to which the patient is exposed in the workplace.

The use of new chemical substances is increasing in the industrial setting, and this is in turn asso-

ciated with an increased possibility of new sensitizations. Specific bronchial provocation is particularly indicated in the case of such new substances with still unknown respiratory sensitization potentials (fig. 3).

## SERICOL

Más que tinta...Soluciones.

### hoja de datos de seguridad

De acuerdo con 91/155/EC y modificado por 2001/58/EC

Fecha de impresión 24.05.2004

revisado el 01.03.2004

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#### 1 Identificación de la sustancia o preparado y de la sociedad o empresa

- **Uso:** Tinta para Serigrafía
- **Nombre comercial:** UVIBOND VARNISH 391
- **Código Del Producto:** UV391
- **Fabricante/distribuidor:**  
Sericol España S.L.  
Mare De Deu De Monserrat 21, 09870 Sant Joan Despí, Barcelona  
Tel: 93 477 22 44
- **Área de información:** Departamento de seguridad de productos

#### 2 Composición/información sobre los componentes

- **Caracterización química**
- **Descripción**  
Mezcla formada por las sustancias especificadas a continuación con adiciones no peligrosas.

##### • Componentes peligrosos:

CAS: 42978-66-5	Acrylic acid, propylenebis(oxypropylene) ester	25-50%
EINECS: 256-032-2	Xi, N; R 36/37/38-43-51/53	
	Acrilato multifuncional en propiedad	10-25%
	Xi, N; R 36/37/38-51/53	
CAS: 119-61-9	benzofenona	5-10%
EINECS: 204-337-6	Xi, N; R 36/37/38-50/53	
CAS: 1254-78-0	Fosfito de didecilo y fenilo	1-5%
EINECS: 215-012-3	Xi, N; R 38-43-50/53	

##### • Indicaciones adicionales

El texto de los posibles riesgos aquí indicados se puede consultar en el capítulo 16.

#### 3 Identificación de peligros

##### • Descripción del riesgo:



Xi Irritante  
N Peligroso para el medio ambiente

##### • Indicaciones adicionales sobre los riesgos para personas y el medio ambiente:

R 36/37/38 Irrita los ojos, la piel y las vías respiratorias.  
R 43 Posibilidad de sensibilización en contacto con la piel.  
R 51/53 Tóxico para los organismos acuáticos, puede provocar a largo plazo efectos negativos en el medio ambiente acuático.

##### • Sistema de clasificación:

La clasificación corresponde a las listas actuales de la CE, pero siempre completada por la literatura especializada y los informes de las empresas.

#### 4 Primeros auxilios

##### • Instrucciones generales:

Nunca hacer vomitar o beber líquidos a una persona inconsciente.  
Quitarse de inmediato toda prenda contaminada con el producto.

##### • En caso de inhalación del producto:

Suministrar aire fresco. En caso de trastornos, consultar al médico.

##### • En caso de contacto con la piel:

Lavar inmediatamente con agua y jabón y enjuagar bien.  
Si la irritación de la piel persiste, consultar un médico.

##### • En caso de con los ojos:

Aclarar los ojos abiertos durante varios minutos con agua corriente y consultar a un médico.

( Continúa en página 2 )

Figure 3.

Whenever possible, exposure must attempt to reproduce the working environment of the patient as precisely as possible. In addition to the diagnostic objectives of the provocation test, the latter is also used to investigate the pathogenic mechanisms of already known or novel causal agents.

The choice of one or other specific bronchial provocation method is particularly dependent upon the type of agent involved. The options range from the most common technique, involving provocation with a nebulizer under tidal volume conditions, to the most sophisticated dynamic exposure chambers.

A description is provided below of the different types of professional asthma caused by low molecular weight industrial agents: chrome and nickel salts, cutting oils, plastic derivatives and acrylates.

### ASTHMA DUE TO CHROME AND NICKEL SALTS

The capacity of metals to cause disease, including respiratory illnesses, has been known for centuries<sup>8</sup>. The relative infrequency of metal-induced respiratory symptoms compared with cutaneous manifestations may be attributed in part to the fact that many cases of asthma caused by metals are not diagnosed. Most occupational respiratory disorders produced by metals are considered benign. It has been estimated that about ten million workers may be affected by such disorders<sup>9</sup>.

Exposure to metals or metalloids in pure form (i.e., fully non-oxidized) is very rare. Exposure to metal salts is much more common. Metals, and particularly transition metals, can form complexes with different ligands such as ammonium, carbon monoxide, organic nitrogen or sulfur.

Asthma caused by metals is a recently described condition, as a result of which no specific classification has yet been developed for this type of professional asthma. Consequently, asthma due to metals is usually classified according to the causal metallic agent: transition metals (vanadium, chrome, nickel, etc.), noble metals (palladium platinum, etc.) and heavy metals (tungsten, cobalt, etc.).

Bernstein et al<sup>1</sup>, in the treatise *Asthma in the workplace*, proposed a classification for the agents causing asthma, according to their location in the periodic table of elements<sup>10</sup>:

- First series of transition elements: vanadium, chrome, cobalt, nickel and zinc.
- Second series of transition metals: ruthenium, rhodium, palladium and cadmium.
- Third series of transition elements: iridium and platinum.

- Group III metals: aluminum.
- Indeterminate metals due to alterations or contaminants present in manufactured products.

Most cases of professional asthma caused by metals are associated with transition metals. In the present study we will focus on professional asthma caused by chrome and nickel salts. However, the absolute number of cases of professional asthma due to exposure to platinum and aluminum greatly exceeds the number of cases of asthma attributable to other metals<sup>11-13</sup>.

Occupational asthma caused by chrome and nickel salts seems to be rare, though a number of cases have been reported in recent years<sup>14-20</sup>. In contrast, skin disorders, particularly allergic contact dermatitis caused by these metals – and particular by chrome – are much more frequent (accounting for 10 % of all positive epicutaneous tests among Caucasians)<sup>21</sup>. The professions and activities related to chrome and nickel exposure are varied: electrolytic plants, cement factories, and construction and welding processes in general. Moreover, in most of these activities the salts of both metals are usually manipulated in combination.

Contact dermatitis attributable to these metals may precede the appearance of respiratory symptoms<sup>16</sup>, though this is not always the case<sup>17,19-20</sup>.

The first case of asthma induced by chrome salts was published in the year 1869<sup>22</sup>. The two largest series to date are those documented by Bright et al<sup>18</sup> and Fernández-Nieto et al<sup>20</sup>, with 7 and 4 workers, respectively, corresponding to different industries involving the use of chrome and nickel salts.

### Diagnosis

The cases published present asthma after provocation under conditions of tidal volume with chrome and nickel salts at a concentration of between 1-10 mg/ml. If the concentrations are too high, irritative responses may result. In any case, the great variety of asthmatic responses obtained after provocation in both published series<sup>18,20</sup>, together with the nonspecific bronchial hyper-reactivity changes observed and the variations in cell count in the induced sputum samples, rule out the possibility of a simple irritant effect<sup>14-16,19,20</sup>.

The usefulness of epicutaneous testing and of the determinations of specific IgE as diagnostic tools in professional asthma induced by metal salts remains unclear.

In an epidemiological study involving workers in the electrolytic industry<sup>18</sup>, the size of the papule

elicited in these patients was unrelated to the result of the bronchial provocation test. Positive epicutaneous tests (> 2 mm) were observed in 10 % of the exposed workers with symptoms suggestive of professional asthma, in 15 % of the exposed workers that suffered rhinitis, in 11 % of the exposed workers without symptoms, and in 2 % of the non-exposed controls. In the series published by Fernández-Nieto et al<sup>20</sup>, a 2-mm papule was recorded in two of the workers. The tested controls proved negative.

Novey et al<sup>15</sup> demonstrated specific IgE antibodies against chrome and nickel conjugates in an electrolytic industrial worker with professional asthma. Malo et al in turn reported the case of a worker in an electrolysis plant presenting professional asthma with a positive bronchial provocation test in response to nickel, and negative epicutaneous tests and RAST findings. Dolovich et al suggested that antigenic determination (for nickel) is dependent upon binding of this metal to human albumin at the primary binding site for copper. Fernández-Nieto et al in turn demonstrated specific IgE against chrome and nickel via enzyme-linked-immunosorbent assay (ELISA) in one of their four published cases<sup>20</sup>.

## Pathogenesis

The pathogenesis of professional asthma caused by these salts is little known. As has already been commented, in some but not all cases, allergic contact dermatitis may precede asthma. An approach to the underlying pathogenesis may therefore be made on the basis of contact dermatitis.

Because of their small size, metal ions are incomplete antigens that must bind to endogenous peptides to become truly antigenic. They associate in a triple-molecular complex composed of the class II major histocompatibility complex (MHC II), the binding peptide and the corresponding T lymphocyte receptor to induce a T cell-specific response. It has been shown that T lymphocyte clones specifically targeted to metal ions recognize haptens in the context of MHC II molecules. No association has been demonstrated among certain human leukocyte antigen (HLA) haplotypes in subjects sensitized to nickel, chrome and cobalt<sup>23</sup>. However, certain T lymphocytes expressing the T cell receptor with the different V-beta chains seem to be correlated to the severity of contact dermatitis induced by nickel.

To date, little is known of the structure of the antigenic epitopes created after epicutaneous exposure to metal salts. Moulon et al<sup>24</sup> have investigated the processing involved in T lymphocyte recognition of

nickel, and hapten recognition has been shown to be independent of processing by the antigen-present cells (APCs) in most of the human T lymphocyte clones studied.

## Cross-reactivity

Concomitant sensitization to different metals is a contrasted clinical observation. an obvious question that may be raised is whether this clinical phenomenon is due to the existence of some type of cross-reactivity among several metal species. In this context, Moulon et al<sup>24</sup> exposed a group of nickel specific T lymphocyte clones from four patients allergic to metals and examined their cross-reactivity with palladium, cobalt, copper, chrome, zinc and platinum. The authors detected cross-reactivity among nickel, copper and palladium – explaining the phenomenon in terms of the structural similarity of these species. Since no cross-reactivity was observed between nickel and cobalt, the authors concluded that *in vivo* reactivity to these metals is the result of concomitant sensitization.

Sastre et al<sup>19</sup> demonstrated the existence of cross-reactivity between chrome and nickel in an electrolytic industrial worker.

## PROFESSIONAL ASTHMA DUE TO CUTTING OILS OR MACHINING FLUIDS

These are products used for the manipulation (cutting) of metal pieces, in order to reduce cutting tool friction heat, and thus avoid deterioration while improving the finish of the manipulated elements. mixed with water, there are a number of types of such products.

## Types

1. Oily fluids (cutting oils).
2. Aqueous fluids: oils or non-oils plus other elements (emulsifiers, amines, etc.), which are in turn classified as:
  - Emulsions
  - Synthetic formulations
  - Semisynthetic formulations
  - Neosynthetic formulations

All of these products may also contain additives such as bactericidal products, deodorants, dyes, soaps, fatty acids, etc., or contaminants such as



traces of the machined elements (chrome, nickel etc.).

Many studies have described cutaneous disorders, particularly contact dermatitis, produced by these substances<sup>25-29</sup>. In contrast, in only a few cases has a causal relationship been established with the appearance of professional respiratory pathology, pneumonitis<sup>30</sup> or asthma<sup>31-33</sup>.

Amines and alcalonamines have been the cutting fluid components related with the documented cases of professional asthma due to these substances<sup>34,35</sup>.

Amines are nitrogen compounds derived from ammonium (NH<sub>3</sub>), in which one or more hydrogen atoms are replaced by hydrocarbon groups. They are classified according to the number of replaced hydrogen atoms as follows:

- Primary amines: Substitution of an H atom by an alkyl or aryl group. (Example: NH<sub>2</sub>CH<sub>2</sub>OH [2-aminoethanol].)
- Secondary amines: Substitution of two H atoms by alkyl or aryl groups. (Example: Piperidine.)
- Tertiary amines: Substitution of three H atoms by alkyl or aryl groups (Example: Triethylamine.)
- Quaternary amines: Substitution of four H atoms by alkyl or aryl groups (Example: Benzalkonium chloride.)

Classification can also be based on the molecule substituting the hydrogen atom:

- Aromatic amines: when the H atom is replaced by a benzene ring.
- Aliphatic amines.

Occupational asthma attributable to amines is infrequent. According to the review published by Haggmar et al<sup>37</sup>, approximately 40 amines have been identified as being able to cause professional asthma. These products are used in a broad range of industrial sectors. Recently, Quirce et al<sup>38</sup> published a case of professional asthma due to piperazine citrate, in a female worker in the chemical industry – demonstrated via specific provocation using a powdered substance inhalation chamber.

As in the majority of substances of low molecular weights, the underlying pathogenic mechanism is not clear. In some cases immediate skin reactivity has been shown. Cross-reactivity among such substances is questionable (table I).

Alcalonamines are ammonium derivatives in which 1, 2 or 3 hydrogen atoms are replaced by an alcohol group (-OH). These products are used in the pharmaceutical and chemical industries as emulsi-

fiers, antioxidants, corrosion inhibitors, solubilizing agents and as intermediates in the manufacture of cosmetics, soaps and detergents. Their use has been related with the appearance of dermatitis (both irritative and contact dermatitis). There have been very few published cases of occupational asthma due to mono-, di- and triethanolamine. In 1994, Savonius et al<sup>34</sup> published two cases of professional asthma in two metal industry workers, caused by triethanolamine contained in cutting fluid.

In 1998, Piriipari et al<sup>35</sup> described a case of professional asthma in a metal worker attributed to diethanolamine contained in cutting fluid.

On the other hand, 2-aminoethanol, also known as ethanolamine, 2-hydroxyethylamine or cholamine, has been identified as the causal agent in two cases of professional pathology: asthma in a worker following exposure to detergents<sup>34</sup>, and a case of contact dermatitis in a metal worker involving exposure to cutting fluid<sup>36</sup>.

The TLV-TWA of 2-aminoethanol is 3 ppm (7.5 mg/m<sup>3</sup>), while the TLV-STEL is 6 ppm (15 mg/m<sup>3</sup>).

## ASTHMA DUE TO POLYVINYL CHLORIDE (PVC) AND POLYETHYLENE

Polyvinyl chloride or PVC was discovered in 1830 by Victor Regnault. In 1912, Fritz Klatte established the principles for its industrial manufacture. Large scale production began in 1938, when its multiple potential industrial applications were established. PVC is obtained by the polymerization of vinyl chloride, which is in turn produced from chlorine and ethylene. In Europe, the PVC industry employs over 542,000 people. In Spain there are over 1750 PVC-transforming compa-



PVC is the second most common plastic material worldwide, after polyethylene. There are basically two types of polyethylene:

– High density polyethylene (HDPE), comprising an unbranched linear chain. It is used in construction and also in the manufacture of prostheses. Objects made of HDPE are identified by the following symbol at their upper or lower portion:



– Low density polyethylene (LDPE), comprising a branched chain structure. This product is widely used in the packaging industry, for cable sheathing and in the manufacture of tubing. Objects made of LDPE are identified by the following symbol:



The thermal degradation of polyethylene and PVC has been reported as a cause of professional asthma since the sixties, in the context of so-called "meat wrapper's asthma" or, as it is now called, "food wrapper's asthma"<sup>39-41</sup>. In 1973, Sokol et al<sup>39</sup> reported three women with symptoms of asthma after heating PVC. Johnston and Anderson<sup>40</sup> in turn described the symptoms of 15 workers in a meat packing factory. Posteriorly, the products resulting from such thermal degradation were identified, along with traces of anhydrous phthalic acid (among other substances), though none of the exposed workers presented specific IgE antibodies targeted to this chemical agent<sup>42</sup>. In 1976, Andrasch et al<sup>43</sup> used provocation testing to reproduce the symptoms of professional asthma in plastic container industrial workers. Unheated PVC dust is also able to cause professional asthma<sup>44</sup>. In the year 2003, the Spanish group led by Muñoz et al<sup>45</sup> published a case of professional asthma, confirmed by specific provocation testing, in a women working in the fish wrapping industry.

As has been commented, polyethylene has been described as a cause of professional asthma in packaging workers<sup>46</sup>, and has also been associated with other industrial applications such as electric cabling<sup>47</sup>, and the paint industry<sup>48</sup>.

In the case of patients with suspected professional asthma due to PVC or polyethylene, as in the case of other low molecular weight agents, it is not easy to develop a specific bronchial provocation test. As a result, controlled exposure in the workplace is carried out. This was the case of a patient recently seen by our own group, who worked in a polyethylene plastic container factory. About six hours after controlled exposure lasting 60 minutes, a late asthmatic response was observed, with a reduction in maximum forced expiratory volume in one minute (FEV<sub>1</sub>) of 20 % with respect to baseline, and the appearance of induced sputum eosinophilia 24 hours after provocation.

## PROFESSIONAL ASTHMA CAUSED BY ACRYLATES

Since Kopp et al<sup>49</sup> described the first case of occupational asthma due to acrylates (in this case it is more appropriate to use the term "occupational" rather than "professional", since the affected patient used glue to assemble models), there have been many reports likewise documented through specific bronchial provocation tests<sup>50</sup> and, in some cases via the measurement of inflammation in induced sputum samples<sup>51</sup>. Acrylates are the fundamental components of the very potent glues used in orthopedics and in dental mechanics, esthetics, and the automobile industry, and in recent years they have been included in other uses as potential causes of professional asthma. In this context, a case of professional asthma has been documented in a worker due to the methacrylate contained in photocopying toner<sup>52</sup>, and another case has been recorded in a graphic arts worker produced by the printing varnish applied to paper containing acrylates<sup>53</sup>. In this latter case controlled exposure to the varnish was carried out in a dynamic exposure chamber.

## PROFESSIONAL ASTHMA DUE TO OTHER LOW MOLECULAR WEIGHT SUBSTANCES

Fernández-Nieto et al<sup>54</sup> described the case of a worker in the automobile industry with professional asthma caused by styrene – a low molecular weight substance. Isocyanates are commonly used in the automobile industry (in paints, solvents, etc.), though the worker was diagnosed with professional asthma by another substance called styrene. In this case the condition was demonstrated by specific exposure testing in a dynamic exposure chamber.

Styrene is a volatile monomer used in the production of polymers, copolymers and reinforced plastics. It is a transparent, colorless liquid obtained from petroleum and natural gas. Polystyrene is the end product of styrene polymerization, and is used to manufacture resins, putties and plastics contained in thousands of products thanks to its flexibility, hardness and low weight. The TLV-TWA is 50 ppm (213 mg/m<sup>3</sup>), while the TLV-STEL is 100 ppm (426 mg/m<sup>3</sup>). Objects made of styrene are identified by the following symbol:



## CONCLUSIONS

The products used in industry in general are not easy to group into list format, due to the permanent renewal and substitution experienced these materials. It is likewise difficult to relate a given product to a specific industrial activity, since change here is also constant. It is therefore necessary to establish a clear causal relationship with the product by means of specific provocation tests. In this way it will be possible to avoid including certain components in industrial product manufacturing practices, and thus contribute to reduce the risk of new sensitizations.

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**Table II****Spirometric control of the challenge test with codeine (30 mg) in patient 1**

Codeine 30 mg	PEF	CVF	FEV1	MMEF 75/25
Basal	7.14 (106 %)	3.67 (94 %)	3.17 (99 %)	86 (109.6 %)
1/4 Dose	6.48 (96 %)	3.38 (87 %)	2.94 (92 %)	86 (109.6 %)
1/2 Dose	6.50 (96 %)	3.13 (80 %)	2.78 (87 %)	89 (112 %)
After 15'	5.14 (76 %)	2.72 (70 %)	2.43 (76 %)	89 (112 %)
Terbutaline	7.44 (110 %)	3.50 (90 %)	3.14 (98 %)	89 (112 %)

**Table III****Spirometric control of the challenge test with tramadol (50 mg) in patient 1**

Tramadol	PEF	CVF	VEMS	MMEF 75/25
Basal	7.06 (105 %)	3.64 (94 %)	3.12 (98 %)	85.1 (107 %)
1/2 DOSE	6.74 (114 %)	3.88 (99 %)	3.28 (103 %)	86 (109.6 %)
1/1 DOSE	7.80 (116 %)	3.84 (98 %)	3.28 (102 %)	85.1 (107 %)

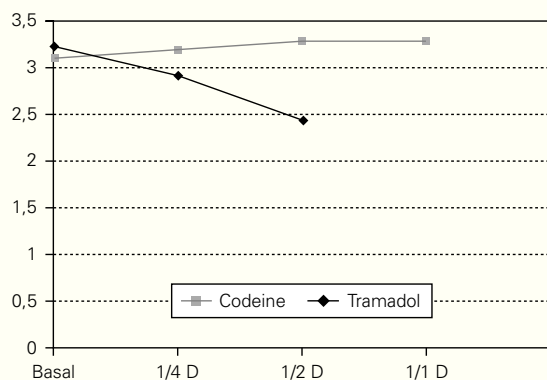


Figure 1.—Difference between challenge test to codeine and tramadol.

**Without contact:**

- Codeine: 8 Prick-test+
- Morphine: 7 Prick-test+. All IDR positive up to  $1/10^5$ ; 9 positive up to  $10^6$
- Tramadol: 2 Prick-test+. IDR 9+
- Pethidine: 1 Prick-test+. IDR 10+
- Fentanyl: 1 Prick-test+ IDR 0+

**With contact:**

- Codeine: 9 Prick-test+
- Morphine: 9 Prick-test+. IDR 9+ up to  $1/10^6$ , 1 up to  $1/10^5$

- Tramadol: 0 Prick-test+. IDR 10+
- Pethidine: 2 Prick-test+. IDR 8+
- Fentanyl: 1 prick-test+. IDR 8+

All patients were advised to use tramadol as analgesic and fentanyl and remifentanyl as anesthetics.

**DISCUSSION**

The singularities of opioids deserve a brief review of their pharmacokinetic characteristics<sup>1</sup>.

**Codeine**

This drug is a pure opioid agonist. It is used in application to moderate pain, cough and constipation. In some cases in Europe it is ineffective due to the high prevalence of fast extensive debrisoquine metabolizers.

Codeine can produce adverse effects requiring a differential diagnosis: cutaneous symptoms (itching, urticaria, rash, angioedema, erythema multiforme, erythema nodosum, occupational eczema). Respiratory: bronchospasm. Others: hypotension (when administered i.v.), pseudo-scarlatiniform fever.

The mechanisms of action underlying these clinical conditions may be: a) Hypersensitivity: one case has been described of IgE mediated response to morphine with cross-reactivity to codeine<sup>2</sup>; b) Histamine release: highly potent; c) Ganglionic vasomotor depression and block: causes important hypotension.

To summarize, we have seen that the prick-test and IDR are of scant utility<sup>3</sup>; indeed, such testing is used as positive control in France, in the same way in which histamine is used in Spain. Therefore, in those cases where the clinical history is insufficient, only controlled oral challenging can yield a diagnosis. In occupational contact eczema among workers who manipulate codeine, it is recommended to perform patch-tests with codeine phosphate a concentration of 0.1 %<sup>4</sup>.

**Morphine**

This drug is a powerful analgesic, with high histamine-releasing potential that occasionally causes respiratory depression. Skin prick-testing and IDR are likewise of little help in this case, and the diagnosis must be based on the clinical findings or controlled oral challenge. Another case of IgE response to morphine has been reported in Spain, in addition to the case commented above with cross-reactivity to codeine.



There have also been reports of occupational cases with clinical conditions in which the symptoms are cutaneous or respiratory.

### Tramadol

This drug is not a pure agonist, and its mechanism of action is partially mediated by its metabolite (o-demethyltramadol), which is a pure  $\mu$ -agonist and possesses another still unknown mechanism. It acts upon the central nervous system binding to  $\alpha_2$ -adrenergic receptors, and also exerts some serotonergic action. This is why the drug is contraindicated in patients receiving treatment with monoamine oxidase (MAO) inhibitors and in epilepsy.

Tramadol produces very little respiratory depression, and even in intubated patients with mechanical ventilation it neither reduces  $pO_2$  nor increases  $pCO_2$ . It is the opioid recommended for asthma by the *British Journal of Anaesthesia*<sup>5</sup>. In addition, tramadol is not a histamine-releasing drug.

It seems to be a good alternative for these patients, though only controlled oral challenge is able to confirm this.

### Fentanyl and remifentanyl

These substances are  $\mu$ -agonists used as anesthetics and also to some extent as analgesics, because of their rapid metabolism. They are not histamine-releasing drugs, and constitute the anesthetics recommended for patients with pulmonary pathology<sup>5</sup>.

In these cases fentanyl and remifentanyl seem to be acceptable options in patients of this kind<sup>5</sup>.

### Pethidine-meperidine

This is the most powerful opioid formulation, as well as the one of the most intense histamine-releasing agents. A case of IgE-mediated pethidine hypersensitivity has been reported<sup>6</sup>.

### General Comments

In the study of opioids, adverse reactions, skin prick-testing and IDR are of scant value and can thus be omitted. The only way to diagnose these patients

is by means of controlled oral challenge, and in highly suspicious cases we may search for specific IgE targeted to the opioid in question. Patch-testing is very useful in occupational contact eczema<sup>4</sup>.

Many substances induce histamine release, including opioids. In these clinical situations  $PGD_2$  and  $LTC_4$  can be determined – the corresponding values being 10-fold lower than in IgE-mediated reactions.

There are two types of mast cells:  $M_{TC}$  (mostly in skin) and  $M_T$  in the lungs<sup>7</sup>. Opioids exert comparatively greater action upon  $M_{TC}$ , which is why skin symptoms are the most common expression in these patients<sup>7</sup>. Naloxone partially inhibits this action<sup>7</sup>.

### CONCLUSIONS

We have presented three patients with clinical pictures of asthma and urticaria following codeine ingestion, attributable to the histamine-releasing action of the drug. All of them tolerated tramadol without problems.

The most common of these adverse effects are not IgE-mediated. Resorting to opioids that do not mediate histamine release, such as tramadol, fentanyl and remifentanyl, can solve the problem.

Skin prick-testing and IDR to opioids are of scant diagnostic utility, and the gold standard in these patients is controlled oral challenge.

Patch-tests in occupational contact eczema are usually used in workers suffering problems when manipulating morphine and codeine<sup>4</sup>.

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# Accumulation of mast cells in the interstitium of eosinophilic colitis

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## ABSTRACT

*Introduction:* The mechanism of eosinophilic colitis remains unclear, and no case has been reported in which the number of mast cells was examined.

*Case report:* A 35-year-old man presented to our hospital with chief complaints of chills and consistent watery diarrhea after eating raw fresh-water fish. In blood examination, peripheral blood eosinophilia was found. Histological examination from biopsy specimens of both the ascending colon and rectum showed a prominent eosinophilic infiltration in the intestinal mucosa. Although a provocation test could not be performed due to lack of informed consent, a diagnosis of eosinophilic colitis was made on the basis of other findings. Immunohistochemical staining for human mast cell tryptase using monoclonal antibody against human mast cell tryptase showed an accumulation of mast cells in the colonic interstitium.

*Conclusions:* We report a case of eosinophilic colitis in which an accumulation of mast cells in the colonic interstitium was demonstrated.

**Key words:** Eosinophilic colitis. Mast cell.

## INTRODUCTION

Eosinophilic colitis, a subtype of eosinophilic gastroenteritis, is a disease characterized by peripheral blood eosinophilia and a prominent eosinophilic infiltration in the intestinal mucosa. Some reports suggested possible involvement of food allergy as the mechanism of the disease<sup>1,2</sup>. Although mast cells are thought to be critical effector cells in gastrointestinal allergic reactions<sup>3-5</sup>, the role of mast cells in eosinophilic colitis still remains unclear. Very recently, we have reported a case of acute pancreatitis possibly caused by allergy to bananas<sup>6</sup>. However, as far as we have examined literary, there has been no case report of eosinophilic colitis in which the number of mast cells was examined. Here we report a case of eosinophilic colitis in which an accumulation of mast cells in the interstitium of colon was demonstrated.

## CLINICAL CASE

A 35-year-old man with chief complaints of chills and watery diarrhea visited the hospital on March 12th, 2004. In blood examination, CRP was 0.33 mg/dl and peripheral blood leukocyte count was within normal range (8200/ $\mu$ l). No remarkable findings on physical examination were observed. Stool culture was negative for pathological bacteria. He was introduced to our allergy clinic by the finding of peripheral blood eosinophilia (17.9%). A total serum IgE was 350 IU/ml, and IgE against Japanese cedar was 19.20 IU/ml. IgE levels against popular food antigens including fishes were all within normal ranges. No possible findings were present for parasite infection. Endoscopic examination of the upper digestive tract showed mild erosive change on the bulb, a small

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polyp at the fornix area and slight reddening change on the body of stomach. Biopsy could not be performed because reflex for vomiting was too strong. In colonoscopic examination, flare with slight edematous change was seen on both ascending colon and rectum, and biopsies were performed in each lesion. Hematoxylin-eosin staining with the biopsy specimens showed numerous eosinophil infiltration in the interstitium with edematous change of the tissue. The diagnosis of eosinophilic colitis was made by these findings with the clinical summary mentioned above. Immunohistochemical staining for human mast cell tryptase using monoclonal antibody against human mast cell tryptase (Chemicon, Temecula, Calif., USA) with the biopsy specimens showed an accumulation of mast cells in the mucosa and submucosa of colon (fig. 1). Counting the number of mast cells was done using an Olympus BX-50 microscope equipped with a 0.1  $\times$  0.1 mm ocular grid (Olympus Eyepiece Micrometer U-OCMSQ 10/10) in 8 grid fields, and the mean was analyzed. The mean number of mast cells in ascending colon and rectum in eosinophilic colitis were 352/mm<sup>2</sup> and 405/mm<sup>2</sup>, respectively.

Eating raw fresh-water fish seemed to be a highly possible cause of the complaints of the patient. However, provocation test could not be performed as the informed consent of the test was not obtained. Therefore, avoiding eating raw fresh-water fish conservatively followed him. He has been followed up without any specific treatment and the laboratory findings including the number of peripheral blood eosinophils became normal in a month. Until now, the patient has not suffered from any further attacks by avoiding digestion of raw fresh-water fish.

## DISCUSSION

Eosinophilic colitis is a subtype of eosinophilic gastroenteritis. Histologic evidence of a predominant eosinophilic infiltration in the gastrointestinal mucosa in the absence of parasitic infection and extraintestinal diseases confirms a diagnosis of eosinophilic gastroenteritis<sup>7</sup>. In some patients of eosinophilic colitis, food allergy seemed to be associated with the disease<sup>1</sup>. However, direct evidence of allergy has not been consistently confirmed in eosinophilic colitis.

Mast cell granules are known to contain chemotactic mediators causing eosinophilic infiltration in tissues. Bischoff<sup>8</sup> reported that eosinophils and mast cells seemed to be mutually related in the allergic reaction in digestive tract mucosa. However, as far as we know, there is no case report of eosinophilic colitis in which the number of mast

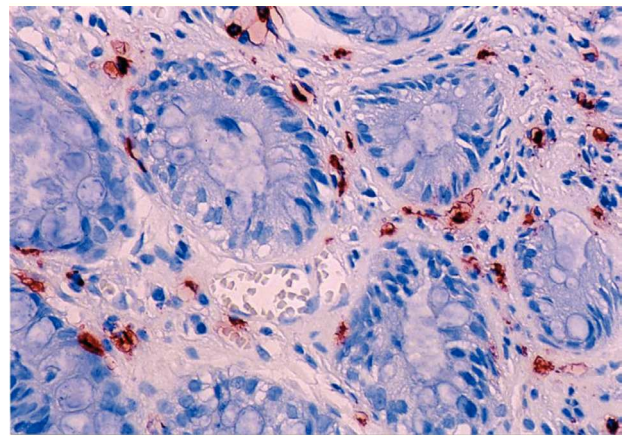


Figure 1.—Immunohistochemical staining for human mast cell tryptase of the biopsy specimen from rectum of the patient. An accumulation of mast cells is seen in the mucosa and submucosa (magnification  $\times$ 400). De Inamura et al.

cells was examined. In this report we examined the number of mast cells in the interstitium of colon. Mean number of mast cells in ascending colon and rectum were 352/mm<sup>2</sup> and 405/mm<sup>2</sup>, respectively. We could not investigate the number of mast cells in colon when the patient's condition became well because the informed consent of the test was not obtained. So as controls, biopsy specimens were obtained from the same site in five normal volunteers, and we examined the number of mast cells for comparison. The mean number of mast cells in normal control in ascending colon and rectum were 150  $\pm$  16 (mean  $\pm$  SD)/mm<sup>2</sup> and 126  $\pm$  63/mm<sup>2</sup>, respectively (data unpublished). Recently Sasaki et al<sup>9</sup> reported in their study that the number of mast cells in ascending colon and rectum from normal control were 122  $\pm$  18 (mean  $\pm$  SD) cells/mm<sup>2</sup> and 110  $\pm$  16 (mean  $\pm$  SD) cells/mm<sup>2</sup>, respectively, and their findings are consistent with those of our study. Taken together, these findings indicate the number of mast cells in the interstitium of eosinophilic colitis may have increased in our present case. Further studies are required.

## CONCLUSIONS

This is the first report of eosinophilic colitis showing an accumulation of mast cells in the interstitium.

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#### ERRATUM:

In the work of the M.T. Montero Vega "New aspects on inflammation in allergic diseases" recently published (*Allergologia et Immunopathologia* 2006;34[4]:156-70) there are several errors. The correct version may be read in the Doyma web (<http://www.doyma.es/ai/>).