Hospital Txagoritxu, Facultad de Medicina, Universidad del País Vasco, Vitoria, Spain.

Correspondence: R. Farré, Unitat de Biofísica i Bioenginyeria, Facultat de Medicina, Casanova 143, 08036 Barcelona, Spain. E-mail: rfarre@ub.edu

Support Statement: This work was supported in part by Ministerio de Ciencia e Innovación (grants SAF2009-02991, PI081908 and PI080277) and SEPAR.

Statement of Interest: A statement of interest for the study itself can be found at www.erj.ersjournals.com/site/misc/statements.xhtml

Acknowledgements: The authors thank Esteve-Teijin (Barcelona, Spain) for kindly providing the gas concentrators used to prepare the gas mixtures. The authors wish to thank R. Nieto (CIBER Enfermedades Respiratorias, Bunyola, Baleares, Spain) and M.A. Rodríguez (Universitat de Barcelona, Barcelona, Spain) for their excellent technical assistance.

REFERENCES

1 Carmeliet P, Dor Y, Herbert JM, *et al.* Role of HIF-1α in hypoxia-mediated apoptosis, cell proliferation and tumour angiogenesis. *Nature* 1998; 394: 485–490.
2 Madi L, Bar-Yehuda S, Barer F, *et al.* A3 adenosine receptor activation in melanoma cells: association between receptor fate and tumor growth inhibition. *J Biol Chem* 2003; 278: 42121–42130.
3 Rofstad EK, Gaustad JV, Egeland TAM, *et al.* Tumors exposed to acute cyclic hypoxic stress show enhanced angiogenesis, perfusion and metastatic dissemination. *Int J Cancer* 2010; 127: 1535–1546.
4 Cormier SA, Taranova AG, Bedient C, *et al.* Pivotal advance: eosinophil infiltration of solid tumors is an early and persistent inflammatory host response. *J Leukoc Biol* 2006; 79: 1131–1139.
5 Terraneo L, Bianciardi P, Caretti A, *et al.* Chronic systemic hypoxia promotes LNCaP prostate cancer growth *in vivo*. *Prostate* 2010; 70: 1243–1254.
6 Yao K, Gietema JA, Shida S, *et al.* *In vitro* hypoxia-conditioned colon cancer cell lines derived from HCT116 and HT29 exhibit altered apoptosis susceptibility and a more angiogenic profile *in vivo*. *Br J Cancer* 2005; 93: 1356–1363.
7 Toffoli S, Michiels C. Intermittent hypoxia is a key regulator of cancer cell and endothelial cell interplay in tumours. *FEBS J* 2008; 275: 2991–3002.
8 Harris AL. Hypoxia – a key regulatory factor in tumour growth. *Nat Rev Cancer* 2002; 2: 38–47.
9 Vaupel P. The role of hypoxia-induced factors in tumor progression. *Oncologist* 2004; 9: 10–17.
10 Bachmann IM, Ladstein RG, Straume O, *et al.* Tumor necrosis is associated with increased $\alpha_v\beta_3$ integrin expression and poor prognosis in nodular cutaneous melanomas. *BMC Cancer* 2008; 8: 362.

DOI: 10.1183/09031936.00185110

Malignant mesothelioma in Metsovo, Greece, from domestic use of asbestos: 30 years later

To the Editors:

Malignant mesothelioma (MM) is a devastating disease, almost exclusively due to inhalation of asbestos fibres, and with higher risk for amphiboles [1]. Mediterranean regions, such as Turkey, Cyprus and Corsica, and others, such as New Caledonia [2], have experienced epidemics of MM as a result of nonoccupational, ''domestic'' exposure to tremolite asbestos and fibrous erionite [3]. In 1987, we reported on the very high incidence, 300 times higher than expected, of MM in the area of Metsovo, a complex of small villages in the prefecture of Ioannina in north-west Greece [4]. This, in conjunction with the previously noted very frequent pleural calcifications among Metsovites [5], led to the discovery of the culprit, a tremolite asbestos-containing whitewash (''luto'' in the local dialect) [6]. The material was used by practically all households until 1940–1950. After that, it was gradually substituted by modern materials that did not contain asbestos. In 1980, luto was used by only 18% of builders and by 1990 it had been abandoned altogether (fig. 1) [7]. In 1996, we reported that the incidence of MM in the period 1985–1994 declined to one-third compared with the period 1980–1984, and we attributed the reduction to the abandonment of the use of luto. As a result, we concluded that the ''Metsovo mesothelioma epidemic'' would decline by 2020–2030 [8].

In the present update, we analyse the epidemiology of MMs after 1994 (1995–2009), compare it with that of the first 15 yrs (1980–1994), and address the question whether, 30 yrs after the first recorded case (1980), an end of the epidemic is indeed expected.

The population under study included inhabitants of the Metsovo municipality, which consists of the villages of Metsovo, Milia, Anilio and Votonossi, with a total current population of 4,417 inhabitants (2001 Greek Population Census; www.statistics.gr/portal/page/portal/ESYE/PAGE-themes?p_param=A1620). The population of the prefecture of Ioannina, as well as the Metsovo population, has been followed-up for 30 yrs (January 1980–December 2009). Taking into account the available census data within that time-frame (1981, 1991 and 2001 Greek Population Censuses), a total of 127,753 person-yrs for Metsovo, and 4,733,915 person-yrs for Ioannina were analysed. No significant change in the population of the Metsovo and Ioannina area has occurred over those three decades since, unlike most Greek villages, there is no migration problem in Metsovo. No data were available regarding the age distribution of the particular population.

MM patients were identified through either the central registries of the two tertiary care hospitals of Ioannina or the death

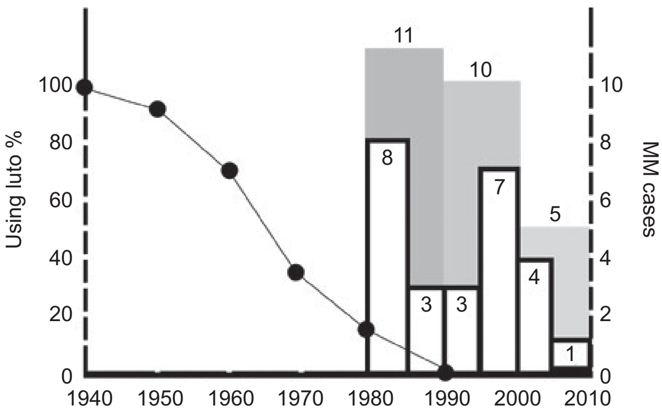

FIGURE 1. Percentage of Metsovo (Greece) households using luto from 1940–1990 (●) and the decline in Metsovo malignant mesothelioma (MM) cases between 1980 and 2009 in 5-yr (white bars) and 10-yr intervals (grey bars).

certificate registry of the Metsovo municipality. All cases of mesothelioma were histologically confirmed. None of the patients had history of an asbestos-related occupation or radiation treatment. The information about the patients, including age, sex, occupation and birthplace, were extracted from the medical records.

We calculated the incidence rates of MM (per 10,000 person-yrs) for each year. For the denominator, total person-yrs were also calculated in 5-, 10- and 15-yr intervals. Direct methods for age-adjustment were not applied, due to the lack of evidence on the age structure of the population under study. Thus, crude incidence rates with corresponding 95% CIs were calculated. All analyses were performed using StataSE 10. (Stata Corp., College Station, TX, USA). All p-values are two-tailed.

There were 26 cases of MM in the Metsovo municipality for the entire 30-yr period, (1980–2009) with a cumulative incidence rate of 2.04 per 10,000 person-yrs. Their distribution in 5- and 10-yr intervals is shown in figure 1, which shows the variability of incidence of MM. As previously reported, 14 cases of MM occurred in the first 15 yrs, while between 1995 and 2009, 12 more MM cases from Metsovo (10 pleural and two peritoneal) where diagnosed at our two hospitals, the last two being in 2002 and 2005 [7, 8]. Of these 12 patients, three were male and nine female, aged 50–86 yrs, and it was confirmed that they had been using luto during 1950–1970. The diagnosis was made by Abram's needle biopsy in three, open pleural biopsy in seven and peritoneal biopsy in two. The observed incidence rates showed no statistically significant differences between the first and subsequent 15-yr intervals (2.2 cases per 10,000 person-yrs *versus* 1.8 cases per 10,000 person-yrs, respectively; $p=0.65$). However, when we analysed the 10-yr incidence rates in a pair-wise fashion, there was a trend of decrease in the last decade; while the observed incidence rates remained practically unchanged for the first two decades (2.6 cases per 10,000 person-yrs *versus* 2.4 cases per 10,000 person-yrs, respectively), the last-decade incidence of cases of MM was less than half (1.1 cases per 10,000 person-yrs) compared with the previous decade ($p=0.1$).

Overall, there was a statistically significant difference in MM incidence rates between the Metsovo population and the Ioannina population outside Metsovo (2.04 per 10,000 person-yrs *versus* 1.48 per 1,000,000 person-yrs, respectively; $p<0.001$) indicating a 137-fold risk increase (95% CI 58.2–375.6). Nevertheless, a considerable decrease in the observed relative risk has occurred between the two 15-yr intervals; the 236-fold increased risk observed in the first 15-yr interval reduced to an 86-fold increased risk in the second.

The present study has shown that a consistent pattern of decline and final end cannot be accurately predicted in the case study of the Metsovo MM epidemic. In 1996, we reported that the incidence rate of MM in Metsovo had dropped considerably in the period 1985–1994 compared with 1980–1984, as in the first 5 yrs, eight such cases had been diagnosed *versus* six cases in the following 10 yrs (incidence rate 3.7 *versus* 1.4 cases per 10,000 person-yrs). Although the difference did not reach statistical significance ($p=0.08$), a 2.8-fold lower incidence following the diminished use of luto could not be ignored. At that time, we hypothesised that the epidemic was fading and was due to complete its cycle in a few decades [8]. Our notion was supported by similar reports on inhabitants of the south-east of Turkey [9]. However, in the present report, we have shown that the initial drop in cases to one-third between 1980–1984 and 1985–1994 did not continue. During the following period, 1995–1999, an exacerbation of MM cases occurred (fig. 1), followed by a new drop (especially after 2002), with only one case of MM in the last 7 yrs (in 2005).

Various reasons could explain the observed fluctuations in MM incidence rates. Random variation due to chance alone could be one explanation; despite the observed profound incidence rate difference, it would take in theory a far longer follow-up period and a potentially far larger population to achieve statistically significant differences. Hence, alternative epidemiological explanations could be pursued. MM cases usually have a latency period of 30–40 yrs since first exposure, but this may be extended to 70 yrs [1], so random events like this can be expected. There is, however, a more attractive, albeit very difficult to prove explanation. There was intense demolition of old houses and luto-free houses were built between 1960 and 1970. This is reflected in the rapid reduction in luto use during this interval (fig. 1). Demolition of asbestos-containing buildings causes very intense release of asbestos fibres into the air [10], with well-known consequences, decades later. In Metsovo, this could have been the reason for the increased number of MM cases between 1995 and 1999.

In conclusion, despite the observed fluctuations, this 30-yr study of the Metsovo mesothelioma epidemic reveals that the abandonment of this tremolite-containing whitewash has resulted in a drop of mesothelioma incidence to one-half and a drop of mesothelioma relative risk to one-third. Thus, our previous notion that, following the gradual abandonment of luto, the Metsovo mesothelioma epidemic could disappear by 2020–2030 may still be valid, although, as a rare case could take up to 70 yrs to develop, no prediction is safe.

A. Gogali*, C. Manda-Stachouli#, E.E. Ntzani¶, M. Matthaiou*, A.K. Konstantinidis*, I. Zampira+, C. Koubaniou*, Y. Dalavanga+, D. Stefanou§, S.H. Constantopoulos* and G. Daskalopoulos*

*Section of Pulmonary Medicine, [§]Dept of Pathology, Ioannina University Hospital, [#]Pulmonary Dept ''G. Hatzikosta'' General Hospital, Depts of [¶]Hygiene and Epidemiology, and [+]Anatomy, University of Ioannina, Ioannina, Greece.

Correspondence: S.H. Constantopoulos, Dept of Medicine, Section of Pulmonary Medicine, Medical School, University of Ioannina, Ioannina 45500, Greece. E-mail: eprevezi@uoi.gr

Statement of Interest: None declared.

REFERENCES

1 Hillerdal G. Mesothelioma: cases associated with non-occupational and low dose exposures. *Occup Environ Med* 1999; 56: 505–513.
2 Constantopoulos SH. Environmental mesothelioma associated with tremolite asbestos: lessons from the experiences of Turkey, Greece, Corsica, New Caledonia and Cyprus. *Regul Toxicol Pharmacol* 2008; 52: 110–115.
3 Baris YI, Simonato M, Artvinli M, *et al.* Epidemiological and environmental evidence of the health effects of exposure to erionite fibres: a four year study in the Cappadocian region of Turkey. *Int J Cancer* 1987; 39: 10–17.
4 Constantopoulos SH, Malamou-Mitsi V, Goudevenos JA, *et al.* High incidence of malignant pleural mesothelioma in neighbouring villages of Northwest Greece. *Respiration* 1987; 51: 266–271.
5 Constantopoulos SH, Goudevenos JA, Saratzis NA, *et al.* Metsovo lung: pleural calcifications and restrictive lung function in North-Western Greece; environmental exposure to mineral fiber as etiology. *Environ Res* 1985; 38: 319–331.
6 Langer AM, Nolan RP, Constantopoulos SH, *et al.* Association of Metsovo lung and pleural mesothelioma with exposure to tremolite-containing whitewash. *Lancet* 1987; 1: 965–967.
7 Constantopoulos SH, Saratzis NA, Goudevenos JA, *et al.* Tremolite white-washing and pleural calcifications. *Chest* 1987; 92: 709–712.
8 Sakellariou K, Malamou-Mitsi V, Haritou A, *et al.* Malignant pleural mesothelioma from non-occupational asbestos exposure in Metsovo (North West Greece); slow end of an epidemic? *Eur Respir J* 1996; 9: 1206–1210.
9 Senyiğit A, Babayiğit C, Gökirmak M, *et al.* Incidence of malignant pleural mesothelioma due to environmental asbestos fiber exposure in the southeast of Turkey. *Respiration* 2000; 67: 610–614.
10 Darcey DJ, Alleman T. Occupational and environmental exposure to asbestos. *In:* Roggli VL, Oury TD, Sporn ThA, eds. Pathology of Asbestos-Associated Diseases. 2nd Edn. Springer, New York, 2004; pp. 17–33.

DOI: 10.1183/09031936.00017011

An audit of hypoxaemia, hyperoxaemia, hypercapnia and acidosis in blood gas specimens

To the Editors:

The emergency management of hypoxaemic patients requires clinicians to avoid the hazard of dangerous hypoxaemia due to under-treatment with oxygen, whilst also avoiding the hazards of hypercapnic respiratory failure (iatrogenic hypercapnia) and oxygen toxicity, which may be caused by over-treatment with oxygen. In the past, many clinicians acted cautiously by giving high concentrations of oxygen to all potentially hypoxaemic patients and a culture evolved that ''more is better''. However, since the 1960s, it has been known that some patient groups, particularly those with chronic obstructive pulmonary disease (COPD), are especially vulnerable to uncontrolled oxygen therapy and a recent randomised study showed that mortality in this patient group was doubled when high-concentration oxygen was used compared with controlled oxygen therapy [1–4]. It has also been demonstrated that hyperoxaemia is associated with increased mortality in patients with stroke, and in survivors of cardiac resuscitation and critically ill patients in the intensive care unit (ICU) [5–7]. The British Thoracic Society (BTS) guidelines for emergency oxygen use recommend a target oxygen saturation range of 94–98% for most emergency medical patients and a lower target range of 88–92% for those at risk of hypercapnic respiratory failure [8]. The proportion of emergency medical patients for whom each target range is appropriate is not known but a recent study of 1,022 emergency ambulance patients in the UK reported that 4% of ambulance patients had exacerbated COPD as the main diagnosis and 5.5% of non-COPD patients had saturation $<90\%$ at some time during the ambulance journey [9].

We studied an anonymised database consisting of blood gas analysis results from 3,524 specimens sent to the Biochemistry Laboratory of the Salford Royal University Hospital (Salford, UK) between June and November 2007. More than 95% of samples were from adult patients (neonatal and paediatric samples were analysed separately). About 5% of samples were arterialised earlobe capillary samples. Most emergency department and ICU samples were analysed on separate blood gas analysers and were not included in this analysis. The results are summarised in table 1. The saturation bands were chosen to correspond with the recommended target saturation ranges in the BTS guidelines, in addition to saturation bands above, below and between these ranges. The majority of patients were receiving oxygen therapy at the time of sampling. 2,693 samples had information about the inspired oxygen concentration, of which 19% were said to be breathing air at the time of sampling and 81% were on oxygen therapy ranging 24–100%.

More than a quarter of samples (26.9%) demonstrated hypercapnia with carbon dioxide tension (P_{CO_2}) >6.0 kPa or 45 mmHg consistent with type 2 respiratory failure, but only 198 (5.6%) samples had evidence of type 1 respiratory failure (oxygen tension (P_{O_2}) <8.0 kPa or 60 mmHg with normal P_{CO_2}). Detailed results are summarised in table 1.

1,458 (41.3%) samples had oxygen saturation $>98\%$ and 1,074 samples (30% of all samples) were hyperoxaemic with P_{O_2} >15.0 kPa (112 mmHg), which is the upper limit of normal in our laboratory at the Salford Royal University Hospital.