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From the authors:

I was very interested by the letter of Z.T. Selçuk and colleagues. Their papers on environmental exposure to erionite initiated by Y.I. Baris are universally known. I completely agree with their observations.

With regard to tremolite exposure, we have found a very similar situation in Corsica [1].

We all agree that thoracoscopy is better than fluid cytology and represents the gold standard for diagnosis and initial prognosis of mesothelioma.

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"Cross-talk" among a multiplicity of pro-inflammatory agents: main cause of tissue damage in pulmonary inflammation?

To the Editor:

I have recently read with much interest two excellent reports in the *European Respiratory Journal* which discussed the role of neutrophil proteinases and defensins in chronic obstructive pulmonary disease [1] and in airway diseases [2]. Reading through these articles, it was surprising not to find any considerations of a major aspect related to the elucidation of the possible mechanisms of tissue damage in the lungs during inflammation. I refer to extensive studies from several laboratories which had proposed that tissue damage in inflammatory and infectious processes may primarily be the result of a synergistic "cross talk" among a multiplicity of pro-inflammatory agents (a multi-component system) [3, 4].

A series of publications [5–14] have shown that a severe and rapid membrane injury (necrosis) could be initiated in mammalian cells by a synergism among subtoxic concentrations of three major groups of agonists. These included a) oxidants (H_2O_2, peroxyl radical, oxidants generated by xanthine-xanthine-oxidase, NO, HOCl, $OONO^-$), b) membrane -perforating agents (microbial haemolysins/phospholipases A_2 and C, lysophosphatides, free fatty acids, cationic proteins, histone [9] and defensins [5], and c) highly cationic proteolytic enzymes, (elastase, cathepsin G) [3, 4, 12]. These synergistic cytotoxic effects can be further amplified by certain cytokines. Furthermore, combinations of oxidants and elastase have also been shown to synergize to cause severe lung damage in animal models [6–10]. It has also been proposed that a deleterious synergism among microbial and host-derived pro-inflammatory agonists may frequently contribute to tissue injury in many infectious and post-infection complications [3, 4]. A notable example is, sepsis and the "flesh-eating" syndrome caused by highly toxigenic and invasive bacteria.

Other studies had also shown that subtoxic amounts of the membrane-active xenobiotics, ethanol, methanol, n-butanol and the pesticide linden [13], could also synergize with subtoxic concentrations of peroxide, proteinases and cationic agents to amplify the damage to endothelial cells in culture. The results with the xenobiotics are of especial interest and concern to pulmonologists as these volatile agents may be inhaled and might then synergize with oxidants, proteinases and cationic proteins released either by accumulating neutrophils or by activated lung macrophages to cause damage to both epithelial and endothelial cells.

It has also been documented that β-lactam antibiotics and a large variety of cationic agents including, elastase, cathepsin G, defensins, lysozyme, myeloperoxidase, spermine, spermidine, histones, polymyxin B and chlorhexidine are all capable of activating the autolytic wall enzymes (muramidases) in bacteria leading to bacteriolysis [14]. Bacteriolysis at least in Gram-positive bacteria induced either by β-lactams or by cationic agents can, however, be strongly inhibited by sulphated polyanions presumably by inactivating the autolytic wall enzymes responsible for breaking down the rigid cell wall. It is accepted that the massive release widely of bacterial wall components (lipopolysaccharide, lipoteichoic acid (LTA), peptidoglycan), *in vivo*, can activate macrophages to release cytotoxic cytokines, NO and also to activate the complement and coagulation cascades leading to sepsis, systemic inflammatory response syndrome (SIRS), multiple organ disfunction syndrome (MODS) and multiple organ failure (MOF) [15].

Today there are controversial opinions and hot debates regarding the approaches to treat sepsis, adult respiratory distress syndrome (ARDS) and additional post-infectious and inflammatory sequelae [15]. Unfortunately, the exclusive use of single antagonists to treat these syndromes has yielded poor results. Such failures may principally be due to, a) the lack of adequate and rapid tests to predict the onset of such complications so that treatment of patients usually starts too late, and b) a lack of sufficient awareness that fighting the deleterious effects caused by synergistic cytotoxic mechanisms necessitates the use not of single antagonists but of cocktails comprised of a multiplicity of anti-inflammatory agents. Hopefully, a wider recognition of synergism concept of cellular injury [3, 4, 11–13] might offer a new and more realistic approach to this complex and still unsolved clinical problem.

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Sarcoidosis and cancer revisited

To the Editor:

The authors of a recent article in the *European Respiratory Journal* [1] have chosen, by identical means, to verify the hypotheses of BRINCKER and WILBECK'S [2] that: a) sarcoidosis and malignancy are associated; b) sarcoidosis predisposes to malignancy; c) this pattern is encountered predominantly in patients with chronic sarcoidosis; and d) the association is limited to lung cancer and lymphomas. This study has disposed of the third part of the hypothesis, the late age of onset of sarcoidoisis in association with malignancy is, as the authors point out, an artefact of the study design, which confines itself to a limited (as opposed to a lifetime) period of observation.

If one pools the author"s male and female data, one finds an odds ratio (OR) observed/expected (O/E) of 1.25, 95% confidence interval (CI) = 0.8, 1.9; if one conforms to the practice of previous studies and excludes nonmelanoma skin cancer, the OR is 1.16, 95% CI = 0.7, 1.8. Does this resolve this vexatious dispute? Not quite. Absence of evidence is not evidence of absence.

For a two-tailed α of 0.05, this study provides a β error of 85%, *i.e.*, an 85% likelihood of incorrectly accepting the null hypothesis if there is a 25% higher incidence of malignancy in patients with sarcoidosis; a sarcoidosis sample size of 4,500, nearly 10-fold that available to the authors, would be required to reduce the β error to 20%; if one excludes nonmelanoma skin cancers the required sample size would be correspondingly larger. The epidemiological approach is even more problematic for specific malignancies: to achieve a 90% power at the same α level, 1,500 patients with sarcoidosis, followed for 10 yrs would be required to demonstrate an association between sarcoidosis and Hodgkin′s disease if the true frequency of Hodgkin′s disease in persons with sarcoidosis was 10-times that in the general population. In brief, the demonstration of an association between sarcoidosis and malignancy by epidemiological means requires unattainable sample sizes, which is why we proposed linkage criteria [3].

By excluding patients with pre-existent or coincidental cancer, the authors limited their hypothesis testing to whether sarcoidosis engenders the development of malignancy. Several authors have suggested the opposite: that malignancy and/or therapy infrequently generate a systemic granulomatous response not easily distinguished from sarcoidosis [3–5]. Can the authors provide any information on this hypothesis from their database?

The authors point out that we observed about half as many cases of sarcoidosis associated with malignancy as they did, 4.5% *versus* 8.6% [3]. The studies are not comparable however, because we did not exclude persons with pre- or co-existent cancer and the duration of observation was considerably more brief.

I was curious to know why the authors excluded persons with bilateral hilar adenopathy known to be of <6 months duration to rule out causes other than sarcoidosis. A recently published study estimated that 99.95% of patients with asymptomatic bilateral hilar adenopathy had sarcoidosis [6]. Could this exclusion have skewed the data?

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