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Reviews

Sick building syndrome, a crossroad in modern occupational medicine assessment

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Abstract

Sick building syndrome (SBS) is a complex syndrome consisting of non-specific symptoms with an onset associated with subjects' presence in some modern building and the disappearance of symptoms shortly after they leave it. The effects of SBS may be the result of a series of protective reactions of the human body triggered by various types of surrounding environment, further suggesting that the human response could be based on a three-phase biological model: sensory perception, low degree inflammatory reactions and environmental stress reactions. Besides stress created by the discomfort of people who develop symptoms, SBS is the cause of an extensive loss of productivity, sickness absenteeism, wasted time in complaints with all the legal punitive issues that arise from them. The subjects diagnosed with SBS are hard to follow-up over time due to workers often leaving their jobs and being lost from cohort databases. Achieving a reputation of a "sick building" may prove difficult to rehabilitate even after expensive repairs and upgrades. In extreme cases closure and even demolition can occur. SBS is an evolving concept and this review we will present part of this evolution and what are the major challenges for its definition.

Keywords: *sick building syndrome, occupational medicine*

"Pollution of the environment is the root cause of all human health problems. Environmental pollution is an incurable disease. It can only be prevented." - Barry Commoner

"Sick" building - When is a building classified as "sick"?

The American Association of A/C Engineers and Heating and Refrigeration Standards (ASHRAE) has determined that a building is considered "sick" when at least 20% of occupants exhibit symptoms of discomfort for more than 2 weeks and if the affected occupants observe the resolution of the discomfort outside the building[1,2]. "Sick" building label applies to many modern buildings that have mechanical ventilation, inadequate flooring and deficient or absent maintenance, inappropriate interior furniture or finishing.

Environment - associated medical entities

Sick Building Syndrome (SBS), as recognized by the World Health Organization, is a syndrome consisting of non-specific symptoms with an onset associated with the presence of subjects in some modern buildings and the disappearance of symptoms shortly after they leave [3]. Although the symptomatology is common in the general population, its pattern of "on-off" expression is determinant for SBS diagnosis. Building-Related Illness (BRI) is a pathological condition with specific symptoms and known etiology, defined in correlation with a dangerous pathological agent not only for occupants of a building but also for visitors or passers-by. BRI includes diseases such as Legionellosis or Aspergillosis, which can be contracted by simply entering a particular building, but continues to affect the subjects even after leaving the building [4]. *Mass Psychogenic Illness (MPI)* occurs when a large number of people are affected or believe they are affected, presenting with a set of symptoms without an identifiable etiological infectious agent. MPI is probably the result of a combination of psycho-sociological factors, but unlike SBS, the symptoms do not disappear after leaving the building [4]. *Neurotoxic Disorder (NTD)* affects people in a building where neurotoxic substances are present. Physical and physiological changes are different from SBS (or BRI), but psychological reactions may be similar [4]. *Sensitivity Related Illnesses (SRI)*. This cluster of environment-associated multi-organ conditions that still lack consensus includes beyond SBS and its homonym Sick House Syndrome (SHS) the following: 1) *multiple chemical hypersensitivity (MCS)* which is a chronic disease manifested by sensitivity or intolerance to a number of chemicals and irritants in small and very small concentrations resulting in multisystem organ damage; 2) *electromagnetic hypersensitivity (EHS)*; 3) *chronic fatigue syndrome* (CFS); 4) *fibromyalgia (FM)*; 5) *irritable bowel syndrome (IBS)*; 6) *Gulf War syndrome* and other. While these morbidities are beyond the subject of the present article, they overlap in risk factors, environmental triggers, symptomatology and pathogenesis with SBS, making them worth mentioning and building momentum for future research [5].

SBS: causes and risk factors

Although SBS has been described since 1970s, its exact etiology is still unclear. The main contributing factors are listed in the table 1 [6]. Although asbestos and radon are included among indoor air quality factors (IAQs) they are NOT considered as causes for SBS or BRI because they lead to very specific chronic illnesses even at distance in time from exposure, whereas BRI and SBS are predominantly associated with acute or immediate health effects [7].

Table 1. SBS contributing factors

inadequate ventilation / thermal comfort and poor indoor air quality (Indoor Air Quality - IAQ)
volatile organic compounds (VOCs) also produced by some molds
internal and external pollution sources
temperature and humidity which promotes the appearance and maintenance of molds
biological contaminants
stagnant water accumulated on ducts, collecting basins, humidifiers, etc., insects, poultry and rodent feces
noise
inadequate illumination
psychological factors

SBS: symptomatology and diagnostic criteria

The presence of non-specific multiple symptoms is a characteristic feature of SBS. It is also essential to correlate the appearance of these symptoms upon entering the building and their disappearance on short notice (< hours) after leaving the building [8]. However, the term SBS must be restricted only to multi-factorial problems without any individual factor exceeding the generally accepted recommended level [9, 10]. Symptoms of SBS are divided into two large groups: 1) muco-membranous symptoms, which should be predominant and 2) general and systemic symptoms, which should not be attributable to any other individual medical problem (asthma, allergy, gastrointestinal disorders, etc.) [6]. By contrast, BRI symptoms are more precisely defined clinically and have clearly identified etiological ca For ease of reference, we will compare the clinical picture for SBS and BRIs in Table 2. BRI pathology is basically the pathology of the diseases already described in their respective clinical chapters, the coined term

Table 2. SBS-BRI clinical comparison (modified after Rostron, 1998) [4]

	Sick building syndrome	Building-related illness
Symptomatology	**Muco-cutaneous sensory irritation of the eyes, nose and throats** - dryness, stinging, stinging sensation voice change, hoarseness - skin irritation - erythema, itching, dryness with exfoliation **Neurological effects:** - mental fatigue, decreased memory, concentration, lethargy, nausea, headache - changes in taste and smell: unpleasant taste and smell **Hyperreactivity of the respiratory tract and of the lacrimal glands:** - rhinorrhea and hyperlacrimation, dry cough, asthma symptoms in non-asthmatic individuals	Clinical presentation is characteristic for each morbid entity diagnosis, but also depending on the anti-infectious and immune response to specific microbes. Other common symptoms: - dry cough - chest constriction - fever - chills - pain, muscle cramps
Associated diseases	Allergic rhinitis Airway hyperresponsiveness	Legionellosis Allergic pneumonitis Bronchopulmonary aspergillosis Cryptococcosis Hantavirus infection
Illness duration	Symptoms appear upon entering the building and disappear within 30 minutes to 1 hour from leaving the building.	Recovery and healing time is prolonged based on clinical evolution and particularities of the respective disease's course. Symptoms do not remit briefly after leaving the building (more than hours or days). Recovery is frequently long.

"building-related" constituting a wider clinical and epidemiological frame of reference. If correctly investigated and documented the building-related illnesses are part of the current occupational diseases tables in many countries, including ours.

SBS Pathology

The initial theory for explaining the SBS was developed by Lars Molhave and Baechler, 1991 [6,11].They stated that the effects of SBS may be the result of a series of defensive reactions of the human body triggered by various types of surrounding environment, further suggesting that the human response can be based on a three-phase biological model: sensory perception, low degree inflammatory reactions and environmental stress reactions. In first phase, the senses, like smell and taste, including peripheral nerve endings that also perceive chemical and physical stimuli (e.g. sneeze defense reaction), interact with the surrounding environment. Weak inflammatory reactions are acute, reversible, systemic, microbiological, metabolic and immune systemic reactions protecting against stimuli. Finally, environmental stress reactions (ex. headache) are a corollary of persistent efforts to identify wanted and override unwanted sensory information, and to maintain protective reflexes. There seem to be a number of unexplained issues with this model: is the sensory stage a mandatory step, or the environmental factor/factors could be the direct initiator(s) of the low-grade inflammation; is there a particular genetic based pre-existent reactivity to environmental triggers in a certain number of individuals that lead to and maintain the chronic status of the inflammation and if so, which are these particular genetic factors?

We see here at least two possible approaches for further research: 1) to constantly extract from the sick building syndrome pool of cases the entities that show a clearer etiological and pathological definition (micro particles, volatile organic compounds) who point more towards building related illnesses and 2) to integrate the previous with the environmental multi-exposure and analyze the overlap.

Despite extensive studies to identify causes in the environment, the reactions and conditions developed cannot be related only to specific exposures [12-16] and therefore, beside the treatment of the somatic symptoms, behavior interventions might be of help [17]. However, more recent research [5] has demonstrated the complex system of biomarkers common to all sensitivity related illnesses (SRIs), which also include SBS/SHS and divided them into three large categories: genetic, immune and metabolic. De Luca and colab. have classified these pathophysiological modifications in three major categories: genetic, immune and metabolic.

Genetic expression of oxidative phase I enzymes (cytochrome 450, CYPs, flavoprotein mono-oxygenase, amine oxidases, xanthine oxidases) followed by phase II reductive and conjugative enzymes (glutathione-S-transferases GSTs, UDP-glucuronyl transferases UGTs, catechol-O-methyl transferases COMT, N-acetyl transferases NATs, epoxide hydrolases, etc.), constitutes a complex array of enzymes produced to detoxify and eliminate toxicants and repair molecular consequences of chemical damage. Overexposure to exogenous or endogenous toxicants, through the interaction with cellular membrane or nuclear receptors, induces the expression of an array of stress-responsive genes, coding for bio-sensing, signal transmission and response elements. Superoxide anion-radical, hydrogen peroxide, lipid peroxides and other ROS play as mediators of the activation of PKs cascades (protein kinases) and /or transcription factors (NFKB, AP-1, ARE, etc.) to start gene transcription and protein synthesis for phase I, phase II and antioxidant enzymes, and modulation of the cytokine-mediated inflammatory response.

Among the possible somatic mechanisms, the more developed approaches include immunological dysregulation, neurogenic inflammation, limbic kindling and neural sensitization, toxicant-induced loss of tolerance, altered xenobiotic metabolism, altered nitric oxide/peroxynitrite cycle, behavioral conditioning and psychological/psychiatric factors. Indeed, adaptation to the chronic non-physiological load of conventional compounds, such as cosmetics, detergents, preserving agents and excipients, pharmaceutical drugs, as well as to brand new molecules, like slow degrading nanomaterials characterizing the rapidly changing environment, requires an extraordinary metabolic effort. Concerning other possible malfunctions of the detoxifying enzymes in SRI, the genetic or acquired alterations of peroxide metabolic processes deserve further investigation, in view of the growing amount of data available on peroxides hyper-production in different environmental intolerances. Of potential interest in the SBS pathology in connection to the characteristic the mucosal symptoms is that both cytosolic GSTs and UGTs are highly expressed in the olfactory epithelium. Also COMT genetic and epigenetic factors are implicated in the impairment of catecholamine regulation, of cognitive tasks and the deregulation of nociceptive signaling of NF-kB. Whether the involvement of other genetic markers present in SRIs could be extended to SBS pathogenesis remains a task for the near future.

Immune markers studied were IL6, eosinophilic cationic reactive protein (ECRP), eosinophil counts (EOS), IgE, etc. Several other authors have proven the direct relationship between various IAQ factors (dampness, mold, temperature) triggering above mentioned immune-inflammatory pathways and the development of SBS symptoms [18].

Metabolic impairment is also reflected by oxidative stress markers such as deficient levels of NO, glutathione GSH, Mg, Vitamin E. All these deficiencies seem to correlate with the impaired capacity to withstand oxidative stress and the enhanced or sustained inflammatory response. Low-molecular-weight antioxidants as reduced glutathione, uric acid, ascorbic acid, ceruloplasmin, lipophilic antioxidants play an important role in counteracting the ROS by-products of the of phase I reactions. Bronchial responsiveness, ECP, eosinophilic counts in blood, total IgE and high-resolution reactive C protein HCRP were predictors of incidence of SBS, indicating that the effect of dampness on incidence of SBS may be mediated by inflammatory mechanisms [19,20]. While not all biomarkers mentioned may be present or involved at all times in the weak reactions present in SBS they prove the common denominator existing with the other SRIs. Further advancements may extend the armamentarium of a modern evidence based personalized medicine with metabolomic, lipidic, proteomic, cytokinomic biomarkers. A 2006 study in Denmark on a group of over 1400 subjects followed for one year long concluded that SBS symptoms predispose to indoor exposure assessment to environmental factors making it difficult to

determine the chronological sequence of exposure and the occurrence of the disease or vice versa due to the bias in data reporting. It has also been observed that subjects with symptoms not associated with SBS have developed SBS symptoms over time by developing the perception of exposure. So, the authors normally asked "SBS - What was first: egg or chicken?" [21]. Awareness of the presence of a potential hazard in the surrounding environment has been shown to affect the self-reporting disease [22-25]. The SBS itself can alter the perception of the indoor environment [26]. All this suggests a very complex dynamic relationship between health or illness and the feeling of risk exposure. These two aspects may influence each other.

SBS socio-economic implications

SBS without creating major health problems to individuals often has potentially problematic socio-economic consequences. Besides stress created by the discomfort of people who develop symptoms, SBS is the cause of an extensive loss of productivity, sickness absenteeism, wasted time in complaints with all the legal punitive issues that arise from them. Achieving a reputation of a "sick building" may prove difficult to rehabilitate even after expensive repairs and upgrades [27]. In extreme cases closure and even demolition occur. In the USA only, for example, the economic consequences of SBS are estimated at 10 to 70 billion USD for commercial buildings [28]. This involves costs for medical care, compensation for 150 million working days and loss of productivity [28].

Discussions and Conclusions

In some economic circles, SBS is considered a management not a health issue. On the other hand, the persistent nonspecific SBS symptoms at work and during work, with complete remission outside this interval raise serious medical treatment and management problems in the given economic context. Often, patients fall through the holes of the medical system, or they get lost in interdisciplinary gaps where they are sent by either physicians who do not find the physical pathology severe enough to treat it, or psychologists or psychiatrists who tell the patients that they somatize their inner conflicts. Neither specialist is able to provide an etiological treatment. Added to this is the economic and social occupational dimension marked by job loss or frequent change of workplaces, in some cases even the loss or change of their private house (Sick House Syndrome - SHS) [5].

The notable economic impact of SBS provides a future framework for all research and studies in this field, with all the difficulties faced by SBS's multifactorial genesis and the increasingly demanding interdisciplinary team to approach it. This morbid entity created and sustained by human activity in an artificial environment intersecting with the natural, biological environment is a challenge for the future. Major changes in the current political-socio-economic paradigms, but also in the medical, technological science are necessary to bring a radical overturn in the perception and approach to solve this complex issue.

Søren Kierkegaard once said that... "There are two ways to be fooled: one is to believe what isn't so; the other is to refuse to believe what is so". In this view, several questions for future research arise: Is SBS a precursor stage for various BRIs or other chronic diseases with distinctive inflammatory baseline such as asthma, COPD, cancer, etc.? As an extrapolation of Molhave's biological model, could it be that SBS is actually the clinical overt manifestation at work of a preexistent underlying subclinical hypersensitivity to multiple environmental triggers? Could be that the discovery of the diagnosis for SBS relies not only on detailed identification of all biochemical, genetic and epigenetic mechanisms that form the root of its pathology, but also on a modern complex statistical integration with lifestyle, socio-economic and environmental factors? Would it be necessary to research for new environmental triggers for SBS that have not yet been taken into account? Are radical changes needed in the existing paradigms of the medical, technological, economic, legal or political responses for SBS today?

These questions need thorough answers in order to complete the picture of the still controverted and enigmatic SBS.

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