

Contribution of Occupational Medicine to Medical Science

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Occupational Medicine is a frontier discipline reflecting progress not only in medical science, but also in related fields and rapidly evolving depending on fluctuating equilibrium among social parties, economic development, and world trades. The formal recognition of Occupational Medicine as a medical specialty dates back to 1700, when Bernardino Ramazzini published *De morbis artificum diatriba* (An account of workers' diseases), which described over 50 occupational disorders along with an account of working conditions at the time, describing occupational asthma in grain workers and providing an accurate account of lead and mercury poisoning. Graduated in Philosophy and Medicine at the University of Parma (on 21 February 1659), Ramazzini worked as a physician in Modena and Padua, and is known as the father of occupational medicine. Ramazzini was also concerned with environmental issues and anticipated modern geographic epidemiology.

Over centuries of economic, industrial and scientific development, occupational medicine has grown in complexity, so that today many other professionals are part of multidisciplinary occupational health teams involved in the promotion and protection of workers' health. Indeed, a constant trait of occupational clinical practitioners has been their commitment to deepen their knowledge and understanding of workplace haz-

ards and processes, calling upon colleagues in related fields in order to arrive at a scientific diagnosis of illness in a particular patient or group of patients.

In the 1990s, considerable conceptual, political, legislative and practical progress in occupational health was observed in many European countries, providing a framework for occupational health practice and strengthening the concept of using multidisciplinary occupational health services and the active participation of employees to improve the working environment and workers' health. Broadening health management practice at work to include environmental and lifestyle determinants of health and maintenance of working ability of employees necessitates the dissemination of workplace health promotion and environmental management methods.

The new model of occupational health practice integrates various occupational health professions, and possibly other specialists, into multidisciplinary preventive services capable of detecting and controlling occupational, non-occupational and environmental risks. It aims at improving working capacity, and employees' health and well-being and their working or general environments. Adequate access to preventive services is necessary to increase equity in health and well-being within and between countries. It is also a prerequisite for establishing socially fair and sustainable trade competition.

Whereas Occupational Medicine has been concerned with workers' health, its continuous search for the etiological basis of work-determined and work-related diseases provided a unique opportunity for re-

search aimed at identifying advances in medicine (prevention, diagnosis and treatment of ill health) as well as advances in toxicology, hygiene, ergonomics, epidemiology. To all these disciplines, occupational medicine provided a significant contribution both assessing the consequences of exposure to occupational risk factors – which can also be considered as “involuntary human experiments” – and contributing basic knowledge and methods.

Another area where Occupational Medicine has been deeply involved in the last decades has been the broad field of biomonitoring, encompassing the development of non-invasive methods to assess not only exposure to harmful agents at the workplace and their early effects, but also workers' susceptibility to noxious agents due to either genetically determined or acquired host conditions. Over the last decades, a tremendous progress has been made in analytical techniques, which today enable us to explore such complex issues as gene-environment interaction in multifactorial diseases.

A lesson learnt from Occupational Medicine during its transition towards Occupational Health is that primary prevention may be effective not only in deterministic disorders, but also in multifactorial diseases and complex traits, in which exposure to environmental agents is both a risk factor and an essential (non redundant) element triggering interaction with host traits. Without exposure to those triggering agents, the whole process cannot take place. A series of examples are available to illustrate these concepts and only a small number will be presented and discussed in this special issue, to illustrate how involuntary human experiments (i.e., occupational exposure to noxious agents) may provide insights on the mechanistic bases of chronic diseases of unknown origin.

Gene-environment interactions are well exemplified by chronic beryllium disease (CDB) and occupational asthma associated with exposure to low molecular weight substances, such as isocyanates. CBD risk has been consistently associated with the expression of a supratypic human leukocyte antigen marker that has been found to be expressed in 84–97% of disease cases in three separate studies and that has been shown to function as the restriction element for Be presentation to Be-specific T-cell clones. It has been hypothesized

that genetically predisposed hosts, when exposed to antigens that trigger an exaggerated cellular immune response undergo the formation of non-caseating granulomas in sarcoidosis, while in CBD the interaction between the HLA class II polymorphic molecules and Be in conjunction with the “right” accessory immune genes, such as tumor necrosis factor α (TNF- α) triggers the chronic immune reaction that characterize CBD. Sarcoidosis has also been associated with major histocompatibility complex (MHC) locus gene markers. As pointed out by Richeldi, an occupational disease caused by the inhalation of Be provided an invaluable model for the study of sarcoidosis, a much more frequent disorder with similar pathological and immunogenetic features. Moreover, at least some of the patients diagnosed as affected by the latter disease were in fact affected by CBD. The application of the concept of studying disorders of unknown etiology using as a model even rare diseases, but with known cause and immune mechanisms will help to advance medical knowledge. In this respect, CBD constitutes a unique model.

Specific IgE antibodies have been documented in only a small subset of affected workers. The absence of demonstrable specific IgE antibodies in subjects with occupational asthma has led to speculation about the existence of IgE-independent mechanisms, with a possible role of T-cell recognition of isocyanates or isocyanate derivatives. Combining clinical, epidemiological, and experimental data has been essential to understand the mechanisms underlying this clinical syndrome, which is well documented in specific working settings, but which could also be associated with exposure to environmental pollutants. As pointed out by Mapp, several lines of evidence indicate that cell-mediated immunity and airway epithelium are involved in the pathogenesis of occupational asthma induced by exposure to isocyanates. Therefore, occupational asthma to low molecular weight substances seems to arise as a consequence of complex traits, including metabolic polymorphisms (e.g. GSTP1), interaction of the agent or its metabolite(s) with macromolecular target(s), T-cell recognition, inflammation and hyper-responsiveness.

Occupational (and environmental) exposure to oxidants, irritants and immunogenic materials dispersed in ambient air either at the workplace or in pol-

luted urban and rural environments may cause adverse effects on the skin and the respiratory tract with either toxicological or immunological mechanisms. A classification of subjects suspected to be allergic into four categories is proposed by Cirila: truly allergic subjects (IgE-mediated), sensitized subjects (with IgE-independent, but immunological underlying mechanisms), hyper-susceptible subjects (abnormally reacting to low doses of irritants) and psycho-allergic (neuro-behavioural responders). This categorization, coming from a historical review of occupational indoor allergies, is currently adopted in the medical practice for environmental outdoor and general indoor allergies.

Since the report by Sir Percival Pott on a cluster of scrotum cancer in chimneysweeps, Occupational Medicine contributed epidemiological and experimental evidence greatly increasing our understanding of molecular bases of chemically-induced cancer. The induction of lung cancer by crystalline silica, firmly established by human epidemiological studies in silicotic patients, received supporting experimental evidence from long-term animal studies and from neoplastic transformation of the target cells in culture, has provided a model for investigating pathogenetic mechanisms that were revealed to be progressively more complex as more advanced methods for molecular studies became available. Saffiotti gives an account of his 50-year experience on cellular and molecular studies on cancer induced by crystalline silica: a choice of animal models is available to study mechanisms and pathways associated with both silicosis and cancer (rats), or silicosis only (mice), or neither (hamsters), which provides experimental data to understand the role of host susceptibility in pathological responses to the same pollutants.

The reactions to silica particles in the lungs stimulate the activation of a number of molecular mediators, including those that are primarily involved with the inflammatory and fibrogenic responses and their immunological aspects, such as interleukins as well as TNF- α . The molecular mechanisms involved in silica-induced carcinogenesis have also been found to include complex molecular mediators and their interactions. The investigation of the molecular mechanisms underlying silica-induced lung carcinogenesis promises to continue to provide new insights into this com-

plex biological response, with its close interaction of mesenchymal and epithelial cells and their cascades of mediators.

A comprehensive view of the biological reactions to silica particles is emerging, according which silicosis is an entirely immunological process that begins with the stimulation of the innate immune system that senses the surface of silica particles as if it were the surface of bacteria or fungi. As discussed by Pernis, the chemical properties of this surface seem to mimic those pathogen-associated molecular patterns (PAMP) that can react with one, or many, of the receptors of the innate immune system, whose activation is followed by a polyclonal hyperactivity of lymphoid cells (adaptive immune system). The whole process reflects the effort to eliminate what is sensed as a potential pathogen, but silica particles are indestructible and the only final solution is to bury them inside collagenous tissue. The immunological pathogenesis of silicosis has much in common with that of the so-called "collagen" diseases, and it is not surprising that these are detected with increased frequency in humans exposed to silica.

Insights into lung pathobiology can now be obtained using non-invasive methods applied to collection and analysis of breath analysis, which is rapidly gaining interest as a tool to diagnose and monitor various aspects of lung injury and disease. Measurement of exhaled breath is safe, rapid, simple to perform, and effort independent. Given that human breath contains upwards of 250 chemicals, the potential for developing new applications is high. As discussed by Corradi and Mutti, much of the current knowledge on breath analysis in Respiratory Medicine derives from years of experience gained in occupational settings, where breath analysis has been used to assess exposure to volatile chemicals. Laboratory based analysis of exhaled air is a complex, expensive and time consuming process and thus is not in wide spread use in occupational medicine. However, recent knowledge of exhaled breath analysis in pulmonology, in particular in bronchial asthma and lung cancer, and the development of fast, and easy to perform non-invasive procedures for breath analysis, re-opened possible application of exhaled breath as a novel approach for biological monitoring of inhaled pneumotoxic substances.

The overview by Costa and colleagues highlights how the study of PON1 has evolved in the past two decades from the field of insecticide toxicology to those of cardiovascular medicine and of drug metabolism. Polymorphisms in the PON1 gene influence both the quantity and the quality of PON1 (i.e. PON1 status). Available evidence indicates that PON1 levels in all cases, and the Q192R polymorphisms in some cases, determine the rate at which a given individual will detoxify a specific insecticide, metabolize harmful oxidized lipids and quorum signaling molecules, and activate or inactivate specific drugs. Given the high occurrence of OP poisonings, the widespread incidence of CHD, and the robust market of pharmaceuticals, research on PON1 is undoubtedly destined to continue and to expand.

Franchini and co-workers illustrate the contribution of studies on the nephrotoxicity of environmental pollutants to nephrology, both in terms of experimental assessment of the target selectivity of some metals or organic chemicals, and in terms of development and validation of biomarkers used to assess early changes in renal integrity and/or function. Microalbuminuria and low-molecular weight proteinuria in subjects suffering from diabetes mellitus and from chronic cadmium poisoning are predictors of an accelerated deterioration of renal function. When persistent microproteinuria is observed in the context of a documented chronic exposure to a suspected or established nephrotoxin, it is prudent to consider that it might

have a similar meaning as in incipient diabetic or cadmium nephropathy. Such a view is corroborated by animal experiments, which support epidemiological studies suggesting that hydrocarbon exposure can accelerate the progression of renal disease towards chronic renal failure. This mechanism seems to be involved in several human renal diseases, where proteinuria is the main prognostic factor to depict progressive renal disease. Avoidance of exposure to heavy metals and volatile hydrocarbons and their derivatives remains essential to prevent the progression of renal disorders towards chronic renal failure.

Despite the use of some agent-specific drugs (e.g., selective chelation therapy of heavy metals in intoxicated subjects) Occupational Medicine has long been committed to the recognition of causal agents and removal from exposure has long been the only available treatment of occupational diseases. On the other hand, the father of Occupational Medicine - Bernardino Ramazzini - already recognized the importance of primary prevention. He not only first asked his patients "*quam artem exerceas?*" (which has been translated as "what you do you do for a living?"), but he also first acknowledged that prevention is more effective than therapy. Despite the tremendous progress of Pharmacology and Surgery over the last three centuries, this may still prove true, and perhaps will remain true even in future, when functional genomics becomes part of routine medical examination.