EDITORIAL

From exposome to microbiome to infectome – pathogens vs. 'sanogens'

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In this issue of the journal, two reviews of major importance are published. Adriani *et al.*[1] give an extensive overview of the risk factors involved in community-acquired meningitis, and provide clinically useful recommendations for prevention and treatment of this often life-threatening disease. The authors identify four high-risk populations, defined by age, medical conditions leading to immunodeficiency, genetic susceptibility or anatomical defects. Lankelma *et al.*[2] report on the recent developments concerning the microbiome, describing the ongoing shift from association studies to intervention studies and clinical trials. In their review, the human gut microbiota is discussed as an organ, involved both in homeostasis and the maintenance of health, and in disease states.

During the previous two decades, our appreciation of microbes has changed dramatically. Microbes were viewed as either directly causing disease, as in the case of bacterial meningitis, or as mere bystanders, like our skin flora, only sporadically causing disease in specific situations, as in a catheter-related sepsis with a coagulase negative staphylococcus. It is only recently that the active role of microbes – not only in causing disease, but also in preventing it – has been recognised and has led to a completely new research field.

Nowadays it becomes clear that direct causality is something uncommon in medicine. In genetic analysis, it has become apparent that monogenic disorders are rare and most diseases are the result of a complex genetic interplay involving many genes. Likewise, the old concept of one pathogen causing one disease is shifting towards a more systems biology based approach. Health and disease can be viewed as the outcome of the interaction between all environmental triggers, both exogenous and endogenous, which we are exposed to in a lifetime, and our genetic make-up. This total of environmental triggers was termed the 'exposome'.[3] Quantification of exposures in time in relation to health or disease is challenging – just as the influence of single genes is difficult to determine in a genome-wide association study (GWAS). However, it has already been proven possible, with modelling and analysis in a manner similar to GWAS in a study focusing on diabetes mellitus.[4]

In a recent review paper, Bogdanos *et al.*[5] introduce the concept of the 'infectome', referring to the part of the exposome reflecting the infectious triggers an individual encounters during life. The authors propose that autoimmunity is generated by a cascade of infectious triggers. It all starts with inflammation, and through cell destruction, autoantigen release, molecular mimicry and activation of autoreactive lymphocytes, it eventually leads to autoimmune disease. In this view, the microbiome is the definition of the collection of microbial genes in a particular region of the body, such as the gut or the oral cavity. The infectome relates to the total of infectious organisms associated with the disease in question, in all body sites. By studying the infectome, and combining these results with the results from GWAS, we may start to understand the connection between genome and exposome. This will enable us to gain insight into the development of disease, which is the first step needed for prevention. Furthermore, as in the microbiome research field, we might be able to identify protective factors, microbes that are working with us against the formation of autoimmunity or severe sepsis. As opposed to pathogens, we might find evidence for 'sanogens', and in the end may even want to use those sanogens in treatment or prevention.

How will this change medical practice? In the coming years, systems biology and modelling will become more integrated in our professional lives, with an increasing need for bio-mathematicians, translating the vast amount of data into clinically useful conclusions. Modelling of infectious diseases as described by Bogdanos *et al.* will greatly influence public health and health politics. Preventive measures will become more personalised. The

public health field will rely more and more on *big data* and the output of systems biology models.

In the end, however, despite all preventive possibilities, people will still get sick. In the age of computational medicine, we will hopefully be able to further understand the totality of determinants of health and disease and to use this knowledge to prevent disease in a more effective way. But for that one patient in your Emergency Department room, presenting with fever and meningism, knowledge of risk factors and treatment options will remain life-saving.

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