EDITORIAL

New morbidities: new challenges

Robert O. Wright

Departments of Pediatrics and Environmental Health, Children's Hospital, Boston, Harvard Medical School and Harvard School of Public Health, Landmark Center East, Boston, Massachusetts, USA

Correspondence to Robert O. Wright, MD, MPH, Associate Professor, Departments of Pediatrics and Environmental Health, Children's Hospital, Boston, Harvard Medical School and Harvard School of Public Health, Landmark Center East, 401 Park Dr, Boston, MA 02215, USA
Tel: +1 617 384 8870; fax: +1 617 384 8994

Current Opinion in Pediatrics 2009, 21:220–221

In the 20th century, medicine and the public health programs of developed nations largely conquered the major causes of childhood morbidity and mortality–infections and poor nutrition. In the 21st century, graduating from childhood to adulthood is no longer a risky venture in Western civilization. In place of these old public health problems are a new set of diseases rapidly rising in prevalence, the so-called 'New Morbidities' of asthma, autism, and attention deficit hyperactivity disorders among others. Researchers refer to such diseases as 'complex diseases' because, unlike infections or Mendelian genetic diseases, they do not appear to have a single major root cause, such as genetic mutations or infectious agents.

These diseases place a large financial and emotional burden on our society and efforts to eradicate them have been largely unsuccessful. Coincidentally, the rise of complex diseases has been parallel to the rise of complex disease genetics, which at first seemed to offer a pathway to understanding mechanisms and, therefore, better informed prevention strategies. Rapid technological advances in genotyping, gene expression analysis and bioinformatics promised to resolve these new morbidities. Indeed, these advances have paved the road for an exciting era of biological discovery. We now understand the structure, diversity and function of the human genome as never before; yet we have made only minimal strides toward better understanding the etiology of common childhood diseases such as asthma.

This is not meant to imply that genetics is unimportant, but that our excitement at these new technologies hid the fact that genetics is only one piece of a very complex puzzle, and alone cannot explain such diseases. The lure of technology has in some ways made us lose, rather than gain, insight. We have been studying complex diseases and child development largely in isolation, staring intently in two dimensions, at a three-dimensional shape. Perhaps we should cease to view our environments or DNA code as causing or determining our health or our development. Instead we should view genetics and environment as modifiable factors for our health. This may seem illogical at first; after all, our DNA sequence is the same the day we are born as the day we die so how can it be a risk factor and not a cause? We know that smoking is a cause of cancer, but not everyone who smokes develops lung cancer, and not everyone with lung cancer smoked. Lung cancer arises from a combination of smoking and host susceptibility, that is, our genetics. In this paradigm, genetics did not cause the cancer, but it made the patient susceptible to the environmental factor – smoking. Smoking 'modified' the genetic risk for cancer, taking it from low to high. Both factors had to be present to develop the disease. You may have a genotype that increases the probability of lung cancer if you smoke, but only if you smoke.

All diseases, at some level, are an interaction between our environment and our genes. Sometimes the importance of one factor overwhelms the role of the other. For example, the genotype for phenylketonuria (PKU) is a more important predictor than phenylalanine intake. However, you may carry the genotype for phenyketonuria, but you will only develop the disease if you are exposed to phenylalanine. The 'risk' of PKU can be modified by diet. With lung cancer, it is the environmental factor, smoking, that overwhelms the effect of genetics, but conceptually it is the same. The weight of scientific evidence suggests that our development and health are a lifelong interplay between our genes and our environment, yet we still conduct studies that search for the 'gene' that causes obesity, or the 'chemical' that causes Parkinson's disease. Such studies often receive excited press releases, fail to be replicated, and then fade from our memory.

What I am proposing is not revolutionary conceptually, and indeed may seem like common sense. Yet the number of studies that rigorously attempt to study both environment and genetics simultaneously is extraordinarily small. I submit that, if we continue down the path of studying DNA sequence or environmental exposures in isolation, we will never understand disease causation. As proof, I offer the intersection of several well known observations. Many complex diseases in childhood (childhood cancers, asthma, epilepsy, autism among others) appear to be increasing in prevalence. Yet these diseases have hereditability estimates of 70% or more, suggesting that genetics plays a major role. If these childhood

1040-8703 DOI:10.1097/MOP.0b013e32832799ca

diseases were mainly genetic, natural selection would reduce their prevalence over time, not increase their prevalence. Furthermore, genetics would work on a time scale of multiple generations, not 10–20 years. Genetics alone cannot explain the increase in these diseases, nor can environmental factors explain the hereditability estimates and the clustering within families. These diseases must be an interaction between our genetics and our environment and we must study them as such.

To further complicate matters, the field of gene–environment interaction is itself changing. Traditionally, we have viewed genetics solely as our DNA sequence, but we now know DNA's function relies on much more than this. Whether a gene is expressed depends in part on the DNA code, particularly in promoter regions of a gene, but it also depends on other factors, such as DNA methylation, modifications in histone binding proteins, and small segments of RNA called microRNA. Many of these factors can be inherited and the field that studies these processes is called epigenetics. Epigenetics is the study of heritable traits that are not coded by DNA sequence. However, epigenetics is also closely related to the concept of Fetal Origins of Adult Disease. Epidemiologic observations by Dr David Barker over 20 years ago that a restricted nutritional environment *in utero* programmed an increased risk of adult diseases, such as hypertension and obesity, were initially met with skepticism. Increasingly, it has become clear that these effects are indeed programmed and that changes in epigenetic marks, such as DNA methylation, can regulate gene expression throughout the life span. Now a plausible mechanism has been found to explain Dr Barker's observations. Fetal life likely represents an opening during which changes in epigenetic marks are particularly malleable to environmental factors. Changes in epigenetic marks, such as DNA methylation, occur from environmental exposures and can program gene expression and health effects later in life without changing DNA sequence. The intersection of the Barker hypothesis with epigenetics means that the very concept of 'gene–environment' interaction is evolving and will undoubtedly change further as other epigenetic marks are discovered.

Although genetics and epigenetics likely play a vital role in causing complex disease, we must not forget that our environments are not all equal. We must also learn the role of environment-by-environment interaction in complex diseases. Poverty and psychosocial stressors such as violence, as well as undernutrition, are not equally distributed in any society. They cluster within specific groups, are themselves toxic, and may also render individuals more vulnerable to toxic chemicals such as lead or particulate pollution. Traditionally, we have viewed poverty as a confounder of chemical toxins, but a more plausible biological role may be that the stressors associated with poverty synergistically augment the toxicity of chemicals. That is, the context in which exposures occur is critical to understanding the degree of chemical toxicity. In this new paradigm, poverty is not an alternative explanation when we observe a toxic effect of chemicals, such as lead, but instead it is a factor that increases the toxicity of these chemicals.

Understanding these biological mechanisms will be daunting and the challenges of the future are far greater than we have ever appreciated; but we are slowly getting closer to understanding complex diseases and unraveling their origins. We are beginning to see that we cannot study genetic or environmental risk factors in isolation. We must study how they interact, and by doing so we will one day learn how to prevent and treat the new morbidities of the 21st century; just as we met the challenges of the 20th century.