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ABSTRACT

The historic debate of nature vs. nurture has emerged as a central yin-yang of contemporary health and disease research. The Human Genome Project provided the capability to define the nature of an individual by one's genetic sequence. But tools are not available to sequence lifelong exposures (i.e., the nurture of an individual). Many believe that nurture has an even greater role than genetics in determining lifelong success, health, and well-being. In contemporary terminology, the cumulative measure of environmental influences and associated biological responses throughout the life span is termed the exposome. This includes all external exposures from the environment, diet, behavior, societal influences and infections, and also cumulative biological responses to exposures and endogenous processes. Pursuit of a "Human Exposome Project" is a vision worthy of our youth: development of strategies and tools will require the brightest and most imaginative. Incorporation of the exposome into education curricula will foster discussion, development of interest, improvement of skills, and promotion of critical thinking to prepare students for civically engaged lives, ongoing study, and future career opportunities. The long-term vision is that sequencing the exposome will support better understanding of healthful and harmful lifelong exposures and lead to improved opportunity for the health and prosperity of all.

Key Words: Environmental health; exposome; cumulative exposures; critical thinking.

○ Introduction

Rapid increases in adverse health outcomes during the past half-century, such as childhood brain cancer and autism, have raised concern about unknown environmental exposures that may affect health. Such unknowns are contributing to a new movement in science to sequence human exposures, much in the way that the previous generation of scientists developed methods to sequence the human genome (Lander et al., 2001; Venter et al., 2001). This effort is termed the *exposome* – the cumulative measure of exposures, including diet, lifestyle, pollutants, and others across

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the life span (Wild, 2005). This brief article is intended to demonstrate why the concepts of the exposome should be taught to young students and how educators might introduce the exposome for the next generation to tackle this challenging endeavor.

The desire for quality of life often translates to affordable convenience in all aspects of day-to-day living, including housing, food, personal products, transportation, education, and recreation. Modern science and technology provide products to support this convenience, with thousands of new products introduced annually. Product safety is maintained by corporate responsibility, along with state and federal policies developed to minimize the most hazardous exposures while assuring access to desired products. Limited effort is focused on low-abundance byproducts and their implications for human health.

Whether there is a need to be concerned about such byproducts is a topic for debate. Paracelsus, the ancient Greek philosopher credited as the father of toxicology, taught that dose makes the poison. This teaching is often interpreted to mean there is less cause for concern with low-dose exposures. Yet, in the case of cancer-causing chemicals, strong arguments support the view that there is no safe level of exposure – especially when considering the multitude of exposures occurring simultaneously in the modern, chemical-filled environment. As more and more health concerns arise regarding cancer, ADHD, endocrine disruptors, obesity, and a multitude of other conditions not explainable by genetics alone, understanding environmental exposures and their complex biological and chemical interactions is key to ameliorating the continual increase in chronic disease across developed and developing countries (Remington & Brownson, 2011; Figure 1).

Studies have demonstrated high estimates for the environment's role in health. Yet a large proportion of the contributing exposures is unknown (Rappaport & Smith, 2010). Even for known exposures, their interaction with each other and ultimate

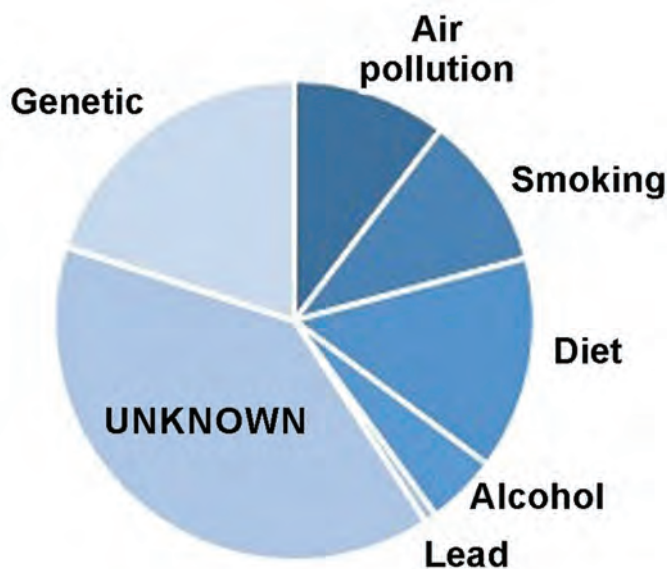


Figure 1. Environmental exposures contribute an estimated 70–90% of disease risk, with a large proportion of these exposures being unknown (Rappaport & Smith, 2010; Lim et al., 2012).

impact on health are poorly understood. A significant gap exists between the current understanding of disease risk and actionable measures to alter these known and unknown exposures that affect health. Figure 1 is based on data from the World Health Organization, showing estimated proportions of exposures implicated in global deaths in 2010 (Lim et al., 2012).

Consideration of these issues presents an important opportunity for students to study and discuss the relevant societal, political, commercial, and personal factors involved in individual decisions and public health policies. From a scientific perspective, the exposome offers students endless opportunity for current study and future research in everything from biochemistry and cell biology to big-data science and wearable medical technologies. Through demonstrating the importance of complex environmental exposures to health and disease outcomes, students can become savvy and empowered citizens with greater investment in their health.

Beyond such discussions and debates lies a critical challenge to address unknowns concerning low-level exposures. In this case, the unknown includes known unknowns and unknown unknowns. Known unknowns include chemicals that have been previously detected and characterized, but for which our knowledge of biological consequences may be limited (Little et al., 2011). Unknown unknowns are a true frontier in biological and toxicological research, representing the undefined chemical exposures that may or may not be detected by current techniques and the completely unexplored biological consequences (Mumtaz, 2010; da Silva et al., 2015). A particularly compelling challenge is to guide and prepare students to address the unknown biological consequences of low-level and complex exposures.

○ Environmental Exposures & the Exposome

Ten years ago, Christopher Wild introduced the concept of the “exposome” as a complement to the genome in defining human

risk of disease (Wild, 2005). He proposed that scientists tackle the question of environmental contributions to disease by systematically studying the link between lifetime exposures and health outcomes. Indeed, much is known about early-life exposures and later disease, but such studies largely address known hazards and often consider only one or two chemicals or classes of chemicals at a time. For instance, fetal alcohol syndrome is a disease process that affects babies of women who drink alcohol during pregnancy. In this case, the hazard is known and public health policies are in place to help minimize adverse health outcomes.

Public health approaches are designed to address the most critical health issues for the population at the lowest cost. Over 30 years ago, scientists studying cancer concluded that many environmental factors contribute to cancer risk (Doll & Peto, 1981). On one hand, the exposome is a simple extension of this line of research: if exposures were studied in more detail, a better understanding could be obtained of the factors and interactions causing disease. So Wild defined the exposome as the cumulative environmental exposures, including diet, infections, drugs, and commercial products (Wild, 2005). A broader view of the exposome includes currently unknown exposures and the biological response due to both known and unknown exposures (Miller & Jones, 2014; Figure 2). Challenges lie in communicating the importance of the exposome to health, creating affordable tools to monitor the broad range of exposures that occur, developing means to accumulate and interpret data from lifelong exposures, and ultimately using such information to predict, mediate against, and manage adverse exposures (Miller, 2013).

○ Implications for Education

Educators face no small task in preparing young students for the complex challenges of adulthood in an interconnected, technology-driven society. Through providing an accessible model to better understand health and disease and increasing exposure to future occupational and educational opportunities, the exposome offers an engaging tool to improve students’ abilities to adapt to a connected and dynamic world.

Today’s educators are faced with many requirements and challenging regulations. Readers may wonder why and how the exposome can fit into a curriculum of competing demands. The “why” is defined throughout this article but can be summarized in two simple and compelling arguments for today’s educator. First, lifelong health is largely determined by one’s environment, and with that understanding, students can be empowered to take action to modify both personal and population-level environmental health factors that directly influence health. Second, the exposome is inherently complex, requiring students to think critically about the integration and application of issues studied in their coursework. The “how” may seem more elusive, but in the examples of classroom applications described below, one can see how integrating environmental health and the exposome into standard science curricula is within reach.

The exposome is an accessible model for understanding health and disease. This paradigm portrays important personal and public health concerns without requiring specific physiology and biochemistry training that students are typically not exposed to in secondary education or, depending on their career track, may never experience before they enter the workforce. By considering issues through a lens

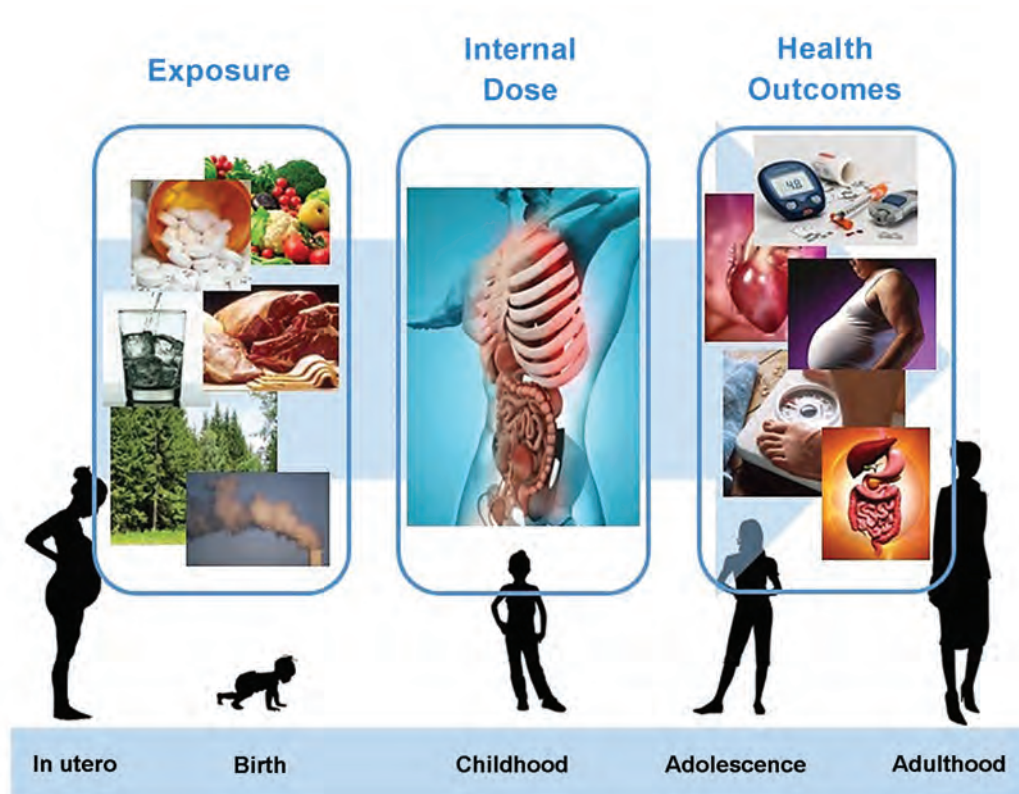


Figure 2. The *exposome* provides a framework to assess complex exposures experienced across the life span. These cumulative exposures, their internal doses, and the body's biological response ultimately contribute to lifelong health outcomes. The exposome offers a new paradigm for understanding how the environment affects health. Photo credits: freedigitalphotos.net for heart and digestive system (by dream designs); internal dose (by cuteimage); baby, child, and teenager (by sattva); all other images public domain.

of health, future occupational and educational opportunities in health disciplines are more accessible. Utilizing the exposome in education offers immediate and long-term personal and professional benefits to the developing student.

○ Opportunities for Innovation

At least four recent developments indicate an exciting future for study of the exposome. Among these, the most important is perhaps the capability to sequence the genomes of individuals. Although the cost is still over \$1000, the information provides knowledge that will enable understanding of how environmental influences interact with one's genes to determine personal health risks. As science advances knowledge of the interactions with genes, personalized diet, exercise, and behavioral strategies will become available to improve health management. The capability to discover one's genetic makeup is available today, and this information is likely to have substantial benefits for some.

A second development is the investment in an electronic medical-record system to collect and assemble knowledge of health-care utilization. This system was initiated by President Obama prior to the Affordable Care Act and mandates that all physicians acquire capabilities for collecting medical records in electronic form. This will enable collection of lifelong exposure information. With this, new opportunities emerge to study health data of populations and individuals. New types of computer search engines are already

being developed for personal health. This is a foundation for cumulative exposure information for individuals and also provides an opportunity for new depth of understanding of the impact of exposures on health. It also brings along ethical questions worthy of critical discussion. Electronic medical records can improve management of disease and continuity of care; new uses and employment opportunities will certainly follow.

A third development is high-throughput devices for personal exposure monitoring. Remote sensing devices and applications for smartphones are revolutionizing capabilities to monitor and record exposures. At the same time, powerful new methods for chemical measurements using high-resolution mass spectrometry hold promise to one day replace traditional laboratory methods for blood chemistry with methods that measure 20,000 or more chemicals in blood and urine (Go et al., 2015). Together these methods allow detailed exposure measurements to be studied for associations with disease risk. The range of possible products and applications is very large. Entrepreneurs will have considerable opportunity to create useful new products while personally profiting from their development and applications.

Finally, computer science, artificial intelligence, and forecasting methods provide new ways to address complex challenges such as interpreting impacts of early-life exposures and later-life events. Much as weather forecasters use time of year and measurements of temperature, wind speed, and wind direction to predict the weather, the cumulative knowledge of exposures along with personal genomics will provide a basis for better predicting health and disease

and therefore will help guide healthy choices for diet, exercise, and other behaviors. Computer-based models and predictions will continue to require human intelligence for appropriate use. The new tools will bring new opportunities for employment, along with new challenges for responsible introduction and use.

○ Scientific Innovation

Cumulatively, these advances foreshadow new approaches to scientific discovery. A key issue for science education is that these approaches often conflict with central principles of scientific method. Scientific method relies on initial observations from which a hypothesis is developed. To test the hypothesis, an experiment is designed, along with controls needed to verify the interpretation. The experiment is then conducted, and the results are interpreted to determine whether the hypothesis is supported by the data. For instance, one can experimentally test whether the bumper on a car is sufficient to prevent damage in a controlled crash when the car is traveling five miles per hour. This process is inherently reductionist, in that it involves controlling all variables except the one being tested. This reduces the complexity to one tested factor.

In the real world, few exposures and outcomes are simple, and this poses limitations on scientific method. In sickle cell disease, one genetic mutation causes different disease responses. In cardiovascular disease, different causes result in the same blockage of arteries. An additional challenge to scientific method is that some important cause-effect relationships cannot be experimentally tested. It is unethical, for instance, to deprive infants of nutrition to test for nutritional requirements. So other methods, such as measurement of nutrients in breast milk of mothers with healthy infants, are used. Such complexities and limitations of scientific method provide motivation for new scientific paradigms.

New research paradigms that help capture high levels of complexity are already gaining momentum. With the explosion of various “omics” technologies, vast amounts of data are being generated, along with new bioinformatics approaches to utilize these data for capturing biological pathway perturbations. For example, integrated personalized omics profiling (iPOP) links an individual’s genetic information with other omics, such as the transcriptome, proteome, and metabolome (Li-Pook-Than & Snyder, 2013). Although the promise of iPOP remains to be seen, it demonstrates one way in which researchers can begin to characterize the exposome and the potential health benefits and/or consequences of complex exposures.

The new societal and technological developments create opportunity for integrative approaches to problem solving. Such approaches are more akin to systems engineering, emergency planning, or hurricane forecasting than to traditional scientific method. A hallmark of exposome research is that it is an intersection of comprehensive approaches and scientific method. An individual is highly complex and not easily characterized. Therefore, researchers must rely on incomplete understanding, with some fairly accurate descriptions while others remain somewhat inaccurate. An individual is also constantly changing – from rest to exhaustion, from sickness to health, from young to old. Some changes are periodic and repetitive while others are progressive and irreversible. New high-throughput methods can provide real-time data on exposures but also can provide information on so many parameters that each cannot be studied individually. Thus,

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the exposome provides a stage for educators to begin a needed transformation of thought and data structure for the future.

○ Applications in the Classroom

The opportunities for innovation are numerous and diverse, holding strong potential for students as they continue on to further education and future careers. And more importantly, in a society with expanding life spans yet increasing chronic disease, there is the opportunity for personal investment in health. Through both individual lifestyle decisions and broader civic engagement, advances can be made to promote long-term health and quality of life by encouraging relevant public policy measures and personal initiative. Given the wide-reaching implications of the exposome, this also extends to a wide range of opportunities for incorporation into secondary-education curricula. A few examples of implementation through different exercises are meant to provide the “how” of the exposome in secondary education science curriculums, a framework for the concept’s utility and integration into the classroom.

○ Levels of Chemical Production

Even if students have heard of the multitude of chemicals put into our environment every day, it is difficult to understand the scale of production and the resulting potential for exposure. A simple exercise can help capture the scale and emphasize the importance of environmental health concerns.

For example, students could be charged with choosing from a predetermined list of chemicals with potential health concerns (e.g., BPA, insecticides, herbicides) and asked to research the level of production in the United States, with the goal of determining the level of production per person per year. Another group in the class can be tasked with determining how many chemicals are produced each year and how many have known health information. Although there are limited conclusions one can draw regarding specific health outcomes, this exercise provides a strong argument for why comprehensive research and policy are needed. This exercise offers students the opportunity to review the current research, discuss the complexities of potential exposures, and propose approaches to better understand the impact on human health and the environment. The process facilitates practicing basic research skills while simultaneously addressing higher-level problem-solving and critical-thinking skills. Depending on the students, the complexity of the exercise can be adjusted to the most relevant level.

○ The Scientific Method

Biology and environmental science coursework are natural avenues to discuss the exposome concept. As students learn the foundational material, applications in the classroom provide the flexibility to incorporate discussions of complex environmental exposures. The scientific method is a long-standing approach taught in most science classrooms. As this process is taught and labs are conducted on the basis of specific hypotheses, a discussion of the exposome paradigm provides a link between current research questions and how to generate the next. Exposome approaches offer a means to generate new hypotheses about the unknowns that science has

yet to define and provide students with an opportunity to critically and creatively think about the future of the scientific process.

○ Individual to Population Health

Biology encompasses many dimensions, ranging from individual anatomy and physiology to environmental ecology and population-scale processes. The shared breadth of subject matter across the exposome and biology curriculums provides one of the greatest opportunities to present the exposome as a comprehensive way of approaching health. Students can explore how various factors such as nutrition, environmental exposures, exercise, social support, and stress all play a role in health. As they assess factors from both an individual and a population level, future education and career opportunities across research, health care, government, and the environment can be discussed.

One exercise for students, particularly as they reach the end of the school year, is to bring together all they have learned. Students start with brainstorming what they think affects their health and, through guided discussion, create a comprehensive list of contributors to health or disease. Once a list is generated, students work together to think about how these might interact with one another (e.g., Venn diagram, flow chart) and what ways these factors can be modified (Figure 3). Particular attention should be drawn to the health consequences of cumulative exposures such as poor diet and lack of exercise in the context of overall environmental exposures. Through this process, the instructor emphasizes how all of these factors play a role in health and how the exposome is a way to approach the complex exposures people face every day. As a wrap-up to their discussions, students think of ways in which these factors can be improved on a personal, community, or public-health level and what future opportunities are available for research, health care, government, and the environment.

Through integration in the classroom, the exposome concept promotes critical-thinking skills required to address the complex exposures faced today and understand the potential implications for health. At the same time, it prepares students to take advantage of the multitude of educational and employment opportunities accompanying recent scientific and technological advances while more broadly setting them up to be civically engaged citizen scientists in their daily lives.

○ The Unknowns

Perhaps the most exciting aspect of the exposome is buried within the concept of unknowns. Analysis of human blood with highly sensitive mass spectrometers provides evidence of many chemicals that no one has identified (da Silva et al., 2015). As students ponder earlier days of exploration, the simple message is that there are many areas worthy of exploration today. The origin and nature of the unknown chemicals are of interest because some are correlated with human disease. Others may be healthful components that have never been studied. This represents a new frontier of science – chemicals that have never been studied before because of an inability to measure them.

Current estimates are that there are more than 10,000 chemicals widely used in commerce and 100,000 agents registered with the U.S. Environmental Protection Agency for commercial use. The most hazardous of these are recognized, monitored, and regulated.

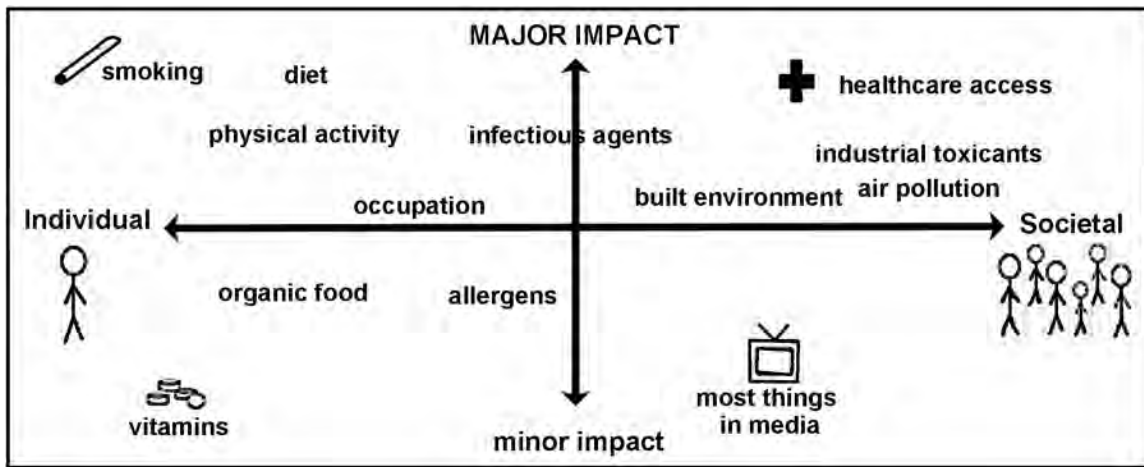


Figure 3. The Modifiable Exposome (adapted from *The Exposome: A Primer* by Gary W. Miller, 2013) demonstrates that not all exposures are created equal. Through understanding the impact of our exposures on health and identifying the level at which they operate (societal vs. individual), improved health outcomes are attainable through personal and public health measures.

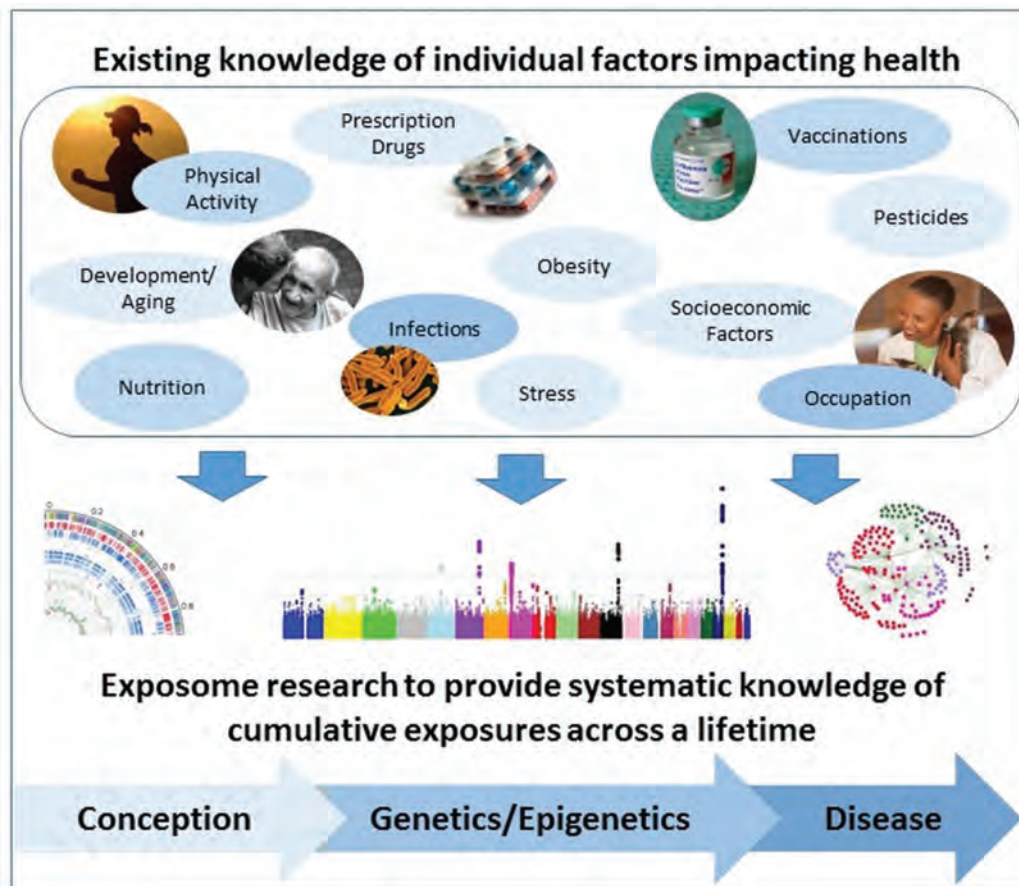


Figure 4. There is a body of scientific knowledge about known individual environmental factors and their impacts on health. The exposome paradigm offers a way to pursue systematic knowledge of complex and cumulative exposures across the life span. The exposome presents a vast opportunity for our youth in terms of improved health, civic engagement, careers, and overall quality of life.

But little information exists on most (Judson et al., 2009). The information that is available is focused primarily on the health impact of individual exposures. Through a systematic approach, the exposome drives research toward a comprehensive understanding of the

complex and cumulative exposures faced across life (Figure 4). Our schools, health clinics, government agencies, and community organizations will benefit from having participants knowledgeable about such exposures and impacts.

An example illustrates the importance of exposure as a frontier for research. Scientists have found that the microbes living in our intestines have important influences on health. Yet these microbes have been portrayed as bad and something to fear. Most microbes in our intestines contribute to the balance of healthy nutrition but some microbes do cause disease. Some microbes, for example, can convert substances in the diet to ones that cause headaches. Thus, if an exposure increases these microbes, it can influence whether a person has headaches.

A key challenge is to learn the types of exposures, any potential interactions, and timings and amounts that cause health problems. This is the essence of sequencing the exposome. With this information, new behavior and lifestyle approaches can be studied to learn how to change exposures to improve health and well-being. While grandiose in scope and importance, this pursuit will require an expectation of humble rewards. Most scientific advances are made through small steps. This is highlighted by genetic studies, which show that even though some genetic differences have large effects on health, most have only a small influence. Similarly, some environmental exposures have a great impact on health, but most are likely to have only a small influence. The greatest need is for study of exposures with small impacts. Small effects from one exposure can be serious when added together with small effects from other exposures. On the other hand, some exposures can also have small effects because only a small number of people are affected, but those individual effects are very meaningful to those who experience them.

Among the greatest challenges is to prepare for the unknowns. If one doesn't know that a threat exists because the threatening agent is unknown, then one is pursuing an unknown unknown. In everyday life, unknown chemicals to which we are exposed represent dark matter of the human exposome (i.e., they are of unknown origin and unknown biological activity). Some are likely to be of dietary origin, and others from commercial products, intestinal microbes, or environmental exposures; within this group, some are of medical interest because they are associated with disease or health outcomes. Tools being developed today will equip those knowledgeable about the exposome to face such challenges.

In the long run, knowledge of the exposome will help forge a sustainable balance for humans and environment by promoting an understanding of the multitude of factors that contribute to overall health. To move toward a sustainable balance in which exposure hazards are minimized for all, science and technology must empower individuals with tools to accurately and systematically monitor individual exposures. This begins with education of our youth about the exposome so that they will be prepared to face this frontier of future science and technology and its ultimate utility for society.

○ For Further Reading

- *The Exposome: A Primer* by Gary W. Miller (2013)
- "Epidemiology. Environment and Disease Risks" (Rappaport & Smith, 2010)
- "Complementing the Genome with an "Exposome": The Outstanding Challenge of Environmental Exposure Measurement in Molecular Epidemiology" (Wild, 2005)
- HERCULES Exposome Research Center: emoryhercules.com
- The Human Exposome Project: humanexposomeproject.com

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