Invited Commentary

Is Phenomenology the Best Approach to Health Research?

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Much research at the National Institutes of Health—for example, the NIH Roadmap (http://nihroadmap.nih.gov/)—has focused on aspects of systems biology and the application of new technologies, which might best be considered descriptive or phenomenological. Unfortunately, etiologic research and social, behavioral, and environmental population studies are at risk of becoming second-class research. In particular, the Roadmap does not address the need for studies of unique populations, determinants of the large variations in disease among populations and over time, and the long incubation period for many diseases. Success in reducing disease in the population will depend on linking the enormous potential of phenomenological methods to excellent etiologic and social/behavioral studies. The phenomenological approach alone will improve our descriptions of disease but may not result in reducing disease burden in human populations.

behavioral research; biological phenomena; delivery of health care; National Institutes of Health (U.S.); research; systems biology; technology

Abbreviations: CHD, coronary heart disease; NIH, National Institutes of Health.

There has been very little commentary about recent changes in research emphasis at the National Institutes of Health (NIH; Bethesda, Maryland) (1, 2). The NIH has focused more on approaches that might best be classified as phenomenological, defined in Stedman's Medical Dictionary as “the systematic description and classification of phenomena without attempt at explanation or interpretation (3, p. 1363)”; for example, measurement of human biology in the host without regard to the agent, etiology, or physical or social environment. This focus appears to be driven by the “nonidentical twins” of reductionism on one hand (a complete understanding of the molecular mechanisms of disease is critical) and, on the other, the concern about using incomplete knowledge, such as from epidemiologic studies, for health policy decisions. A currently popular view is that descriptive phenomenological approaches can be the primary method to reduce morbidity and mortality from specific diseases. I disagree and put forward my arguments below.

TYPES OF RESEARCH

Health researchers can be arbitrarily divided into three groups based on their primary approach to biomedical research (table 1). This classification provides a contrast with regard to the different methodological approaches to biomedical research. First, the etiologic approach focuses primarily on the “causes of disease” in populations. Epidemiology is a key discipline in the etiologic approach, focusing on the interaction of the host, for example, measurements of genetic susceptibility, with the agents that cause specific diseases and the physical and social environments. Epidemiology is not the only approach to etiologic research. The experimental biology approach focuses on etiology by using animal models or human experimental methods to identify the interaction between the specific agents and the host. The experimental biology approach, unlike the epidemiologic approach, provides far greater control over both the genetics (through the development or selection of unique...
TABLE 1. Comparison of etiologic, phenomenological, and social environmental approaches to biomedical research

<table>
<thead>
<tr>
<th>Approach</th>
<th>Outcome</th>
<th>Population selection</th>
<th>Study: longitudinal case-control (human, animal)</th>
<th>Genetics</th>
<th>Clinical trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etiologic</td>
<td>Host-agent-environment</td>
<td>Prevention, identification of risk factors</td>
<td>At risk (epidemics)</td>
<td>Host, genetic susceptibility, gene-environmental effects, phenotypes</td>
<td>Large, primary and secondary prevention</td>
</tr>
<tr>
<td>Phenomenological</td>
<td>Host</td>
<td>Systems biology to improve treatments, identify specific molecules</td>
<td>Not very important animal models, convenience samples</td>
<td>Animal models, molecular biology, systems biology, new imaging techniques in small samples</td>
<td>Genetic analysis, single nucleotide polymorphisms, haplotypes, etc.</td>
</tr>
<tr>
<td>Social environmental</td>
<td>Environment</td>
<td>Public health, reduce disparities, adverse physical environment</td>
<td>Communities</td>
<td>Ecologic, participatory research</td>
<td>Racism: lower priority, effect of social variables on gene product</td>
</tr>
</tbody>
</table>

Animal models) and the environment (through the control of both physical and social factors and, in the case of experimental therapeutics, the dose of an experimental agent). Findings from animal experimental research have led to important epidemiologic studies, for example, the diet hypothesis of atherosclerosis, as subsequently described in this commentary. The relevance of the animal experimental models to human disease is often not simple to evaluate. In the end, the animal of greatest interest in the study of humans is the human.

Second, the phenomenological approach focuses on a detailed description of the host. The human being is basically a “black box” of complex biology. The underlying belief is that a more complete description of the components of cellular, molecular biology and their interactions will lead to a better understanding of the causes, treatment, and prevention of disease (4). The phenomenological approach postulates that, without this thorough understanding of biology, treatment and prevention of disease are unlikely. Unlike the epidemiologic approach, the modern phenomenological approach focuses almost exclusively at the molecular level using systems biology (5). The phenomenological approach emphasizes molecular events that lead to disease. For example, Zerhouni (2) defines “preemption of disease” as removing the molecular events. The phenomenological approach stresses improved treatment of disease, especially pharmacologic therapies based on an understanding of molecular biology. The etiologic or epidemiologic approach focuses more on identifying the external “agents” of disease. Epidemiologic approaches are more oriented toward the primary prevention of disease by removing the causal agents from the environment.

Third, the social science and environmental approaches focus primarily on the environment, not necessarily on either the agent or the host (6). The common theme is that studying the environment, especially the changing environment, provides a major clue to the development of diseases. A major focus of the environmental approach in recent years is the effects of global warming on health (7). A second major area of interest is trying to explain the striking socioeconomic and educational differences in disease across populations (8). The social-class gradient of many diseases is as large as that attributed to most major risk factors (9). Changing the social environment, for example, a better education, income, and occupation, has had a major effect on health outcomes, perhaps as great as or greater than that provided by many of the advances in biomedical sciences (10).

In recent years, behavioral science has been more closely integrated into epidemiologic research, including epidemiologic studies of the effects of social variables on risk factors and biologic determinants of disease (11, 12). There has been an increasing emphasis on using animal models to evaluate the effects of social factors such as stressors on disease pathogenesis (13). Another growing area of interest in the social-behavioral area has been the social and physical determinants of the distribution of lifestyles and risk factors in the population, including studying transmission models similar to those that have been used in infectious disease epidemiology (14).

Although I have classified the research methodology into three areas, overlap across methodologies is substantial.

RESEARCH SUCCESSES

The growth of phenomenological approaches at the NIH is based on successes in basic science methodologies and techniques, especially in the area of molecular biology (e.g., the Human Genome Project), and on equally impressive advances in medical and molecular imaging. This approach has been very successful in identifying therapies for diseases (15–18). The phenomenological approach, because it deals primarily with the host and not with the agent and environmental
interactions, involves little emphasis on studying unique populations, such as the marked geographic variation in disease, trends over time, socioeconomic or ethnic variations, or lifestyle-related differences in morbidity or mortality. Convenient samples, such as volunteers from large managed care programs, are usually adequate for the phenomenological approach as long as tissue, imaging, DNA, and so forth, are available for analysis.

Use of the etiologic approach also has resulted in major successes, for example, finding associations between aspirin and Reye’s disease, lead and cognition, sleep position and sudden infant death syndrome, papillomavirus and cervical cancer, hepatitis B and liver cancer, folic acid and neural tube defects, and hormones and breast cancer (19).

The remarkable success over the past 40–50 years in understanding the epidemiology and prevention of coronary heart disease (CHD) and stroke has led to a dramatic decline in these diseases and increased longevity (20). This research is an example of the combined approaches of etiologic research—epidemiology, animal experimental, and molecular biology (genetics). Critical observations were first made in the 1930s that individuals with physical evidence of high cholesterol, xanthomas, xanthomas, and very high blood cholesterol levels had premature coronary artery disease and then in the 1950s by Keys (21) that the marked differences in CHD incidence and mortality among the countries were related to dietary intake of saturated fat and cholesterol and blood cholesterol levels. The International Atherosclerosis Project led by Holman, McGill, and others in the 1960s went on to demonstrate striking differences in the amount of atherosclerosis among populations in relation to both the CHD mortality rates and dietary differences and blood cholesterol and other risk factors (22). These and subsequent longitudinal studies (23) were the cornerstones of the successful identification of the etiology of CHD. The substantial decreases in population blood cholesterol levels and risk factors followed and led, in part, to a 50–60 percent reduction in CHD mortality in the United States and other countries.

The animal experimental approach contributed very substantially to this research by demonstrating that increased dietary saturated fat and cholesterol led to atherosclerosis in animal models, especially in primate models, and further that dietary modification in these models reduced the progression of atherosclerosis (23). Subsequently, Brown and Goldstein won the Nobel Prize for identifying the specific genetic abnormalities associated with familial hypercholesterolemia. Their work played an important role in the development of potent statin drug therapy to reduce blood cholesterol levels and the risk of CHD (24).

Dahl et al. (25) and others described the strong association of salt intake among populations with risk of hypertension in the 1950s. Stamler (26), in the 1980s and 1990s, further refined the association of salt with blood pressure. Numerous clinical trials have subsequently demonstrated the reduction in blood pressure associated with decreases in salt intake (27). Lifton (28) described genes related to salt retention and hypertension or salt excretion and lower blood pressure.

Baker and Resch, in the 1960s, documented the striking variation in the extent of atherosclerosis in the Circle of Willis in the brain and its relation to blood pressure levels and risk of stroke (29). The development of drugs to treat hypertension beginning in the 1960s, first after studies by Fries and others among individuals with very high blood pressure (30) and gradually highlighting the benefits of lower levels of blood pressure in both younger and older individuals, has led to a dramatic decline in stroke mortality and morbidity in the United States and other countries.

The successes in substantially reducing morbidity and mortality due to vascular disease and in increased longevity have been based, to a considerable degree, on control of risk factors, cholesterol, blood pressure, and smoking and on improved treatment of both CHD and stroke (31, 32).

Jonas Salk, working with Francis and others in the Department of Epidemiology at the University of Michigan School of Public Health, recognized the potential of immunization based on work regarding measles immunization. He found through his surveillance studies that there were only three circulating types of polio and, therefore, that a vaccine against the three different types of poliovirus could likely reduce the incidence of polio in the population (33). The vaccine and oral vaccine by Sabin essentially eliminated polio in the United States and most other countries. We do not know, even now, why only one in a thousand children infected with the poliovirus developed clinical polio and an even smaller percentage developed bulbar polio. Only a very small number of children actually benefited from the vaccine in the trials because most had already developed natural immunity (34). It is very unlikely that Salk could have moved forward in the current research environment without demonstrating the reason why only one in a thousand infected with poliovirus developed clinical disease, that is, the need for understanding the effect of virus on anterior horn cell biology, based on better animal experimental studies, phenomenology.

Epidemiologists are very successful when the differences in diseases among populations or groups of individuals being studied are large or are changing rapidly over time, for example, the epidemic of acquired immunodeficiency syndrome. The tools of the etiologic, epidemiologic approaches are often very crude when trying to understand the relation between agents or environmental exposures and host and disease in relatively homogenous populations.

**CRITICISMS OF METHODS**

Epidemiologic research in recent years has been criticized for its lack of biologic relevance and specific hypothesis testing in research studies. The results of the logistic regression equation have been interpreted as the cause of the many diseases without biologic interpretation of the data.

Epidemiologic studies have been limited by poor definition of host susceptibility defined by such general characteristics as race, education, gender, and age. Studies have also been criticized because they require large samples sizes, require long follow-up, identify only a relatively small number of cases, and have little power to identify subgroups of interest or interactions of key variables. Such studies are expensive. Many diseases have a long incubation period (26); therefore, it is necessary to measure risk factors and determinants long
before clinical presentation of disease in order to understand the relation between the risk factors and disease.

Phenomenological approaches alone have substantial limitations regarding their method of studying human disease. First and foremost, by focusing on the “black box,” they fail to recognize the great variation in the incidence of disease among populations that are due to the effects of the distribution of the agent, host susceptibility, and mode of transmission of agent(s) in the population in unique physical and social environments. The phenomenological approach fails to recognize that epidemics of disease are often related to specific changes in the social and physical environment and therefore that new agents are continuously introduced into the population that lead to both increases in the incidence of existing disease and evolution of new diseases such as acquired immunodeficiency syndrome, obesity epidemiology, and severe acute respiratory syndrome as well as of new strains of influenza virus, introduction of so-called high-caffeine drinks, and the epidemic of cirrhosis of the liver in Great Britain due to the substantial increase in alcohol intake (35). Failure to understand both the temporal and geographic variations in diseases and the interrelation with specific host attributes, that is, genomics, has a stifling effect on research, resulting in a continuous description of “biology” but little focus on etiology.

Underlying the phenomenological approach is the concept that only a small subset of the population is at risk. This concept is probably incorrect. The lifelong risk of clinical coronary artery disease for a man in the United States is about 50 percent and, for a woman, about 35 percent. By age 65–70 years, practically all men in the United States have substantial subclinical cardiovascular disease and are at elevated risk compared with men with a lower atherosclerotic burden risk. Current research often fails to recognize the importance of the subclinical disease and the long incubation period of many diseases (36, 37).

GENOMICS AND PERSONALIZED MEDICINE

The recent successes in genomic analysis of diseases such as CHD, diabetes, prostate cancer (38, 39), and breast cancer (40) have generated new enthusiasm for genomic analysis. Such approaches clearly have substantial value and will likely identify genes that will relate to unique molecular pathways for disease and new therapies. However, it is much more probable that such studies of host susceptibility, that is, genomic analysis, in combination with careful evaluations of the “agents” of disease in well-defined phenotypes, will lead to the advances in health. The etiologic approach views genomic analysis as a measure of host susceptibility by assuming that most diseases, except for unique major genetic abnormalities (41), are the result of a combination of the host susceptibility, the agent, and the environment. An important challenge in genetic-epidemiology research will be to design studies that can evaluate both low prevalence but high relative risk mutations, that is, <1 percent, and polymorphisms, usually >5–10 percent, with lower relative risk in the population (42).

The public and much of the scientific community believe that individualized, personalized medicine, defined by Turner et al. as “the use of diagnostic and screening methods that exploit knowledge of the patient’s unique molecular or risk profile to achieve optimal health and medical outcome” (43, p. 1), refers to the ability to identify specific genotypes that will have a high enough sensitivity and specificity, that is, the area under the receiver operating characteristic curve (44), to enable identification of the majority of the population at risk of disease. For example, if only 10 percent of cigarette smokers develop lung cancer, then the argument is made that identification of those 10 percent of individuals by genome analysis will allow others to smoke cigarettes. However, many argue that the likelihood of finding such genes with high enough sensitivity and specificity is low (45). The recent successes in whole genomic analysis clearly are very important. They must, however, be placed in context. For instance, a recent interesting observation is that a single-nucleotide polymorphism on chromosome 9 (39) is associated with about a 20 percent increase in the risk of CHD for a little over half of the population. In contrast, for subjects in the Multiple Risk Factor Intervention Trial follow-up study, high diastolic blood pressure, high serum cholesterol levels, and cigarette smoking were associated with almost a 20-fold increased risk of CHD compared with lower diastolic blood pressure, lower cholesterol levels, and non-cigarette smoking, all preventable risk factors (46).

Many important diseases are examples of “common source epidemics,” that is, a large segment of the population is exposed through such common sources as diet, air, or water on a continual or daily basis (47). This concept is similar to the exposure of a population to a contaminated water supply. In the exposed population, risk of the disease will vary; an example is diarrheal disease being related to the pathogenicity and virulence of the organism. It would be nice to believe that the genomic approach would be so helpful that individuals would know prior to a waterborne epidemic whether they were susceptible or not susceptible to clinical disease and the severity of the disease or diseases. Perhaps, in the future, we could get rid of water treatment plants and just have a subsample of the population that was susceptible be provided with home chlorination systems or drink bottled water. It would be nice to assume that, in the future, we would have separate, but equal grocery stores for those who are salt sensitive or not salt sensitive (48). We can identify genetic “very high risk” individuals, but they represent a small subset of the population (49).

It is likely that many of the polymorphisms that increase or decrease risk of disease will be related to fundamental biologic processes such as inflammation that are important in determining reproductive outcomes and susceptibility to infectious agents and nutritional deficiencies during the reproductive lifetime rather than to the chronic diseases that have their major effects in the postreproductive years (50–52).

DISEASE PREVENTION

The phenomenological approach focuses its preventive efforts through gene therapy, molecular methods such as islet cell replacement for type 1 diabetes, and use of molecules that can prevent disease in high-risk populations. The
phenomenological approach is probably having its greatest impact in cancer research, because cancer is basically a genetic disorder of somatic mutations in the cell (53). This approach has been very successful for a limited number of cancers and clearly offers the potential in the future for more targeted, individualized therapies (53). Molecular typing of microorganisms has similarly led to improved individualized therapies and better understanding of the epidemiology and control of infectious diseases (54).

The etiologic approach has focused primarily on prevention of disease by modifying the interaction between the agent and environment and the host. The biggest success in reducing incidence of solid-tumor cancers now comes from the merger of good epidemiology and laboratory research, for example, that regarding tobacco and occupational exposures and lung and other cancers. Further examples include hepatitis B and liver cancer, human papillomavirus and cervical cancer, hormones and breast cancer, alcohol and head and neck cancer, and antiinflammatory drugs and reduction of risk of polyps and probably colon cancer. The development and application of early detection, that is, screening, has also contributed to a reduction in cancer mortality. We are much more likely to reduce cancer morbidity and mortality by understanding etiologic pathways, host (genetic) agents(s), and unique environment(s) (55, 56). New therapies, especially for metastatic cancer morbidity and mortality by understanding etiologic pathways, host (genetic) agents(s), and unique environment(s) (55, 56). New therapies, especially for metastatic disease, are needed and likely will benefit from new molecular approaches. Prevention will be the big winner.

DISCUSSION

I propose that we link all three approaches—etiologic, phenomenological, and social/physical environmental—for a successful research agenda. They are all equally important. The key is high-quality research. For example, it is most likely that the successes of genomic analysis will depend on the combination of "host susceptibility, genomics" and better identification of the likely agents of disease in the environment (57). The ability to identify these environmental agents is currently a major challenge (58–60). Well-designed and implemented epidemiology studies will be a key component.

We need to train new investigators to appreciate all three approaches so they can work together in an environment in which the pitfalls and the successes of each methodology are understood. Laboratory investigators who do not understand the determinants of disease and their distribution in the population (e.g., the true meaning of the word epidemic) are unlikely to be nearly as successful as those who do understand such information. Similarly, the epidemiologist who fails to make an effort to combine the new techniques in systems biology with etiologic research will be left behind and be equally unsuccessful. We need to learn from past remarkable research successes, especially in cardiovascular disease and infectious diseases. We need to develop improved training programs that are effective in first explaining and then integrating the methods of the etiologic, phenomenological, and social and physical scientist approaches.

Large, multidisciplinary studies such as the Coronary Artery Risk Development in Young Adults (CARDIA) study; the Cardiovascular Health Study (CHS); the Multi-Ethnic Study of Atherosclerosis (MESA); the Health, Aging and Body Composition (Health ABC) Study; the Study of Osteoporotic Fracture (SOF); and the Women’s Health Initiative (WHI) have provided an excellent platform for training by combining disciplines from laboratory research, imaging, epidemiology, genetics, and so forth, to test specific hypotheses. In recent years, these studies have expanded training opportunities to other new investigators not affiliated with the primary funded institutions. The keys to success have been a well-defined population, testing of specific hypotheses that both have biologic relevance and offer potential new information, application of new technology, availability of biologic samples (including DNA, cells, etc.), testable hypotheses, and excellent multidisciplinary mentoring for basic sciences and for clinical, epidemiologic, and social sciences. Unfortunately, the NIH has not developed an effective approach for long-term support of these types of studies. We should develop a mechanism for study-specific rather than institutional-specific types of training programs. The loss of these valuable resources will have a detrimental effect on research.

In addition, it is time to develop strong cross-institutional research programs at the NIH and universities that focus on specific high-priority topics and include a multidisciplinary approach incorporating the etiologic, phenomenological, and social-behavioral sciences. For example, the obesity epidemic cuts across many NIH institutions. It makes little sense to have separate programs at each institute. Why should the National Cancer Institute have a program on obesity, the metabolic syndrome, and cancer; the National Heart, Lung, and Blood Institute have one on the same topic, with heart disease as an outcome; and the National Institute of Diabetes and Digestive and Kidney Diseases study the molecular biology of obesity and treatments? The goal should be to reduce the prevalence of obesity by understanding the etiology, molecular biology, and genomics of obesity and to decrease the morbidity, disability, and mortality attributed to obesity.

We need to reorganize training so the programs are really multidisciplinary and do not just pay lip service to one or two components. Poor study designs, selection of inappropriate population(s), and lack of relevant hypothesis testing given prior information about the distribution of disease in population(s), incubation period, "risk factors" and phenotype(s) still result in lesser quality research. Unfortunately for many nonepidemiologists, hospitals, and clinic-based case-control studies or analysis of existing large administrative data sets, clinical epidemiology is considered primary epidemiology research (61). The rich methodology of epidemiology and the important leads from epidemiologic studies that will greatly enhance phenomenological research are lost. The large and consistent difference in disease incidence by time, place, and person—that is, host characteristics—is the core of epidemiology research and greatly enhances understanding of the etiology and prevention of disease.

The true value of the extraordinary, new scientific technologies will therefore depend on integration. Recently, for
example, epidemiologists have begun to model the systems biology approaches to epidemiology research (62–64). Such an approach may be useful but only if combined with good epidemiologic-type research that results in testable hypotheses.

Finally, and perhaps most important for the public health, is when do we determine that the focus of research should shift to prevention and applied public health? Do we need to know the specific molecular biology of a disease to apply good preventive, public health programs to reduce morbidity and mortality? The answer is obviously no. Do we really need to know the exact pathophysiology of the evolution of atherosclerotic plaque to prevent CHD? For example, how much of the morbidity, disability, and mortality due to vascular disease and diabetes would be prevented by much better modification of the three common source epidemics of high salt intake, high saturated and low polyunsaturated fat intake, and consumption of too many calories and not engaging in enough exercise (65)? How much of the cancer incidence could be reduced by better preventive approaches (66)? Prevention and public health not based on good science, whether epidemiology, phenomenology, or environmental research, will not be very successful and could even have negative consequences. The future for etiologic, social, environmental, and phenomenological approaches is very positive. We need the vision and leadership to work together to improve the health of the population. A parochial view (1, 2, 4) that one approach is king is not a good approach, even when funding is more limited at the NIH.

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