The invitation to give the Thomas Parran Lecture is both a pleasure and an honor for me. I wish first to indicate something of the life and contributions of Thomas Parran. Dr. Parran was born in 1892, and received the Master of Arts degree at the University of Maryland and his medical degree from the Georgetown University, both in 1915. He joined the Public Health Service shortly after graduation, became Chief of the Division of Venereal Disease, and then was appointed Health Commissioner of the State of New York by Franklin Delano Roosevelt when he became Governor of that state. When Roosevelt was elected to the Presidency he appointed Dr. Parran to Surgeon General of the Public Health Service. In addition to these important posts in the practice of public health Dr. Parran was a founder of the World Health Organization and both the founder and first Dean of the Graduate School of Public Health at the University of Pittsburgh. On retirement from Pittsburgh he became President of the Avalon Foundation. Some of Dr. Parran’s contributions to public health included his courageous attack on venereal diseases, his promotion of clinical research at the National Institutes of Health, his emphasis on the right of individuals to good health and medical care, his promotion of improvements in diet, particularly in good milk supplies, and his participation in international health movements, such as the WHO and the Pan American Health Organization. Dr. Parran’s book on syphilis, entitled Shadow on the Land: Syphilis (published by Reynal and Hitchcock, New York, 1937), in which he presented his program for the control of venereal disease in the United States, was a pioneering publication that dared to bring this problem to the open attention of the public. It should still be of interest to those concerned with the control of infectious diseases in this country.

HENLE-KOCH POSTULATES

In my presentation on the chronology of causation and disease, I wish to emphasize three points: first, that the Koch postulates should really be termed the “Henle-Koch postulates”; secondly, that those postulates...
were not regarded as rigid criteria by Koch himself at the time they were presented and should not be regarded as such today; and thirdly, that all of our concepts of causation are limited by the technology available to prove them and our understanding of the pathogenesis and epidemiology of the disease at the time of the investigation. A fuller exposition of this chronology has previously been published (1). Let us first turn to the Henle-Koch postulates. Jakob Henle was a German-born physician who went to Zürich at age 31 as Professor of Anatomy where in addition to his brilliant contributions to our understanding of the histology of the retina and the kidney and many other organs he wrote in 1840 an essay, "On Miasmata and Contagie" (2), in which the concept was advanced that "Before microscopic forms can be regarded as the cause of contagion in man they must be constantly found in contagious material. They must be isolated from it and their strength tested." This essay was written some 42 years before the first bacillus, that of tuberculosis, was discovered by Henle's pupil, Robert Koch, in 1882. Henle left Zürich, went to Germany and finally became Professor at the University of Göttingen where Koch studied under him and adopted the concepts of his teacher. Koch's contribution to causation was made originally in 1884 and more formally presented in a lecture given in 1890 at the International Congress in Berlin (3). These postulates have become our classical point of reference in relating causative agents to disease. The major features were that the parasite must be present in every case of the disease under appropriate circumstances, that it should occur in no other disease as a fortuitous and non-pathogenic parasite, and finally that it must be isolated from the body in pure culture, repeatedly passed, and induce the disease anew. These criteria of causation have been slavishly held up as the only true basis for establishing causation. As recently as the October 29, 1977 issue of Lancet (4) some putative bacterial causes for Crohn's disease were discarded because they did not fulfill these postulates. Yet it is clear that failure to fulfill them fully was not regarded by Koch himself at the time of presentation as being grounds to exclude the possibility of a causal relationship and they certainly should not be so regarded today. Koch recognized that the cause of anthrax, tuberculosis, erysipelas, tetanus and many animal diseases fully fulfilled his criteria. At the same time he recognized that there were many causes of illness which did not fulfill the criteria, such as typhoid fever, diphtheria, leprosy, relapsing fever and Asiatic cholera. Cholera, in particular, should be noted because Koch isolated the organism of this disease in Egypt and was well aware of its capacity to produce epidemic disease in man. So, even at the time of presentation, Koch emphasized that not all the criteria were necessary for proof and that just the first two were sufficient. The second criteria of the postulates became a problem in fulfillment when the carrier state was recognized for diphtheria by Park and Beebe (5) and by the work of Chapin (6) and by Koch himself for typhoid fever (7) in the period 1895-1902.

CAUSATION IN VIRUS DISEASES

The virus era opened in the 1900s, and by 1930 many viruses had been identified in mice and tissue culture. In 1937, Thomas Rivers, in his Presidential Address to the American Society of Immunology (8), emphasized the following limitations of the Koch postulates for virus diseases: 1) more than one agent might be needed to produce a given disease; 2) viruses could not be grown on lifeless media but required living cells in contrast to bacteria; and 3) asymptomatic carriers existed. Rivers proposed a set of criteria quite similar in essence to those of the Henle-Koch postulates but included two additional concepts: 1) the reproduction of the disease experimentally should exclude the possibility that the laboratory animal was infected with some laboratory virus and include appropriate con-
controls, and 2) that antibody to the disease should appear during the course of the illness.

**Huebner: Guidelines for Establishing a Virus as Cause of Disease**

These concepts of Rivers on the etiology of virus diseases became untenable when many viruses were sometimes found to be simultaneously present in ill persons and even in healthy people. In 1957 Dr. Robert Huebner who is now Chief of the Laboratory of Tumor Virology, National Institutes of Health, discussed the virologist's dilemma (9). He indicated that the presence of many viruses—even in normal people—made the identification of the presence of a virus of low order in establishing causation and one could derive spurious causative associations if you based the conclusions on this fact alone. He recognized that some infections were due to multiple viruses, and that sometimes viruses could produce chronic diseases, or carrier states, or that viral reactivation occurred. Huebner's contributions included what he called a bill of rights for prevalent viruses. They emphasized that the mere presence of the virus should not be regarded solely as the basis for etiology and he introduced epidemiologic principles by longitudinal and cross-sectional studies as an element of proof in causation. He also emphasized that the disease should be prevented by a specific vaccine to the suspected agent. This concept is of great importance in establishing the etiologic relationship of a suspected infectious agent to that disease. Huebner also emphasized that one needed money in order to accomplish the establishment of proof and included this as a ninth criteria for etiologic studies.

**Broadening of the Concepts of Causation for Virus Diseases**

These concepts of causation for virus diseases were then broadened over the next 10 years by the recognition that the same clinical picture or syndrome could be produced by a variety of different agents, that different agents predominated under different epidemiologic circumstances, and that the host response to a given virus would vary from one setting to another. These ideas were expressed by Evans in 1960 (10) and 1967 (11) as they related to acute infectious diseases. It also became clear that the agent alone was a necessary but not sufficient factor needed to cause most diseases. Co-factors and the susceptibility of the host were of key importance in the occurrence of clinical illness.

**Immunologic Proof of Causation**

The next problem arose with the isolation of a virus now known as the Epstein-Barr virus (12) and with the identification of an antigen known as the Australia antigen by Blumberg and his associates (13). These two agents were established as causally related to infectious mononucleosis and to viral hepatitis B, respectively, mainly by serologic studies. The agents were a particular challenge in terms of the Henle-Koch postulates because they could not be grown in pure culture nor did their injection reproduce the disease in experimental animals. This resulted in the establishment of an immunologic proof of causation. The criteria required that antibody to the agent is regularly absent prior to the disease and that it regularly appears during illness. The absence of the antibody should indicate susceptibility to infection and its presence indicate immunity. Antibody to no other agent should be similarly associated with the disease unless it is a co-factor. These criteria of immunologic proof were the basis for the association of Epstein-Barr virus and infectious mononucleosis (14). The discovery of this relationship was made in 1968 by Dr. Werner Henle, his wife, Dr. Gertrude Henle, and a young associate, Dr. Volker Diehl, in Philadelphia (15). It is a particular irony that Dr. Henle, who is the grandson of Jakob Henle, established the causative relationship of EBV to infectious mononucleosis without fulfilling a single
one of the postulates set up by his grandfather and by Robert Koch. This serves to emphasize that we must change our criteria with our technology.

**SLOW VIRAL INFECTIONS AND CHRONIC NEUROLOGIC DISEASE**

The next challenge to the Henle-Koch postulates arose with the recognition of agents called slow viruses. These caused kuru, a disease occurring in the Fore tribe in New Guinea, and Jakob-Creutzfeldt disease, a pre-senile dementia. The work on these agents carried out by Dr. Gajdusek and his associates at the National Institutes of Health resulted in the award of the Nobel prize to Dr. Gajdusek in 1977 (16). The particular difficulties posed by these agents in relation to causation were their long incubation period, their association with chronic neurologic diseases and, most importantly from the standpoint of the Henle-Koch postulates, the fact that the agents could not be isolated in tissue culture in the laboratory. Furthermore, these unique agents did not produce an immune response and were highly resistant to a great variety of physical and chemical agents. A new set of criteria for causation was therefore needed for this group.

Dr. Richard Johnson of The Johns Hopkins University and Dr. Clarence Gibbs, an associate of Dr. Gajdusek’s at the NIH, proposed guidelines (17) for establishing causal relationship which were based on 1) the consistency in animal transmission of the agent, 2) the fact that the agent should be serially transmissible in experimental animals with filtered material and 3) that similar results should not be obtained from normal tissues. In light of our knowledge of the presence of many viruses in the intestines and throat of healthy persons, it would not be surprising to me if normal brain tissue may not sometimes contain latent agents. It is well recognized that herpes zoster and simplex and papova viruses can remain latent in many tissues, including nerve tissue. Thus, their third criteria may produce difficulties in interpretation in the future. There are also some “conventional viruses” associated with chronic neurologic diseases, namely measles virus in relation to subacute sclerosing panencephalitis (SSPE) (18) and papova virus in relation to progressive multifocal leukoencephalopathy (PML) (19). In both of these conditions reactivation of a virus in which the primary exposure was years before is responsible for the chronic disease observed. In SSPE the main epidemiologic event appears to be infection with measles virus very early in life at a time of inadequate host response (20). With PML, alteration in our immune system by immunosuppression either naturally induced, as in Hodgkin’s disease, or artificially induced by immunosuppressive drugs is responsible for the reactivation of this agent (21). Thus the criteria for causation in these diseases depends on the identification of the agent in brain tissue, the presence of high antibody titers to the virus and, at least for SSPE, the experimental reproduction of the disease in a laboratory animal (22).

**EVIDENCE RELATING VIRUSES TO CANCER**

The possibility that viruses might cause cancer required new criteria of causation. The problems in establishing this relationship include the long incubation period between exposure to the putative agent and the cancer and the probability that disease results from reactivation of the virus rather than from a primary infection. The agents most commonly recognized as the best oncogenic candidates are the herpes viruses. But proof of causation is difficult because they are common and ubiquitous viruses, probably require co-factors, and there are difficulties in reproduction of the cancer in animals. In addition, human volunteer studies are not possible. There is also the probability that the cancer may have different causes in different geographic areas or under different epidemiologic settings (23). The most likely oncogenic candidate is Epstein-Barr virus in relationship to Af-
rican Burkitt lymphoma and to nasopharyngeal cancer. The elements of causation consist immunologically of the presence of higher antibody titers in cases than in healthy, matched controls and the demonstration of high levels of antibody prior to the cancer; and virologically of the presence of the viral genome in tumor cells and the ability of the virus to transform cells; and thirdly, (at least for Burkitt lymphoma), experimental evidence that the virus can induce a malignant lymphoma in animals. Similar virologic and serologic proof exists for EBV and nasopharyngeal cancer, except this cancer has not been reproduced in experimental animals. It is important to emphasize that co-factors are involved in the appearance of both of these cancers. In Burkitt lymphoma the essential co-factor appears to be malaria. Infection both by EBV and by the malarial parasite in the first year of life may be requirements for a malignancy to develop. This infection occurring early in life is reminiscent of the relation of SSPE and measles. The presence of high antibody titers prior to the development of Burkitt lymphoma has recently been demonstrated in a massive prospective study of 45,000 children in West Africa (24). It is important to recognize that not all tumors fulfilling the histologic criteria of Burkitt lymphoma are associated with EBV. American Burkitt lymphoma, for example, is not usually associated with high EBV titers, the genome has been absent from the tumor tissue and in some cases EBV antibody has been entirely absent from the blood, indicating that EBV infection had never occurred (25). In nasopharyngeal cancer genetic factors seem to be an important risk factor since HLA antigen 2 and a new antigen called Singapore 2 have both been associated in Chinese with a fivefold higher incidence of their susceptibility to nasopharyngeal cancer than in Chinese lacking these characteristics (26). Another virus of the herpes group associated with possible malignancy is herpes type 2 in cervical cancer. Here the virologic and serologic evidence is much less convincing than in African Burkitt lymphoma (27). It is clear that at least 40 per cent of cancer of the cervix may occur in the absence of antibody to HSV 2. My own view of the relationship of viruses to cancer is that the host plays a critical role in the development of the malignancy. Such factors as the age at the time of infection, the immunologic state of the host, the presence of co-factors such as concurrent infection, and the genetic attributes as expressed by human leukocyte antigens, all play a role in the pathogenesis of the malignant process.

CAUSATION IN CHRONIC DISEASE

Let us now turn to the issue of causation in chronic disease. Interest in this began around 1957 and was based on the Henle-Koch postulates. Important in this early work was the contribution of the late Dr. Yerushalmy and the late Dr. Palmer (28) who proposed a series of relationships that include the concepts that 1) the suspected characteristic must be found more frequently in persons with the disease than in persons without, 2) that persons possessing the characteristic should develop the disease more frequently than those not possessing it, and 3) that this association must be tested for its validity by investigating the relationship of the characteristic to other diseases in order to establish the specificity of the characteristic and the disease. These guideposts for implication of an etiologic factor in a chronic disease were amplified by Dr. Abraham Lilienfeld, who proposed five additions: 1) the incidence of the disease should increase in relation to the duration and intensity of the suspected factor, 2) its distribution should parallel that of the disease in all relevant aspects, 3) a spectrum of illness should be related to the exposure to this suspected factor, 4) reduction or removal of the factor should reduce or eliminate the disease and 5) human populations exposed to the factor in controlled or even in natural experiments should de-
velop the disease more commonly than those not exposed (29).

The contributions of the committee appointed by the Surgeon General to delineate the relationship between smoking and health should also be recognized (30). They included five features of association between a putative cause and the disease; namely, consistency, strength, specificity, temporal relationship, and the coherence of the association.

CRITERIA FOR CAUSATION: A UNIFIED CONCEPT

A review of these various concepts of causation in infectious diseases and in chronic diseases has led me to try and formulate a unified concept (1). It combines the elements of many of the guidelines previously mentioned. The main features are 1) the prevalence of the disease should be higher in those exposed than in those not exposed, 2) that exposure to the putative cause should be present more commonly in those with the disease than in those without the disease, 3) that the incidence should be higher in persons who are so exposed than in those not exposed as shown in prospective studies, 4) that exposure to the suspected factor should precede the disease, 5) that there should be a measurable biologic spectrum of host responses, 6) that experimental reproduction of the disease should be demonstrated, 7) that elimination of the putative cause should decrease the incidence of the disease, and 8) that prevention or modification of the host response should decrease or eliminate the expression of the disease. These concepts are not original with me but put together a concept of causation applicable to both infectious and non-infectious diseases. Just as the Henle-Koch postulates cannot be regarded with any finality, so too, these concepts should be taken only as guidelines, subject to our changing knowledge of technology and causation.

In summary, the original Henle-Koch postulates had many limitations, some recognized then, and others later (table 1). Fulfillment of the postulates is certainly reasonable grounds for accepting a causal role of the putative agent but lack of fulfillment of the postulate should not exclude such a relationship. This chronologic view has focused primarily on the relation of a single cause to a disease. This is a simplistic view because most infectious agents are a necessary but not sufficient cause of disease; indeed many viral infections are inapparent. Causation in both infectious and non-infectious disease involves a complex interplay of agents, environmental, and host factors. The latter include the host's immunologic status, genetic background, socioeconomic level, hygienic practices, behavioral patterns, age at the time of exposure and the presence of co-existing disease. Different qualitative and quantitative mixes of the agent, environment, and host may result in the same clinical and pathological diseases under different circumstances. These more sophisticated approaches to causality are discussed in recent books (31-33) and articles (34-39).

Another view of the causal relationship of an agent to disease might be framed in legal terms. Table 2 presents some of these comparisons (35). In criminal law, the presence of the criminal at the scene of the

<table>
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<th>Limitations of Koch's postulates of causation</th>
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<tr>
<td>1) Not applicable to all pathogenic bacteria.</td>
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<tr>
<td>2) May not be applicable to viruses, fungi, parasites.</td>
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<td>3) They do not include the following concepts:</td>
</tr>
<tr>
<td>a) The asymptomatic carrier state.</td>
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<td>b) The biologic spectrum of disease.</td>
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<td>c) Epidemiologic elements of causation.</td>
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<td>d) Immunologic elements of causation.</td>
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<tr>
<td>e) Prevention of disease by elimination of putative cause as element of causation.</td>
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<td>f) Multiple causation.</td>
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<td>g) One syndrome has different causes at different settings.</td>
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<tr>
<td>h) Reactivation of latent agents as cause of disease.</td>
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<td>i) Immunologic processes as cause of disease.</td>
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* More properly termed the Henle-Koch postulates.
CAUSATION AND DISEASE

Table 2

Rules of evidence: criminality and causality

<table>
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<th>Mayhem or murder and criminal law</th>
<th>Morbidity, mortality and causality</th>
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<tr>
<td>1) Criminal present at the scene of the crime</td>
<td>Agent present in lesion of the disease.</td>
</tr>
<tr>
<td>2) Premeditation</td>
<td>Causal events precede onset of disease.</td>
</tr>
<tr>
<td>3) Accessories involved in the crime.</td>
<td>Co-factors and/or multiple causality involved.</td>
</tr>
<tr>
<td>4) Severity or death related to state of victim.</td>
<td>Susceptibility and host response determine severity.</td>
</tr>
<tr>
<td>5) Motivation—the crime must make sense in terms of gain to the criminal.</td>
<td>The role of the agent in the disease must make biologic and common sense.</td>
</tr>
<tr>
<td>6) No other suspect could have committed the crime in the circumstances given.</td>
<td>No other agent could have caused the disease under the circumstances given.</td>
</tr>
<tr>
<td>7) The proof of the guilt must be established beyond a reasonable doubt.</td>
<td>The proof of causation must be established beyond reasonable doubt or role of chance.</td>
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Crime would be equivalent to the presence of the agent in a lesion of the disease. Premeditation would be similar to the requirement that the causal exposure should precede the onset of the disease. The presence of accessories at the scene of a crime might be compared to the presence of co-factors and/or multiple causes for human diseases. The severity of the crime or the consequence of death might be loosely equivalent to susceptibility and the host responses which determine the severity of the illness. The motivation involved in a crime should make sense in terms of reward to the criminal, just as the role of a causal agent should make biologic sense. The absence of other suspects and their elimination in a criminal trial would be similar to that of the exclusion of other putative causes in human illness. Finally, need that the proof of guilt must be established beyond a reasonable doubt would be true for both criminal justice and for disease causation.

What will the future hold in terms of new infectious diseases in which it may be necessary to look for causal relationships? First, we have those new diseases which might be produced by changes in the agent or its point of entry. Resistant organisms will continue to emerge which are resistant to antibiotics and other therapeutic drugs, or will appear as a result of plasmid transfer of genetic factors of resistance. Recently we have recognized the plasmid transfer of resistance of typhoid organisms to chloramphenical, of the gonococcus to penicillin and most recently of penicillin resistant forms of the pneumococcus. All these indicate that there is an epidemic potential of these highly resistant organisms. It is also frightening to think that this resistance might be transferred in vivo to other organisms. For example, is it possible that a resistant gonococcal infection of the mouth might lead to the transfer of that plasmid to a streptococcus or to a meningococcus present in the same environment? Then we have new agents in old portals. The recognition of new agents of infectious diseases—probably transmitted by the respiratory routes, such as Lassa fever and Marburg fever, are examples of this. We also have old agents in new portals, such as the transfer of herpes type 2 virus from its normal habitat beneath the diaphragm to a new habitat in the oropharyngeal cavity as a result of changing sexual practices. New agents will be identified for old diseases like the common cold of which we now only recognize about half of the causative agents or for encephalitis in which only 25-50 per cent have a recognized cause or for diarrheal diseases. There are important new advances in the discovery of rotavirus in infant diarrhea, of toxogenic Escherichia coli in the traveler, and of Giardia lamblia in the camper, but the majority of common
gastroenteritides remain unexplained. Finally, there are latent infections that are being reactivated which were formerly unrecognized as human pathogens. For example, reactivation of latent papova virus causes progressive multifocal leukencephalopathy but we have not recognized any disease syndrome associated with the common primary infection with this agent.

There are also environmental factors which may result in new diseases. The expanded tourist travel, research exploration, and military excursions to the remote corners of the globe may bring us in contact with new pathogens not previously identified. Our exploration of the ocean bottoms and of outer space may expose us to new microbial forms. Our own creation of special environments, such as intensive care units or kidney dialysis units may produce new and unusual host responses.

Changing economic factors are more likely to result in the re-emergence of old diseases than the creation of new ones. Funds which are now provided for the surveillance and immunization of important diseases, like smallpox, cholera, polio and measles may not be appropriated as these diseases are brought under control and lose their emotional and political clout. Increased economic development and better hygiene may delay exposure to common agents like polio, infectious mononucleosis, and hepatitis from early childhood to young adult life. This may result in the occurrence of more clinical illnesses due to these agents because the host response is more severe in older life.

There are also host factors which may play a role in the emergence of new diseases. These include those which are associated with our increasing use of new therapies, such as immunosuppressive drugs, new antibiotics, organ transplants and tissues from man and perhaps other primates, and the use of synthetic organs and valves. With a large proportion of our population now living into the sixth, seventh and eighth decade, latent infections may reactivate and cancer increase as our normal immunologic controls diminish in efficacy. The control of umbrella diseases like malaria and schistosomiasis in tropical settings may permit recognition of host responses which were previously hidden by the co-existence of these infections. Changing host susceptibility may occur as a consequence of new environmental stresses, of immunologic manipulations, or possibly even of genetic engineering. Changing social and cultural habits may result in new patterns of illness. So we may be faced in the future with a variety of new and unrecognized infectious diseases whose etiology must be established. Proof of this relationship must be based on common sense, good guidelines of causation appropriate to existing technology and a keen sense of the biologic basis of disease.

Causation of health

This presentation has reviewed our changing concepts of the causation of disease. Perhaps it is time we also look at the causation of health (table 3). Let us direct our attention not only to those factors that produce disease but also to those that produce health. Let us change our "don'ts" for "do's" in medical practice and public

| Table 3 Postulates for the causation of health |
| 1) The preventive factor must be consistently present in persons of good health or free of a particular disease. |
| 2) The factor must be isolatable in a pure form, (i.e., can be identified as causal). |
| 3) The extent to which the factor is effectively applied must parallel an increase in good health and/or freedom from that disease. |
| 4) Experimental application of the factor to one segment of a population should significantly increase their good health as compared with matched controls. |
| 5) Withdrawal of the preventive factor should be associated with an increase of disease associated with that factor. |
| 6) The effect of the factor shall be measured in terms of lower morbidity and mortality, longer life, and lower medical costs. |
health. Let us approach the proof of causation of health with a keen scientific, statistical, and biologic orientation.

Let us do studies of what makes us survive and not only of what makes us die. Let us do case/control studies of healthy persons as the control; let our prospective studies of populations focus on those who remain in good health rather than only those who become ill. Let us recognize that there will be multiple causes for health just as there are multiple causes for disease and that health like disease is a biologic spectrum. Let us recognize that establishing the proof of the causation of health will be more difficult and challenging than the causation of disease. But let us begin.

REFERENCES