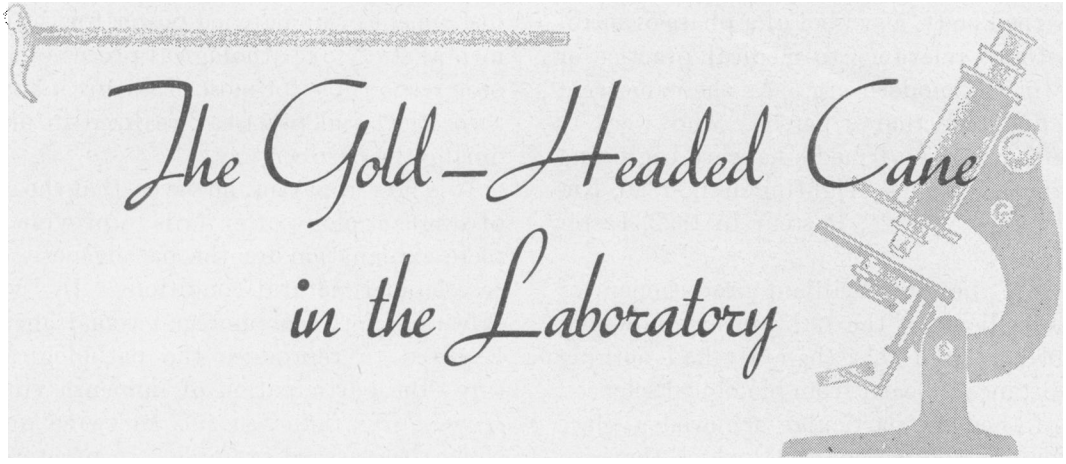

By RENÉ J. DUBOS, M.D., Sc.D., Ph.D.

ALTHOUGH most of medical science is of very recent acquisition, the healing art has been practiced effectively for thousands of years without the benefit of laboratory knowledge. The skill of ancient physicians was largely empirical, but it permitted them, nevertheless, to formulate prognoses, relieve symptoms, and not uncommonly effect cures. It was an empiricism based on wisdom, experience, and knowledge of human nature.

The fashionable English physician of the late 17th century went on his sick calls dressed in a silk coat, breeches and stockings, with buckled shoes, lace ruffles, full-bottomed wig, and carrying a gold-headed cane. Typical of this class was John Radcliffe (1650–1714), physician to William and Mary and to Queen Anne.

Empiricism vs. Experimental Science

For 150 years, Radcliffe's gold-headed cane was passed along in succession to some of the most successful practitioners of England. In Matthew Baillie (1761–1823), however, it found a master of a different mentality. With a few of his contemporaries, Baillie considered that science was rendering obsolete the assumed gravity and pompous airs of fashionable physicians. Indeed, it was obvious that the clinical art had then come to represent a formal tradition rather than an attitude based on living experience with disease. No longer regarding the gold-headed cane as a necessary appendage of the medical profession, Baillie discontinued carrying it on his sick calls. After his death, his wife found the cane in a corner of the con-

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Dr. Dubos, member of the Rockefeller Institute for Medical Research, presented the third R. E. Dyer lecture October 22, 1953. The major portion of the lecture is printed here. The full text will be published by the National Institutes of Health. Dr. Dubos enjoys wide recognition not only for fundamental work in bacteriology but also as an author. He pioneered in the study of antibacterial enzymes and antibiotics and isolated tyrothricin and gramicidin, the first crystalline antibacterial substance, from spore-forming bacteria. Another contribution was the development of new media for the cultivation of the tubercle bacillus.

The R. E. Dyer lecture, honoring Dr. Rolla E. Dyer, was established in 1950 and is administered by the National Institutes of Health, Public Health Service.

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sulting room and presented it in 1825 to the museum of the Royal Academy of Physicians. There it has remained, among other relics of that learned body, a symbol of a phase of medicine without relevance to medical practice or science in the modern era. As the cane went to its final sanctuary, persons who were to change the course of medicine were beginning their lives—Florence Nightingale in 1820, Rudolf Virchow in 1821, Pasteur in 1822, Lister in 1827.

Many of the most brilliant practitioners of clinical medicine of the 19th century, however, continued to hold that their art had nothing of importance to learn from biological sciences. Some of them in particular achieved a place in history by the passion with which they opposed the germ theory of disease. The French clinician Pidoux, a representative of traditional medicine—always impeccably clad in a gold-buttoned coat—was one of those who took up the cudgels against Pasteur at the Paris Academy of Medicine. Where Pasteur saw disease as caused by specific kinds of microbes, Pidoux invoked the concept of diathesis, emphasizing that disease was determined by the particular constitution of the patient. He held the view that any disease could be caused by a multiplicity of external and internal causes and could not be regarded as due to one single specific agent. Necrotic processes could take place "along a number of roads each of which the physician should endeavor to close."

Pidoux and his like spoke in broad clinical terms, basing their doctrines on the phenomena of disease as observed in man. But their vague arguments were no match for the precise experimentation by which Pasteur, Koch, and their followers defended the doctrine of specific causation of infectious disease. Experimental science triumphed over clinical experience, and within a decade the theory of specific etiology of disease was all but universally accepted, soon becoming the dominant force in medicine. Eventually, the doctrine of specificity was generalized to encompass the concept of specific "biochemical lesion" which is proving today as fruitful in the fields of metabolic, degenerative, and neoplastic diseases as the concept of specific microbial etiology has proved in dealing with the problem of infectious diseases. There is no doubt that the doctrine of specific etiology has constituted an instrument of unmatched power for the experimental study of pathological processes and has been responsible for most of the great advances, theoretical and practical, realized in medicine during the past century.

It is now apparent, however, that the concept of single etiology often fails to provide a complete explanation for the pathogenesis of diseases under natural conditions. In "complex infections," two or more microbial agents are required to reproduce the pathological picture—the participation of influenza virus and *Hemophilus influenza suis* in swine influenza being the classical example. In practically all infectious and metabolic disorders, physiological and environmental factors can readily be shown to be important determinants of the disease process.

Tuberculosis Infection vs. the Disease

In general, the accounts of the controversies which heralded the germ theory of disease dismiss the views of those who objected to some of its extreme tenets as the voice of obscurantism and reaction in medicine. Yet there were shrewd thinkers among the physicians who were not convinced that micro-organisms alone could account for the causation of disease. They did not deny that micro-organisms were present in diseased tissue. They emphasized rather that micro-organisms could invade and cause disease only after the tissues had been weakened by some form of physiological misery.

Rudolf Virchow was one of those who believed that micro-organisms are secondary invaders and that physiological disturbances are always the primary cause of disease. In 1847, while still a young man of 26, he had served as a member of a medical commission sent by the Prussian Government to investigate the widespread occurrence of epidemics in the industrial sections of upper Silesia. There he noticed that fevers were particularly prevalent among those living under miserable circumstances, and he became convinced that poverty was the real breeder of disease. He pointed out,

furthermore, that Negroes living in Europe were much more likely to acquire tuberculosis than those who had stayed in their native lands or than white persons of the same age working at the same trades and exposed to the same risks of infection. Did not this incriminate the physiological disturbance brought about by the change from the tropical to the northern climes as primary cause of the disease?

Although Virchow recognized the importance of Koch's discovery of the tubercle bacillus, he had good epidemiological reasons to remain unimpressed while presiding at the now famous meeting of the Berlin Physiological Society in 1882 where Koch first presented his report. Indeed, Virchow would have been even less impressed had he known, as we know today, that almost every adult individual in Europe at that time was infected with virulent tubercle bacilli and that Koch himself was certainly infected, as indicated by the violence of his reaction when he injected tuberculin into his own arm in 1891. Virchow could have argued that since the tubercle bacillus was an ubiquitous component of the environment, the factors which converted mere infection into overt symptoms and destructive pathological changes were the real determinative causes of tuberculosis.

The knowledge accumulated during the past 75 years has left unsolved many of the problems of the pathogenesis of tuberculosis. Tuberculin tests reveal that even in our communities a very large percentage of the adult population has been at some time infected with tubercle bacilli. Yet, the morbidity and mortality of tuberculosis have decreased by ten- to twenty-fold during the past century. It is obvious, therefore, that while the tubercle bacillus is the specific etiological agent of infection, there are other factors which are responsible for converting infection into tuberculous disease. In other words, the etiology of disease cannot be explained entirely in terms of the etiology of infection.

Multiple Etiology in Human Disease

Another example illustrates the contrast between infection and disease. In man, the herpes simplex virus is usually acquired during early years. Throughout most of the life of the infected individual, the virus lies latent in the body, without causing any symptom or obvious pathology until "provoked" into activity by some physiological disturbance. As is well known, fever (herpetic) blisters can be elicited by a variety of nonspecific unrelated stimuli, as different one from the other as menstruation, colds and fevers of various origin, ultraviolet radiation, or eating cheese. Herpetic blisters thus provide a striking example of an infectious disease of man in which, contrary to the original tenets of the germ theory, the living agent of the disease (the germ) may be present all the time in the host—be intrinsic so to speak—whereas the determinant of the pathological process is some physiological disturbance or some other extrinsic factor of the physicochemical environment.

There are many examples of infections caused by either protozoa, fungi, bacteria, rickettsia, or viruses which are ubiquitous in their distribution among human, animal, or plant communities but which remain in a latent, essentially inactive state under ordinary "normal" circumstances. These latent infections express themselves in the form of disease only after some physiological or environmental factor has caused a primary disturbance which allows the microbial agent to manifest its potential pathogenicity. In fact, the nature of the pathological processes may to a large extent be independent of the specific microbial agent associated with it. Thus, it has been frequently observed during recent years that the intensive use of chemotherapy in the treatment of subacute endocarditis caused by green streptococci, while successful in eliminating these organisms from the lesions and blood stream, often results in their substitution by other microbial species. As a consequence, forms of endocarditis associated with staphylococci or even gram negative bacilli are not uncommon in patients treated with antistreptococcal drugs. Seventy-five years ago, this would have appeared to the opponents of the germ theory as just one more example of a situation in which the fundamental disease is the organic lesion (on the heart valves) and the microbial agents merely opportunistic secondary invaders.

It is known that most, if not all human beings can acquire bacillary dysentery when first exposed to the disease under the proper field conditions, as shown by the fact that new bodies of troops transported to areas where dysentery is endemic rapidly fall prey to the disease. Yet, despite all the available knowledge concerning dysentery bacilli and despite the overwhelming evidence of the communicability of the disease, it has proved extremely difficult to establish experimentally in man or in animals an infection presenting the typical symptomatic and pathological characteristics of bacillary dysentery.

A few years ago, human volunteers ingested dysentery bacilli of the Flexner group recently isolated from patients and known to be virulent for mice. All precautions were taken to favor the establishment of the infection. It was first determined that the volunteers were not carriers of *Shigella* and had negative histories of diarrheal disease. They were given paregoric and sodium bicarbonate before and after receiving the infective dose, and water in order to dilute the gastric secretions and wash the material through the stomach quickly. Yet, administration of up to 95 billion bacilli failed to produce significant symptoms of dysentery in most volunteers, even though the bacilli could be recovered from their stools on several successive days. No greater success was achieved by introducing along with the bacilli a gelatin capsule containing 1 gram of feces collected from a patient with clinical dysentery and containing large numbers of living bacilli.

Few are the human beings who do not suffer from the common cold once or several times every year, and few are the epidemiologists and laymen who do not believe that the affliction spreads readily by contact and that certain environmental circumstances, such as wet and cold weather, draughts, and fatigue, increase susceptibility to it. Since men find it so difficult to avoid "catching" a cold although they are most reluctant to "take" it, one could expect that it would be easy for the experimenters to "give" the disease to human volunteers willing to submit themselves to all the conditions assumed to be favorable for its transmission. But this has not proved to be the case. It has been known for almost two decades that one can elicit mild symptoms of coryza in a certain percentage of human beings by administering to them filtrates of nasal washings and discharges from individuals in the early stages of the common cold. Thus, the etiological agent appears to be a filterable virus. It has also been found in early experiments that human beings are less likely to develop symptoms when exposed to the infective dose in an environment conducive to physiological and mental well being.

Experimentation seems to confirm what had been suspected from observations in daily life, namely, that man is highly receptive to the common cold agent under special circumstances. But these circumstances are not easy to define as was the experience of the workers of the Common Cold Commission in England. In experiment after experiment, they introduced, intranasally into human volunteers large volumes of presumably infective discharges freshly collected from patients in the acute phase of the disease, but only a small percentage of the would-be victims developed acute signs of cold, even if exposed to air draughts in wet socks for hours immediately after having received the infective dose. Whatever the technique of infection used and whatever the environmental circumstances, the common cold so difficult to escape in ordinary life manifested itself to the experienced investigators who tried to conjure it only in a small percentage of their human volunteers.

Germ Theory Limitations

It is somewhat entertaining to muse over the fact that although all textbooks of bacteriology and infectious disease present the Henle-Koch postulates as the very bedrock which gives permanent basis and scientific dignity to the germ theory of disease, these postulates have hardly ever been satisfied in man. In reality, the faith that micro-organisms play the primary role in the causation of disease grew out of the forcefulness of Pasteur's and Koch's convictions, rather than out of the unimpeachability of the evidence which they presented.

Lest this statement be considered as a facile and irresponsible exercise in "debunking," let us admit immediately the obvious fact that

Pasteur, Koch, and their disciples and followers based their conviction on facts of absolute validity. But these facts were valid only for the very limited and well-described circumstances under which they were observed. It was no small part of Pasteur's and Koch's vision and genius that they selected for the demonstration of their thesis experimental situations in which it was not only necessary but also sufficient to bring the host and parasite together in order to reproduce the disease. Farm and laboratory animals never carry the anthrax bacillus; all guinea pigs are susceptible to tuberculosis; injection of rabies virus under the dura of dogs always gives rise to paralytic symptoms, and so forth. Thus, by the skillful selection of their experimental models, Pasteur and Koch could eliminate from their studies the factors other than the parasite which are necessary to demonstrate that infection can result in symptoms and pathological alterations. The techniques of experimentation which they worked out were designed to test the pathogenic properties of parasites under reproducible conditions—ideally a highly susceptible animal placed in a simple, defined, and constant environment. Useful as this artificial system has been for the study of some of the properties of microparasites, it has led to the neglect, and indeed has often delayed recognition, of the many other facts which are essential to the causation of disease under circumstances prevailing in the natural world—the physiological characteristics of the host and the physicochemical as well as social environment.

Disease Complex in All Life Forms

The examples used so far have been taken from human pathology to illustrate the view that the causation of disease under natural conditions often involves the simultaneous operation of several independent etiological factors. In reality, however, this holds true as well for many varied types of pathological processes in all classes of living things.

In nature, many bacterial species called "lysogenic" carry in an inactive form (prophage) one or several bacteriophages potentially capable of causing their lysis. Under ordinary conditions, the prophage is apparently reproduced with each bacterial division without causing any detectable disturbance in the cell. This equilibrium can be upset by a number of nonspecific procedures—for example, irradiation of the lysogenic culture—in such a manner that the prophage is converted into active bacteriophage, multiplies abundantly, and causes the destruction of its host cell. Thus, the prophage behaves as a pathogen for the cell that carries it only when the latter is subjected to the proper kind of stimulus. One might say that the prophage makes the bacterium sensitive to the radiation, or that the radiation makes it susceptible to the phage, or that both agents are required for the causation of lysis. In fact, it has been shown that, in certain cases at least, the activating effect of radiation can take place only in media of certain composition, thus making even more complex the etiological determination of lysis.

As is well known, the agent responsible for mammary carcinoma among breeding female mice has all the characteristics of a virus. Although the Bittner virus occurs throughout the tissues of infected animals, it causes no obvious sign of disease and in particular no tumors until lactation has begun. Male mice do not develop breast cancer even if they carry or have ingested the virus, nor do female mice unless under the stimulus of continuous reproductive activity. Thus, whereas the virus can remain latent in the animals which harbor it, the hormonal and other stimuli which accompany reproduction and lactation are necessary and sufficient to induce it to elicit pathological reactions. In other words, these physiological stimuli are, as much as the virus, etiological agents of the mammary tumors of mice.

All the pathological processes so far mentioned to illustrate the concept of multiple etiology involve the participation of microorganisms or of viruslike agents. But one could also find in other fields of pathology many examples in which the causation of disease probably requires that several independent factors act together or in succession. Thus, it is well recognized that conditions as varied as hemorrhagic shock, peptic ulcers, or degenerative diseases are multifactorial phenomena requiring for their genesis the simultaneous occur-

rence of several physicochemical and vascular disturbances conditioned by a variety of organic and psychogenic controls.

The problem of causation of the plant cancer, known as crown gall, because of the precise knowledge which has been gained of its physiological determinants and chemical basis, illustrates in a striking manner the conceptual difficulties involved in the determination of etiology. It is possible to induce at will characteristic tumors (crown galls) by inoculating sunflower or certain other plants with pure cultures of *Agrobacterium tumefaciens*. Since no other foreign organism or substance is known to be capable of causing this pathological reaction, it seems fair to regard *A. tumefaciens* as the specific etiological agent. It has been established, however, that many of the secondary tumors developing on the same plant at sites removed from the initial infection are free of bacteria, and yet can be transferred in series to new plants, or propagated in tissue culture as self-reproducing structures. It is possible also to eliminate the bacterium from the tumor tissue by controlled heating, without affecting the power of autonomous growth of the latter. Thus, production of the cancer can be made independent of *A. tumefaciens*, which was at first its essential etiological agent.

It is known furthermore that extensive invasion of the plant by the bacterium may take place without resulting in tumor formation. Only plant cells which have been conditioned by certain stimuli associated with wound healing are rendered susceptible to transformation into tumor tissue by the bacterium. The physiological state of the host cells should, therefore, be considered also an etiological determinant of crown gall.

Finally, it can be shown that whereas the normal plant tissue requires indole acetic acid and the cocoanut-milk factor for growth in tissue culture, the self-reproducing tumor tissue can synthesize these essential growth factors (and perhaps others) and therefore does not need them. It is this biochemical characteristic which permits it to grow profusely and in a completely uncoordinated manner. Thus, at the present state of the analysis, the biochemical etiology of the disease appears to reside in an increased synthetic power, but on the other hand, it takes *A. tumefaciens* originally to induce the change.

Depending upon the specialized interests of the investigator and the techniques that he chooses to use, the primary etiology of crown gall can be regarded as a specific bacterium, a transmissible cellular change dependent upon a certain physiological state of the cell, or a biochemical disorder. The problem of etiology can be studied at different levels by the bacteriologist, the oncologist, the physiologist, or the biochemist. All points of view are justified, and discoveries at any one of the levels of investigation can add to the understanding of the mechanisms of the disease and probably lead to some technique of control.

Biological and Environmental Equilibrium

Obviously the "normal" existence and performance of any living organism demands a state of subtle equilibrium between its different component parts, as well as between them and the factors—living and physicochemical—of the environment. Hippocrates referred to the ideal state of nature as a "universal sympathy." Biological equilibrium, being the outcome of evolutionary forces, is maintained only if nothing changes in the environment. Any change is likely to disturb the balance of forces upon which depends the maintenance of the normal state. "Disease," Virchow said, "is life under altered conditions."

The factor which disturbs the equilibrium may affect only one or a few individuals and give rise to isolated cases of clinical disease, or it may affect simultaneously many members of the community and cause crowd diseases.

The fact that peptic ulcers, arterioscelerosis and other vascular disorders, and even certain forms of cancer are markedly influenced by various social and economic factors is sufficient proof that here again, as for infectious diseases, it is necessary to broaden the concept of etiology if one is to achieve a comprehensive picture of pathogenesis.

It is because the physician must deal with situations involving so many independent variables that clinical medicine has remained an art even today—an art based on wisdom and

skill derived from experience as much as on scientific knowledge and reasoning. The skill symbolized by the gold-headed cane was not mere charlatanism. Experience had taught the good physician to manipulate many of the factors—physiological, psychological, and social—which affected the reactions of his patient.

But knowledge based on empirical experience either remains static or at best develops slowly. Progress demands systematic experimentation. Methodologically, there is danger in adopting too broad a biological and clinical point of view in the study of disease—the danger of substituting meaningless generalities and poor philosophy for the concreteness of exact knowledge. It is one of the most important contributions of the doctrine of specific etiology that it saved the science and practice of medicine from the morass of loose words and concepts. But insistence on concrete facts need not deter one from acknowledging that, under natural conditions, the etiology of most diseases is multifactorial rather than specific. The laboratory worker can always circumvent the difficulty resulting from the multiplicity of etiological determinants by devising operations that permit him to study each of these separately and in various combinations.

By using a broadened concept of etiology, encompassing intrinsic and extrinsic determinants of disease, he will eventually develop a therapeutic science that will incorporate the human wisdom and empirical skill of the traditional medical art. "The variable composition of man's body hath made it an Instrument easy to distemper . . ." Francis Bacon wrote. "The Office of Medicine is but to tune this curious Harp of man's body and to reduce it to Harmony."

Russell M. Wilder Fellowship Established

The National Vitamin Foundation is inviting individuals holding doctorate degrees in medicine or one of the biological sciences, who are interested in continuing their training in nutrition, to become candidates for the newly established Russell M. Wilder Fellowship.

This postdoctorate fellowship was created by the Foundation to honor Dr. Wilder of the emeritus staff of the Mayo Clinic "for his more than 40 years of devoted service and significant contributions to medicine and public health, and particularly for his leadership in advancing our knowledge of diseases of metabolism and nutrition."

Dr. Wilder was the first director of the National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Public Health Service. He retired on July 1, 1953. He is a member of the Board of Editors of *Public Health Reports.*

The fellowship is for 3 years and pays the recipient $4,500 for the first year, $5,000 for the second, and $5,500 for the third year. It becomes effective September 1, 1954. Candidates must give reasonable assurance that they will complete the fellowships and continue to work in the field after completing their studies. Further information may be obtained from the National Vitamin Foundation, 15 East 58th Street, New York 22, N. Y.