REVIEWS AND COMMENTARY

With this issue, the section entitled “Commentary” is broadened to include reviews of topics of epidemiologic interest. The “Reviews and Commentary” section will include both articles solicited by the editors and appropriate articles submitted for consideration, as well as brief reports and letters to the Editor.

EPIDEMIOLOGY OF INFECTIOUS AND NON-INFECTIOUS DISEASE: SOME COMPARISONS

THE FIRST WADE HAMPTON FROST LECTURE

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At the start, I would like to express my feeling of tremendous honor and pleasure at having been selected by the Council of the Epidemiology Section to deliver the first Wade Hampton Frost lecture. To whatever extent my epidemiological work has been responsible for this, certainly this honor must be shared with my colleagues, many of whom are among you in the audience and with whom I have collaborated on many studies, Alexander D. Langmuir, Warren Winkelstein, Jr., Milton Terris, Leonard M. Schuman, Philip E. Sartwell, to name a few, as well as past and current members and students of my department.

Those of us who have been engaged in epidemiological investigations during the past 20 to 30 years are well aware of the profound influence of Wade Hampton Frost on our discipline. That this influence still permeates epidemiological thought today was brought home to me while I prepared this lecture and reviewed many of Frost’s publications, noting, with few exceptions, how au courant was his mode of reasoning, particularly concerning the derivation of inferences from epidemiological data.

I will not attempt to review in detail the various contributions made by Frost. This has been ably presented in the preface to a select collection of Frost’s papers by Maxcy, Papers of Wade Hampton Frost: A Contribution to Epidemiological Method (1), which I highly recommend to those who have not as yet read them. A clear statement of what Frost exemplified was expressed by Maxcy in commenting on Frost’s...
studies of diphtheria: "They are splendid examples of orderly and logical statement derived from carefully collected material, a considerable part of which is quantitative, concerning factors affecting the prevalence of an endemic acute infectious disease."

The great influence of Frost on our discipline has been best described by Gordon in his review of American epidemiology in the twentieth century (2). He points out that, "In 1921, Wade Hampton Frost became the first professor of epidemiology in America. He remains the first among all who have followed, for no one has done more to further epidemiology as a scientific discipline." He further comments that, "The accumulating knowledge of epidemiological theory and the increasing use of statistical methods led progressively to a turn of epidemiology from a descriptive and comparative procedure to an analytical discipline. If one American is to be singled out as contributing most forcefully to this change, he is W. H. Frost. In his teaching, through his students, and by his own contributions, Frost developed means for quantitating mass phenomena of disease and for measuring the biologic attributes of disease as evidenced in populations of people. Once established as an analytical discipline, the way was clear for epidemiology to make full use of the technical methods originating from other medical and biological sciences, and to perfect field methods of study."

Gordon specifies a few of Frost's contributions: "Wade Hampton Frost contributed more to quantitative method than any other American epidemiologist, through his studies on poliomyelitis (1913), the common cold (1932), and tuberculosis (1933); and through developing the modified life table technic and the index case concept." To these we must add the cohort analysis of mortality data, the use of morbidity surveys, the importance of the study of the familial distribution of disease and the concept of using the community as, what today is popularly labeled, "a human population laboratory."

Frost also had a continued interest in the application of epidemiology to the practice of public health of his day. As stated by Maxcy (1), "...he was cognizant at all times of the usefulness of this tool (of epidemiology) for the improvement of public health practice." Thus, Frost presented papers on "Rendering Account in Public Health," "Authoritative Standards and Association Policy," and his oft-quoted classical "How Much Control of Tuberculosis?" (1). He integrated epidemiological investigation, public health practice, medical science and public health teaching. This holistic viewpoint could well serve as an example today to those in our discipline who seek to separate the science from practice.

His only attempt at a systematic exposition of the scope, principles and methods of epidemiology is contained in an article prepared in 1927 that summarized the thinking of that time (3). He stated that epidemiology is "essentially a collective science,
and its progress is largely dependent upon that which has been made in other fields. For example, since description of the disease in a population obviously requires that the disease must be recognized when it occurs, the development of epidemiology must follow and be limited by that of clinical diagnosis, and of the rather complex machinery required for the systematic collection of morbidity and mortality statistics. Epidemiology must also draw upon statistical method and theory, because even the simplest of quantitative descriptions must be stated statistically; and more minute descriptions, involving perhaps the demonstration of complex associations, may require the application of quite elaborate statistical technique. Moreover, quantitative epidemiological descriptions, in terms of the frequencies of diseases in different population groups, require, as part of their data, more or less detailed statistics of population, implying the prior development of demography; and for descriptions of the relations of disease to climate and weather, systematic meteorological records are necessary.

"... Usage has extended the meaning of epidemiology beyond its original limits, to denote not merely the doctrine of epidemics but a science of broader scope in relation to the mass-phenomena of diseases in their usual or endemic as well as their epidemic occurrences. Although it is clear from current usage that the definition of epidemiology has been thus extended beyond its original sense, it is not clear just how far it has been extended. It is certain that its scope is not usually limited to the diseases in which epidemics are characteristic, since it is entirely in conformity with good usage to speak of the epidemiology of tuberculosis; and it seems customary also to apply the term to the mass-phenomena of such non-infectious diseases as scurvy, but not to those of the so-called constitutional diseases, such as arteriosclerosis and nephritis. Therefore, in view of the latitude which the uncertainty of usage allows, epidemiology will be considered here as referring exclusively to the diseases of man which are classed as specific infections, since this will permit of a more coherent discussion."

Frost's views were somewhat limited by the perspectives of his time. However, Frost's methodological contributions to the study of tuberculosis have been applied to other chronic diseases. It seems fair to assume that had Frost lived beyond 1938, the year of his death, his conceptualization of epidemiology would no doubt have extended to include all the diseases and conditions which concern us today.

Since this is the first lecture in this series, it appeared appropriate to review a broad area in epidemiology. More specifically, I thought it would be interesting to compare some of the similarities and differences of the infectious and non-infectious diseases, to indicate some of the concepts in the infectious diseases that might be applicable to the non-infectious diseases and to briefly consider a few specific related topics. In a modest way, such discussion might serve as a bridge between Frost's times and current areas of activity. I should like to discuss these in some detail within the following different areas of epidemiological activities:

1) Observations of occurrence of disease in man
2) "Natural" experiments
3) Experimental epidemiology—randomized controlled experiments
4) Theoretical epidemiology (mathematical-statistical)
   a) Models
   b) Computer simulation

Most epidemiological research consists of observational studies on the occurrence of disease in man; it is to this area that Frost devoted much of his intellectual energy. An important difference between infectious and non-infectious diseases is the element of time. This is clearly observed by comparing the incubation period of a definitely infectious disease (figure 1) with
one of a non-infectious disease (4). For the non-infectious disease, which may very well prove to be a misnomer in terms of some current thinking, figure 2 presents some data on radiogenic leukemia which Cobb analyzed a few years ago (5). It is of more than just passing interest that the pooling of such data on incubation periods for leukemia was based on the infectious disease analogue. In fact, Cobb attempted to estimate possible incubation periods for what were essentially single exposure epidemics of leukemia in order to identify that time period prior to the occurrence of the disease which should be studied in searching for other potential etiological agents.

The incubation period is much shorter in infectious diseases than in radiogenic leukemia; the former is measured in weeks and the latter in years. It is of interest to speculate on possible explanations for this difference. In infectious diseases, the incubation period is the time interval between receipt of the infection and onset of illness and depends largely on the growth rate of the particular infectious agent and to a lesser extent, on the portal of entry and degree to which the host can mobilize his defenses. In infectious diseases, these intervals generally are relatively short.

In non-infectious diseases, one cannot attribute the long latent period to the time required for the growth of organisms. One possible explanation for the length of the
latent period which has received some attention, particularly with respect to radiation effects, is the influence of independent multiple etiological factors, which has been termed the "multi-hit" theory of leukogenesis or carcinogenesis (6). Basically this concept suggests that for clinical disease to develop, a sequence of cellular changes must take place; in fact, estimates have been made on the number of multiple hits necessary before clinical disease occurs. These steps are often equated with somatic mutations, but this presupposes knowledge, presently unavailable, regarding the mechanism of cellular changes. If such multiple independent steps are necessary, one would expect a lengthening of the incubation period.

This biological concept is an important reminder to the epidemiologist in his search for possible etiological factors that he must attempt to ascertain multiple factors and their possible interrelationships; this becomes an integral part of his research strategy.

As an illustration, I would like to present some data on childhood leukemia from the Tri-State Leukemia Study, a cooperative venture in which all patients with leukemia diagnosed between 1959 and 1962 in Upstate New York counties, Baltimore and Minneapolis-St. Paul were interviewed as were probability samples (1:3000) of the population in these areas. The methodologic details have been presented elsewhere (7).

In the analysis, it was suggested that several factors were related to the occurrence of leukemia in children: 1) preconceptional radiation; 2) maternal reproductive wastage; 3) history of childhood virus diseases; and 4) intra-uterine radiation (8); these risk factors for leukemia are classified and defined as follows:

**Pathologic**

**History of childhood virus diseases**—Measles, rubella, chickenpox, mumps, polio, herpes zoster, encephalitis and infectious mononucleosis more than 12 months before diagnosis of leukemia.

**Reproductive wastage**—Mother's history of miscarriages and stillbirths before conception of subject.

**Radiologic**

**Preconceptional radiation** of mother before conception of subject.

**In utero radiation** of mother while pregnant with subject.

Initial analyses were limited to the effect of each factor separately. Then, the data were analyzed in combinations of multiple risk factors, grouped according to whether the factors were radiologic or pathologic; the results are presented in table 1. The pattern shown in this table does not support the notion that the risk for leukemia increases merely by the addition of other risk factors. Whenever there is only one factor, the relative risks are low. The addition of two single factors increases the risk somewhat, to 1.6. However, when there is a combination of multiple factors, the risk increases markedly.

It occurred to me that a different approach might be preferable. These factors should not be combined according to the radiologic and pathologic aspects since these categories do not consider the temporal sequence of events, and it might be
TABLE 2
Pattern of estimated relative risks for leukemia in children 1-4 years of age by risk factors re-arranged by order of occurrence

<table>
<thead>
<tr>
<th>No. of preconceptional factors</th>
<th>No. of postconceptional factors</th>
<th>Relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>None</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>1.1</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>1.8</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>1.2</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>1.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.7</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>1.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4.6</td>
</tr>
</tbody>
</table>

useful to view the matter, crudely of course, in just such terms. One could classify the individual risk factors for leukemia as preconceptional and postconceptional factors, as follows:

**Preconceptional**
- Reproductive wastage
- Preconceptional radiation

**Postconceptional**
- In utero radiation
- History of childhood virus diseases

The relative risks for these groups were computed and are presented in table 2; they are not strikingly different from those presented in table 1. The relative risks for combinations of factors are practically unchanged. The major difference is that there now appears a sharper gradient of relative risks for each class of risk factors—preconceptional and postconceptional—which was not present in table 1. This can only be considered as suggesting that the temporal sequence might be of importance.

One might even consider adding another dimension to this two-dimensional pattern, that of dose for each factor. Then, one could speculate that an increased dose for an individual factor might be equivalent to the combined effects of several factors.

I present these data to indicate that the finding of a low relative risk for an individual factor of etiological interest should not deter us from further consideration of that factor. All of us have experienced the frustration of finding such low order associations with individual factors. However, it is quite conceivable that these may still be important when considered together with other possible etiological factors. Of course, such a possibility makes investigative life a bit more difficult.

As many of you know, all lengthy incubation periods are not necessarily the result of multiple factors. In some instances, they may reflect a cumulative lifetime exposure to one or more factors. In others, they may be related to chronologic age, with the aging process per se, having some effect. As an aside, I might point out that the process of aging has not received the epidemiological attention it deserves. It is a virgin research area with many potential dividends, such as ascertaining in human population groups whether some characteristics determine differential risks of aging, whether there are methods of measuring biologic age in contrast to chronologic age, and whether biologic age has an independent effect on disease causation.

In searching for etiological factors, the epidemiologist should have some notion to what extent the disease under investigation can be explained by or attributed to definite or possible etiological factors that have already been ascertained. One statistic that is of considerable value but not widely used in this area is the attributable risk as derived by Morton Levin in 1953 (9). Attributable risk means the following: given a population with a certain rate of occurrence of a disease, what proportion of the cases of that disease can be attributed to one or more specific etiological factors? This is expressed by the formula:

\[
\text{Attributable risk (AR)} = \frac{b(r - 1)}{b(r - 1) + 1}
\]

\[b = \text{Proportion of population with characteristic that is being considered as an etiological factor}\]
\[r = \text{Relative risk}\]
It should be pointed out that this definition for attributable risks differs from that used by MacMahon and Pugh (10) by taking into account the frequency of the population with the characteristic (b).

The most outstanding attributable risk among diseases of current interest is that of cigarette smoking in lung cancer. Given the frequency of smoking in the appropriate age groups of the U.S. population and a relative risk of 10, it is estimated that 80–85 per cent of lung cancer in the United States can be attributed to cigarette smoking. This estimate is not only important to the public health administrator but also to the epidemiologist, since it identifies cigarette smoking as a major factor, and indicates that other environmental factors probably play a relatively minor independent role. This observation can influence the research strategy of an investigator as he pursues the ascertainment of additional possible etiological factors; for example, as an initial approach, he may decide to limit his studies to nonsmoking lung cancer patients.

To further illustrate the use of the attributable risk, I have taken the childhood leukemia data from the Tri-State Study presented earlier and have computed the attributable in addition to the relative risks for each individual factor and the proportion of the study population (the one- to four-year old children) exposed to these factors (table 3).

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>% among controls (b)</th>
<th>Relative risk (r)</th>
<th>Attributable risk (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individual:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preconceptual radiation</td>
<td>52</td>
<td>1.39</td>
<td>16.7</td>
</tr>
<tr>
<td>Reproductive wastage</td>
<td>18</td>
<td>1.83</td>
<td>13.0</td>
</tr>
<tr>
<td>In utero radiation</td>
<td>28</td>
<td>1.60</td>
<td>14.4</td>
</tr>
<tr>
<td>Childhood virus diseases</td>
<td>31</td>
<td>1.32</td>
<td>9.0</td>
</tr>
<tr>
<td>Cumulative:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 or more risk factors</td>
<td>81</td>
<td>1.54</td>
<td>30.0</td>
</tr>
</tbody>
</table>

It is evident that only between 9 and 17 per cent of the leukemia cases can be attributed to each individual factor. However, when one views the cumulative effect, that is, the presence of one or more of the risk factors, one obtains a relative risk of only 1.54, but the attributable risk is 30 per cent, indicating that 30 per cent of the cases are now explained. The reason for the increase in attributable risk is clear; 81 per cent of the population is exposed to one or more of these factors. This combination of a rather low attributable risk with a large segment of a population suggests that there are other factors involved but they are principally found among those individuals already exposed to these four risk factors. This requires a different research strategy from that proposed for lung cancer. I do not think that a consideration of the relative risks alone would provide similar suggestions.

The complexities imposed by time and multiple factors are not limited to the non-infectious diseases. Similar considerations exist with regard to some infectious diseases, particularly those that are due to the "slow" viruses. It is also possible that some of the non-infectious diseases may have simple unifactorial etiologies. I hope, however, that this discussion will stimulate an increased use of the attributable risk in evaluating epidemiological data.

I would now like to turn to an area of current epidemiological interest. Given the possibility that some forms of cancer, more specifically leukemia and the lymphomas, are of infectious origin, perhaps even communicable, what would be the most productive epidemiological test of this hypothesis? Those who have tried to answer this question over the past several years have attempted to evaluate the hypothesis by determining the clustering of cases in time, space or in both time and space. A variety of elaborate statistical methods have been
developed to decide whether the degree of clustering is more than would be expected by chance. A critical assessment of these approaches suggests that the data are not consistent with the communicable hypothesis (11, 12).

An epidemiological problem in cluster analysis is that it is usually limited to the distribution of cases. One strong and lasting impression early in my career was made by Alexander Langmuir, who pointed out that clinicians are interested in cases with the disease, the statisticians with the population from which the cases are derived, and the epidemiologist is interested in the relationship between cases and the population in the form of a rate with the cases represented in the numerator and the population in the denominator.

When the epidemiologist is interested in determining communicability or infectiousness in studying an infectious disease and requires a rate, he uses the family as the unit or perhaps some larger population aggregate to compute an attack rate; the specific rate would be some form of the secondary attack rate.

It is a source of some curiosity that those concerned with the communicable or infectious hypothesis in cancer have not borrowed a page from infectious disease epidemiology and conducted a study to estimate the secondary attack rate for various social aggregates of exposed population groups, including families. Admittedly, such a study would be more difficult to carry out than in an acute disease because of the lower frequency of diseases such as leukemia and the longer incubation periods, so that studies would be needed over longer periods of time and in larger population groups. However, the likelihood of obtaining a clear-cut answer as to infectiousness is considerably increased. I think that if Frost were here today, he would support this for we know that after Chapin developed and introduced the secondary attack rate, Frost broadened its applicability and used it widely in many of his own studies (13).

There are other areas where studies of familial aggregation might provide useful leads, such as studying the relationship between different disease entities. There is evidence, for example, that suggests a relationship between some forms of benign breast disease and female breast cancer (14, 15). It would be worth knowing whether the frequency of breast cancer among relatives of those with benign breast disease differs from that of the general population. An area of current research activity concerns the cerebrovascular diseases. It would be helpful to determine whether there is familial aggregation not only of each form of cerebrovascular disease but also of definite or related risk factors, such as elevated blood pressure, cholesterol level and other forms of vascular disease.

In reviewing the epidemiological studies of non-infectious diseases, one becomes immediately aware that many studies report an association of a disease with a very general variable. For example, disease frequency by social class is frequently analyzed as well as the differential frequency of a disease between states or regions of the country or even between different countries. But, after obtaining such results, no effort is made to determine the underlying reason for such relationships. I would like to stress the importance and need for our field studies to go beyond these broad relationships and into as many specific ones as possible. Table 4 illustrates a possible sequential pattern of relationships with regard to social class. If one can modify the general population variable, such as social class, to prevent the sequence of events leading to the disease—if one could, for instance, eliminate poverty—it is possible that the disease would decrease in frequency and negate the need for further studies. However, such a direct attack on a variable is usually not feasible and it then becomes necessary for the epidemiologist to explore the specific components
of the general variable and search for a factor that can be altered to permit disease control, as is suggested in table 4. In many epidemiological studies, it would appear highly desirable to include measurements of physiological or biochemical variables together with the specific population components.

THEORETICAL OR MATHEMATICAL EPIDEMIOLOGY

An area of epidemiology which has always evoked considerable interest is one I term theoretical or mathematical epidemiology; here the focus has been on the description of the epidemic occurrence in mathematical terms, that is, as a mathematical model.

In infectious diseases, there is a continuing effort to develop mathematical models to describe epidemics; we know this as epidemic theory and, in fact, Frost, collaborating with Reed, contributed to this development. What we know as the Reed-Frost model is included among some unpublished lectures used in his courses (16, 17). More recently, these methods have been extended to include computer simulation of epidemics under varying conditions.

The development of mathematical models has also been of some interest in the non-infectious diseases, particularly in considering the effects of radiation and carcinogenesis. (6). Models have been developed to represent various types of theories, e.g., the 2-hit theory, meaning that cancer results from a sequence of exposure of the cell to two events, separated in time, which finally result in a malignant transformation; this has been extended to a multi-hit theory, with the malignant transformation resulting from a sequence of series of multiple exposures. From these probability concepts, one can derive equations regarding the age-specific incidence rates of cancer and determine whether the rates resulting from the theoretical model are consistent with observed data.

My primary purpose in mentioning these developments is to illustrate the similarities between the infectious and non-infectious diseases. The Reed-Frost model presented below has a relatively simple interpretation:

$$C_{t+1} = S_t (1 - q^{r_t})$$

$C$ = Cases.
$S$ = Susceptibles.
$q$ = Probability of individuals not having contact.
$1 - q^t$ = Probability of having contact with at least one case.
$t$ = Time.

When a susceptible has a contact with a case, he will develop into a case and the occurrence of cases over time is a function of susceptibles and probabilities of having contact with cases. The equation can mathematically be reduced to the following:

$$C_{t+1} = S_t (1 - e^{-rt})$$

$r$ = Proportionality constant

One of the multi-hit models which has been developed to fit the age distribution
of several specific forms of cancer is the one proposed by Burch:

$$P_{r,t} = S_0(1 - e^{-k_r t})$$

$P_{r,t}$ = Age-specific prevalence at age $t$ years of condition initiated by $r$ random events.

$S_0$ = Per cent population genetically predisposed.

$k_r = Lm$; $L$ = Number of cells.

$m = Mutation rate per cell/year.$

It is most striking that the form of the model is essentially the same as in the epidemic theory; I must admit to having been unprepared for this result. However, upon reflection, the biological similarities become evident. A hit is similar to a contact; a conversion from a susceptible to a case is similar to a mutation which converts a normal cell to a malignant one. I have no desire to overstate the similarity of these specific models since other models which have been developed are not as similar. However, it is clear that in both the infectious and non-infectious diseases this particular approach has been used in similar ways.

The mathematization of biological or of natural phenomena has considerable appeal to man in his effort to understand and control nature. Although such approaches have been powerful in other disciplines, it is not clear what they have contributed to epidemiology. My personal feeling is that their role thus far has been a limited one; although I must admit that it may be too early to pass judgment. This type of theoretical model building should be assessed in terms of its ability to stimulate and influence a change in direction or methods in a discipline; frankly, I do not believe it has had this influence in epidemiology. True, it has led to increased precision in the thinking and defining of some ideas and concepts and frequently has been of assistance in the teaching of concepts and perhaps that is all that one can expect.

One of the most succinct statements on this type of model building was made by Robert Solo, in a critical assessment of econometric models, which represents a similar approach in economics (18). He stated: "Ultimately, the mode of expression that will most conform to the scientific ideal will not be the image-free symbols of mathematics but rather the imagery of normal communication and intercourse with its reference base in the specifics of experience, for only if the general statement is so framed can it be continuously bridged into direct observations and contrasted with ongoing experiences." This judgment, it seems to me, applies equally well to epidemiology.

**EXPERIMENTAL EPIDEMIOLOGY**

The last area we shall consider is that of experimental epidemiology, broadly defined to include experimentation in both animals and man. For the past two decades, this has become a major area of epidemiological activity. As far as I have been able to determine, Frost did not consider either animal or human experiments within the realm of epidemiology. Perhaps, he considered experiments in the infectious diseases to be an appropriate concern of microbiology and experimentation in the non-infectious diseases the concern of that clinical specialty or laboratory discipline dealing with the specific problem. There is no indication in his writings as to the role of experimentation within the inference-making framework of epidemiology, except of course for the "natural" experiment, which, although occurring naturally, closely approximates the conditions of a randomized controlled experiment such as John Snow's studies on cholera in London, which Frost resurrected from obscurity.

A comparison of the types of epidemiological experiments in these two categories is shown in table 5. We can consider the experimental work in animals with various etiological agents in non-infectious diseases as a form of experimental epidemiology, conceptually equivalent to similar experimental work in animals in the infectious diseases. However, very few non-in-
fectious disease epidemiologists do actually engage in such experimental work. This type of research is complex, requiring a different set of skills and disciplines; perhaps, it should not even be considered within the scope of epidemiology. In any event, such experimental work does make important contributions to our understanding of the biology of specific diseases. These animal studies provide a means for determining the possible pathogenetic mechanisms by which an exposure to a particular etiological agent produces the disease. They may also provide information on the sequence of the intermediate pathological, biochemical or physiological steps between exposure and disease. Once these have been ascertained, it may then be possible to return to the human situation in observational studies to determine whether these steps in fact do pertain. The converse is also true in that human observational studies lead to animal experiments.

It is not necessary to elaborate upon the problems encountered in generalizing from the results of animal experiments to man. Although they exist for both the infectious and non-infectious diseases, extrapolation is somewhat more difficult for the non-infectious diseases. For example, one of the problems encountered in experimental carcinogenesis and atherogenesis is that of the specific metabolism of the animal species in the experiment which may determine whether a particular agent produces the disease. As an example, in the experiments on aniline dyes and bladder cancer, the aniline dyes were not carcinogenic in rats, rabbits, cats or in several other species (19). It was not until dogs were used as the experimental animal that bladder cancer was experimentally produced. Apparently, dog metabolism, at least with respect to aniline dyes, is similar to that of humans and different from other species. The converse is also often true, and in many diseases the human situation may be unique and not reproducible in any animals, which leaves us completely dependent upon observational studies. This type of situation is obviously much different from Webster's and Wilson's experiments on the progress of an epidemic in colonies of mice in which herd immunity and susceptibility were investigated (20, 21). Those experiments were not dependent on metabolic differences between species, etc., and generalization of behavioral principles of epidemics from animal colonies to humans would appear to be more reasonable. Realistically, however, it will probably never be possible to generalize from animals to humans except in a very limited way. For practical purposes, the significance of positive results from animal experiments, without data on human populations, is that such results do indicate a possible human risk which can be taken only at the possible cost of human lives.

Let us now turn our attention to experiments using volunteers. It is unnecessary to describe the details of randomized controlled trials, which is what I mean by human experimentation, nor the advantages and general type of problems encountered in such trials; these are dealt with in many publications (22, 23). It does seem worthwhile, however, to focus our attention on the three types of studies indicated in table 5 and the problems encountered in the non-infectious diseases, particularly those having some of the characteristics mentioned earlier.

The first type of experiment, i.e., the trial of etiological agents, is best illustrated by
the randomized trial of exposure of newborn infants to varying concentrations of oxygen in the incubator to determine if a high concentration of oxygen was of etiological importance in retrolental fibroplasia. This type has no special conceptual problems.

The second type is demonstrated by a drug trial for hypercholesterolemia in the prevention of coronary heart disease. If one is interested in the possible etiological relationship between elevated serum cholesterol and coronary heart disease and if, in a randomized controlled trial, a drug successfully lowers serum cholesterol which in turn results in a decreased incidence of coronary heart disease, a strong link has been successfully added to the chain of evidence showing a causal association between the two.

The third type, which is slightly different from the first, is the cessation experiment. Let us assume we are interested in the causal association between cigarette smoking and lung cancer; we select a group of cigarette smokers and randomly allocate them to two groups, one which continues to smoke and one which we convince to stop smoking. We then determine that the mortality from lung cancer in the smoking-cessation group is lower than in the smoking-continuing group. Such a result would considerably strengthen the etiological interpretation of the smoking-lung cancer relationship.

The last two types of experiments have a special problem reflecting the biological feature of some chronic, non-infectious diseases. Let us assume that in both examples cited, the coronary disease and lung cancer trials, negative results were obtained. Would this indicate that there was no causal relationship between the risk factors that were experimentally modified and the specific disease? Definitely not, since it is quite conceivable that the underlying pathological process leading to the disease may be the result of the long term effects of the etiological agent and that this pathologic process had already reached a nonreversible stage in our experimental subjects. Thus, it is possible that exposure to an elevated serum cholesterol may have passed the point where the atherosclerotic process is reversible. Similarly with regard to cigarette smoking and lung cancer. We may be left in the unenviable position of obtaining a negative finding, from which a conclusive negative inference cannot legitimately be derived.

I do not believe that one can postulate any general rule that would apply to this type of situation. Each study must be evaluated in the light of our knowledge of the epidemiology and biology of the specific disease.

Another characteristic of the non-infectious chronic diseases that may pose a problem in the planning and interpretation of the results of human experimentation is the presence of multiple etiological agents. This problem becomes especially important when selecting a population or sample study group for a particular study. Let us assume, for example, that we would like to study the effect of dietary change on coronary heart disease by means of a controlled human trial and that the study will be carried out in a single medical center or community. Since multiple factors, many still unknown, are involved in the etiology of coronary heart disease, the question might be asked how generalizable are the results obtained from a study in one community. Different communities may be exposed to other etiological factors which may interact with the dietary factor. And, it is obviously impossible to sample all mankind.

In this presentation I have primarily attempted to emphasize the similarities in the epidemiological approach to infectious and non-infectious diseases, particularly the methods used and the inferences to be derived. I have also considered several types of differences. Unfortunately, much too often I hear that there are "Two Epidemiologies" and I have therefore tried to demonstrate that investigators dealing with
one of these disease categories have much to learn from those dealing with the other.

There is, however, one distinct major difference in the epidemiological study of these two groups of diseases; in infectious diseases, there is an underlying germ theory of disease. It is important to remember that, with the exception of the few brilliant epidemiological observations in the pre-Pasteur era, epidemiology really flourished after the germ theory had a firm base. In the non-infectious diseases there is no general all-embracing theory; each disease group has its own underlying biological base, which imposes a serious limitation on epidemiological studies. Despite this, epidemiologic studies and data have contributed directly and significantly to our present understanding of the biologic basis of several non-infectious diseases. Many of these, 20 to 30 years ago regarded as degenerative, constitutional and nonpreventable diseases, are now regarded in whole or in part as environmentally determined, preventable or potentially preventable. Much of this change is the result of epidemiological studies, an impressive achievement. But, much remains to be done. I am certain that epidemiologists can look forward to an active future, as well as a most productive one.

REFERENCES