DISCUSSIONS

NAJERA: Perhaps we should start by emphasizing the interrelatedness of the factors that cause disease. Today, everybody talks of multicausation, but if you read the studies, most researchers still search for "a cause," they still think in terms of a single or a few simple causes of disease. They haven't really begun to understand disease as a result of the interaction of factors working within a real web. It was MacMahon who first talked of a "web of causation," but too often this is still interpreted as a complicated but linear chain of causation rather than a complicated interrelationship of many factors. A web really means interrelation. I think we have to emphasize this.

BUCK: But, you see, it is so hard to keep the web in mind when you are actually looking for a cause. When we were debating the causes of the epidemiologic transition we fell into exactly the same trap. It is still so easy to fall into this trap.

NAJERA: True, it is easier to talk about a web than to work with it. I remember a very good paper by Capra that traced the great evolution in physics from Newton to the theory of relativity and compared it with the relative lack of such development in the applied sciences. In medicine, for example, we are still stuck with a Newtonian approach. This is why we still think of the causes of disease in terms of one or two, at most a few, factors. We really can't understand the web of causation because this would be comparable to understanding the concept of relativity. We should know at least a little more of modern physics. When we were children we were taught Newtonian physics; we know very little, if anything, of relativity, Einstein, and quantum physics. We have to force ourselves to think differently. Even if it is very difficult for us to understand the meaning of interrelations, of a real web, we have to change our way of thinking and working. Perhaps it will be easier for the new generations to do so.

TERRIS: The concept of web of causation should be discussed in contrast to single-cause and multifactorial-cause concepts. In my basic course in epidemiology, I give a lecture called "The Web of Causation." To illustrate the concept I give the

example of the long-standing prevalence of diarrhea and enteritis in India. I point out that the British occupation of India was a major factor in why India has had so much diarrhea and enteritis for so long. Not all students appreciate this kind of analysis. In fact, I recall one student who responded by launching into an emotional defense of the British Empire.

But perhaps one of the most fascinating illustrations of the web of causation is the British epidemic of gout in the eighteenth and nineteenth centuries. Before that, Portugal's flourishing textile industry had competed with the British textile industry. England, involved in the War of the Spanish Succession, signed the commercial pact known as the Treaty of Methuen. The treaty allowed British textiles to enter Portugal duty-free; in exchange, the British allowed Portuguese wine to enter Britain with a lower duty than French wine. The treaty resulted in the destruction of the Portuguese textile industry. This is one of the reasons that Portugal failed to develop as an industrial country.

The British, at war with France at the time, could then substitute Portuguese wine for French wine. But in order to preserve the wines for the long voyage from Portugal to Britain, they were fortified with alcohol that presumably had been distilled or stored in lead vessels. The Portuguese wines apparently contained large amounts of lead that caused the gout. This possible scenario was described by two clinicians from the University of Alabama in an article published in the *Bulletin of the History of Medicine*. The article reported an outbreak of 37 cases of gout in moonshiners who distilled their illegal whisky in old automobile radiators which had been repaired with lead. They drank leaded alcohol and developed gout as a result. The authors of the article described this sequence of events and hypothesized that a similar process had occurred in England.

BUCK: Did they have other symptoms of lead poisoning in eighteenth-century England?

TERRIS: The lead content was not enough to produce massive poisoning, just enough to damage the kidneys and raise the uric acid in the blood.

To test their hypothesis, the Alabama clinicians went to England and analyzed four bottles of port dating from the late eighteenth and early nineteenth centuries. They found large amounts of lead in the old wine, but only traces in new wine. Who would have thought that the Treaty of Methuen would have had a hand in the eighteenth-century gout epidemic? Yet it all fits epidemiologically: only the

rich were affected; they ate a lot of meat, drank a lot of port wine, and they suffered from gout.

NAJERA: Using a play as a metaphor is another good way to understand how the concept of the web of causation differs from other approaches of disease causation. For example, in some plays one actor, one main character, practically carries the whole play. This would be analogous to thinking of disease causation in terms of one agent that is more prevalent, more necessary, more important. In other plays, however, there are many actors with equally important roles; you need all of them to reach the play's outcome. This is comparable to approaching disease causation in terms of how people and other factors interrelate in a complicated web of causation. Some factors would be more important than others, of course, just as in most plays you can have many actors but fewer lead roles. Investigations should aim at understanding all the factors involved. This should facilitate separating confounding factors in the analysis.

TERRIS: There's another way to look at this: "The agent is necessary, but not sufficient."

NAJERA: When we say "necessary but not sufficient," however, I think it is important that we analyze necessary for what. In many of the acute diseases, the infectious diseases, we say that the specific agent is "necessary but not sufficient" because we need the specific agent to name the disease. But in the noninfectious diseases, which agents are necessary? In many cases, we don't really know.

TERRIS: Yes we do. Cigarette smoking is necessary.

NAJERA: Not for lung cancer. There is lung cancer without cigarette smoking.

TERRIS: Very little. Cigarette smoking is almost always involved.

NAJERA: But the fact is that there is some lung cancer without cigarette smoking. If you have lung cancer without cigarette smoking, then it is not necessary.

TERRIS: Air pollution, chromates, uranium: there are a number of agents that cause lung cancer.

NAJERA: Sure, there are a number of agents, but no single one is necessary in the same way we were talking about in infectious diseases.

TERRIS: But that is also true of infectious diseases. You can have a respiratory infection caused by 30 different viruses; there is no single agent.

NAJERA: This is what I wanted to come to: the condition of "necessary" is not so clear, even for the infectious diseases. For instance, tuberculosis mycobacteria are necessary for a diagnosis of tuberculosis only because we don't call the disease tuberculosis if there are no mycobacteria. But, after all, what is the real difference between a chronic pulmonary disease with mycobacteria and a chronic pulmonary disease without? Not much, except perhaps in the way we study and describe it, or in how we treat it—if there is a specific treatment for a specific agent, that is. Aside from this, most infectious diseases could be considered in a completely different manner. We could reclassify acute respiratory diseases epidemiologically, rather than accepting pathological or therapeutical classifications.

BUCK: Not entirely. I don't think the complexity of causation comes into infectious diseases in terms of whether there is a "necessary" cause. Just as you pointed out, disease nomenclature says there is a necessary cause. We name the disease by what we regard as the necessary agent. I think that what Terris is talking about is a *sufficient* cause. It is never enough just to have the agent, because a substantial proportion of people do not develop the illness. So the web comes more into the problem of sufficiency of causation.

NAJERA: Yes, yes. I wanted to emphasize that there are very few necessary lead roles in the "plays." Unless you have a very, very severe toxin such as strychnine. Strychnine is enough; it is the only cause. You take it and you die. But there are very few things like this.

TERRIS: But in certain noninfectious diseases, I could say that a vitamin deficiency is a necessary cause.

NAJERA: Sure, but even deficiency diseases can warrant further analysis. Say there is a vitamin deficiency; isn't it just as important to establish *why* there isn't a satisfactory supply?

TERRIS: Well, that is a situation where the agent is not sufficient. Given the basic epidemiologic triad of agent-host-environment as a conceptual framework, if you don't think in terms of the web of causation, you are forgetting about the host and you are forgetting about the environment. The agent must reach the host in sufficient quantities to cause

trouble, and the host must be susceptible. That is the key to the whole process.

NAJERA: Yes. What's important is how and why—under which environmental conditions including social ones—these factors can reach the host to cause disease. It is not enough to accept the concept of agent-host-environment, one should also consider what factors influence these agents to go through the environment and reach the host. This becomes much clearer with chronic diseases. Here you find factors—you could call them "through factors"—that give origin to the agents and also influence the host. In my opinion, these are mostly social factors. Given this, one can discuss the non-validity of the so-called lifestyles. After all, lifestyle is a product of the environment, the social environment.

TERRIS: To return to our discussion on the web of causation, my guess is that there are very few lectures about it in today's epidemiology courses.

NAJERA: I teach it.

BUCK: Me, too.

TERRIS: You teach it? Very few teachers give that lecture. My students don't like it. It is too theoretical for them.

NAJERA: I am often called *maraña*. In Spanish, the word for web is *trama*, but I prefer *maraña*, which means tangled web. I am always talking about the importance of thinking in the *maraña epidemiológica*, the tangled web of causation.

TERRIS: I might say that much of the epidemiology taught in the United States is single-cause oriented, both for noninfectious and for infectious diseases. Take cigarette smoking. According to this approach, the tobacco companies have nothing to do with it, just the cigarette is to blame.

NAJERA: Also, nowadays people rely too much on statistics as the only method, forgetting that statistics should be only a helpful tool to ascertain whether events occurred by chance. Yet everyone maintains that things have been scientifically proven if they have been statistically proven. The truth is that you can never prove anything statistically. All you can do is try to eliminate chance, although it can never be completely eliminated—even if it is only one chance in a million.

TERRIS: Besides, if the results are not statistically significant, it may only mean that you don't have a big enough sample. That's all it means. People don't understand that.

NAJERA: Exactly. This is very important, because in epidemiology you have to search for relationships, even if they are not very apparent. This is the way to learn more. We have to be careful not to eliminate good theories simply because they are not statistically significant, or replace them with something else just because that is statistically significant. This margin of 95 percent or 5 percent that seems to be the basis for everything, does not really mean anything. On what basis can we say that 6 percent or 10 percent is bad and 5 percent is good?

TERRIS: As we all know, traditionally mortality has been the most highly developed measure of health status, because it is easy to measure the fact of death. However, there are a number of issues to discuss regarding the measurement of mortality. For instance, I think the recent development of the "years of life lost" concept as an alternative to the old approach of mortality rates is important, as is the question of age adjustment. By the way, did you know that it was a Hungarian statistician who first brought age adjustment to the United States? He gave a paper in Chicago at a national meeting of statisticians. Soon after, everyone began to do age adjustment. It caught on.

BUCK: As far as years of life lost goes, I suspect this may have been established as a methodological approach by Farr when he used Halley's life table concept.

NAJERA: Did you know that this Halley was the famous astronomer for whom the comet that has just "visited" us again was named? You are right, Carol, his mortality tables for the city of Breslau, published in 1693, were one of the first to relate mortality and age.

TERRIS: Another problem in measuring health status is accuracy in diagnosis. For example, the British found that coronary heart disease was more prevalent in the professional classes than in the working classes, that there was a socioeconomic gradient. One of John Ryle's mistakes was to look at this finding and say it was because the upper classes had more anxieties and responsibilities than the lower classes. Abe Lilienfeld wrote a beautiful paper in which he analyzed the English data for coronary heart disease and showed that indeed it was higher in the upper classes. Then he turned

around and did the analysis for degenerative heart disease and it went the other way; it was higher in the lower classes. He then combined the two diagnoses and found that the death rate was the same for all social classes. Of course, the difference was not in the diseases but in the doctors. The upper classes had young, bright internists and cardiologists who knew all about coronary heart disease, whereas the working class had the old general practitioners who all their lives had called the disease degenerative heart disease and were not about to change. That is where the difference was. Lilienfeld's paper is important because it points to the problem of inaccuracy of the death certificate and the basic data.

Ruth Puffer also did a very important study for PAHO on the accuracy of diagnosis in San Francisco, Bristol, and some Latin American cities. To test the accuracy of death certificates in these cities, they very carefully evaluated all death certificates for a given time period. It was a fascinating study that really dealt with the question of accuracy of the basic data. And the interesting part of this study, for me, was that in the Latin American cities examined, diagnoses were as accurate as those in San Francisco and Bristol. The problem in Latin America was accuracy in diagnosis in the rural areas. Of course, the problem of accuracy in morbidity data is much worse than in mortality data, and it is even more difficult when we try to look at the epidemiology of health rather than of disease.

BUCK: It would be worthwhile to mention, at this point, that Sydenstricker's early surveys in the United States probably constitute the landmarks in measurement of morbidity.

In terms of measuring health, some years ago a study done in the United States compared two groups of children with different degrees of positive health. It wasn't sick versus controls in the usual sense, instead the study looked for determinants of the more positive health of one group. The idea is good because we seldom ever investigate health, great or good health versus all other levels. We are still so disease oriented. There is a problem, of course, in studying the determinants of good health—the problem of the direction of causality. Hours of sleep, for example, could be either the result or the cause of your state of health.

TERRIS: There was a study of Guatemalan children that linked maternal and child nutrition to performance. It would seem to me that this, too, is positive health, because it measures performance rather than illness. And another study, done by the Institute of Nutrition of Central Amer-

ica and Panama (INCAP), measured the ability to function. They took two groups of adult Guatemalan peasants doing hard physical labor and supplemented the diet of one group. It was found that those in the group without the dietary supplement lived in negative balance: they did not get enough calories and so they lost weight. They also didn't have much energy. Both groups would work in the fields, but after the work was done, those with the supplemented diet went out and played soccer or socialized, while the ones without the supplemented diet slept or rested at home. They were simply so fatigued because of malnutrition that they couldn't really live beyond the working day. I have calculated from their data that if this is really true, most of humanity in Asia, Africa, and a good part of Latin America loses one-quarter of active life because of malnutrition. This shows that the issue of the epidemiology of health is not merely a luxury or fringe benefit for industrialized nations; it is a crucial question for the developing world.

BUCK: There also was a study comparing the intelligence of Guatemalan children with that of American children. This study showed that the difference between Guatemalan and American infants increased steadily after birth. This suggested that the difference in intelligence did not have a prenatal origin; rather, it was the post-natal nutrition which was the important factor. Speaking of intelligence reminds me that mental health is one of the most difficult areas to measure. To quote Susser: "psychiatric researchers, aware of the problem, tried at least to specify caseness, a condition a psychiatrist would judge in need of treatment." He was trying to bring together survey-detected, self-reported, and psychiatric measures of mental illness. That is interesting, because I don't believe that problem has been solved yet.

TERRIS: Going back to your comment on the early use of "years of life lost," I believe that the landmark paper is not in those early writings. This concept is a wholly new approach which had never been used in the past 50 to 100 years. It was either the United States or Canada that first used it and it has now caught on.

Do you know how "years of life lost" came to be used? When heart disease, cancer, and stroke legislation was proposed as a major priority in the United States, the people in Maternal and Child Health (MCH) were furious because the legislation did not take into account years of life lost. In light of this protest, people began to think of redoing

mortality to take account of the years-of-life-lost concept. When they applied the concept in Toronto, it showed that suicide in that city was much more important than everyone had thought it was.

NAJERA: That was in the seventies.

BUCK: Well, I think it goes back further than that, though. People have been working for a long time on what they call "health status indicators." The idea of the years of quality life rather than just life was put forward by Daniel Sullivan earlier than the seventies.

TERRIS: But he did not develop the method.

BUCK: Well, Sullivan did have a method consisting of a double life table: there was a column for mortality and there was a column for disability; by using the two columns simultaneously he was able to calculate the expectancy of years of nondisabled life.

John Last's "The Clinical Iceberg," was also a key paper in health status measurement. Much of the earlier morbidity data had come from treatment services: mental illness information from hospitals and other illness data from general practitioners. Last's paper showed that only a tiny fraction of people's illness turned up in the doctor's office. This is common knowledge now, but Last's paper showed that measuring morbidity on the basis of treatment wouldn't work. We had to do surveys of some sort.

I would like, for a moment, to go back to the web of causation discussion and have us consider the factors that may be involved in heart disease. Ancel Keys found something very, very provocative in his international study. He used regression equations containing suspected causal variables. There were two equations, one for the northern countries and one for the southern countries. When the northern equation was used to predict coronary disease in the southern countries, it predicted too many cases. When the southern equation was applied to the northern countries it predicted too few. For me, this showed that, in addition to the variables in the regression equation, there were other important factors, for example, occupation.

TERRIS: Why should you call it occupation?

NAJERA: Well, perhaps occupation and environment.

BUCK: I didn't say we have shown it.

TERRIS: But what in the environment?

NAJERA: What else could it be?

BUCK: Well, it could be genetic variables because different ethnic groups were involved in the international study of heart disease.

I think that we also need to look at old problems in new and imaginative ways. Take, for example, Rosenman and Friedman's work. They were the first who had the nerve to spend a lot of money looking at the psychological factors in heart disease, while everybody else was happy looking at fat consumption, cholesterol, smoking, and blood pressure. I know that recently some doubt has been cast on the whole thing by the Multiple Risk Factor Intervention Trial (MRFIT) Research Group study, but I wouldn't rush to discredit the idea. Experimental evidence, some of which already came in, will settle the issue.

TERRIS: I think the whole thing is still up in the air, the relation of stress and heart disease.

BUCK: Well, I see it as a new kind of variable being introduced here.

TERRIS: Stress is the oldest variable there is in heart disease.

BUCK: Yes, but the new variable brought to light by the study is not so vague. The concept of Type A behavior is different from the global kind of variable called stress, isn't it? However, I agree that we're not yet sure about Type A, and that this poses an interesting question about whether something can be significant if it is still up in the air. I don't know. You could argue both ways.

TERRIS: Irrespective of that, I feel that you are giving that issue a credence I am not willing to give it. Besides, having a lot of stress management courses to prevent heart disease is ridiculous. What we have to do is work on the important things, like saturated fats and high blood pressure and smoking. Stress management is a gimmick now, and a good deal of money is being spent on it. First of all, how are you going to control stress with this stress management business? There's no proof that stress management does a damn thing. It's a fad, as far as I'm concerned. The relation of heart disease to psychological factors has always been a fad.

BUCK: You may be right, but I doubt it.

TERRIS: Yet I must admit they *may* be right. But at this point, it's a little bit like fiber and cancer of the colon; I don't accept that. I don't accept salt and hypertension, either. If you really look at the data, it's very unclear what the facts are.

BUCK: But one thing you have to think of (and I'm not saying that this book is the place to put the position forward) is that a lot of these other factors—diet, fiber, salt, calcium, and all that sort of thing—may protect target organs from developing a disease that is really a response to stressors. We may not get the best results if we try to prevent disease by manipulating these factors one by one. It's conceivable that if the basic stressors or the stress response can be modified, the target organs would remain healthy.

TERRIS: That's a global hypothesis which I don't accept. I must tell you that many people will not accept a global hypothesis.

BUCK: It's another way of looking at disease. I have an idea that disease is like a fire: you stamp it out here and it breaks out somewhere else.

TERRIS: That is a basic issue. I've heard this said too many times now. For instance, I've heard people at meetings say, "Well, if you cut out one disease, something else takes its place." It's not true. If you look at the data, nothing takes its place. There is a decline in the death rate. It was true of infectious diseases and it's true of noninfectious diseases. People die much later. Fries is right, there is a compression of morbidity.

BUCK: No, not necessarily a compression of morbidity, although there is a postponement of mortality. Fries may be indulging in wishful thinking when he talks about a compression of morbidity.

TERRIS: But that's not true, either. This is a basic question. When you have primary prevention you're not only postponing mortality, you're preventing morbidity.

BUCK: You're right, but only if you really have achieved primary prevention.

TERRIS: But that's what we're doing with heart disease, cerebrovascular disease, accidents. It's all primary prevention. It's not secondary prevention.

BUCK: What's the primary prevention of cerebrovascular disease?

TERRIS: Hypertension control.

BUCK: By what method?

TERRIS: By drugs.

BUCK: I see.

NAJERA: That's not primary prevention.

TERRIS: It is primary prevention of stroke.

BUCK: Maybe "secondary primary."

TERRIS: What would you do with risk factors? As far as I am concerned, hypertension is not a disease but a risk factor, just like high serum cholesterol. If you control serum cholesterol, we know this will lower mortality *and* the incidence of coronary heart disease will also decrease. The same is true of stroke: if you decrease the prevalence of hypertension, the mortality and the incidence of stroke will be lower. This is compression of morbidity. I have criticized the United States Social Security Administration because they publish statements that if mortality goes down, people who get older will have more morbidity. It is not true. You can also reduce morbidity because you're preventing stroke, you're preventing heart disease, you're preventing accidents.

BUCK: A lot of this is still theoretical.

NAJERA: You will not have later death in a pure sense, though. The average age at death will remain unchanged. What you will have is more people reaching that age, but later death, real later death, you will not have.

TERRIS: Sure you will.

NAJERA: Up to when?

TERRIS: Up to the average lifespan, which Fries has estimated to be about 85 years, with individual variations falling almost entirely within the range of 70 to 100 years.

NAJERA: O.K. We will have an age curve that shows that all people will die at the same time, at the end of the lifespan.

TERRIS: Right.

NAJERA: O.K. Then you have prevented all this morbidity, and all this mortality. People will live healthy lives. . . .

TERRIS: . . . until they've reached the end of the lifespan; then they'll die.

BUCK: They'll go out like light bulbs, I suppose.

TERRIS: We may completely disagree, but I think we all recognize that these issues are terribly important.

NAJERA: They are very important.

TERRIS: I don't buy the idea that if we lower the mortality and the incidence of a disease, something else will take its place. Nothing else takes its place.

NAJERA: You're right, it should not. It has not happened with the diseases affecting the young. Nothing has taken their place.

TERRIS: Manning Feinlieb showed this very well at one of the International Epidemiological Association meetings. He said that if you look at the rates, they are going down. That's all there is to it. But let's go back to the topic at hand; we were talking about etiologic investigations and I would like to go back to Goldberger. I think he was important because his studies show the similarity between infectious and noninfectious disease methodologies. Goldberger was a master of observation and experiment.

While he was working in entomology in the United States Public Service, there was an outbreak of a skin disease called Schamberg's disease. Goldberger was sent to solve the problem, which he did in a few days. He discovered that the disease only struck people who slept on straw mattresses. He then experimented on himself and other volunteers by sleeping on contaminated straw mattresses—they all contracted the disease. Then he sifted particles from the straw into two clean Petri dishes. The contents from one of the dishes was applied to the left axilla of a volunteer, and the skin eruption appeared. The other dish was exposed to chloroform vapor, and its contents then applied to the right axilla; there was no eruption. They examined siftings and found five very small mites which they applied to the axilla of another volunteer; the characteristic eruption appeared. They identified the mite and solved the problem.

Goldberger also was part of one of the three groups that raced to demonstrate that typhus fever is louse-borne:

there was a French group, Rickett's group in Mexico, and Anderson and Goldberger's group, also in Mexico. The French group won, by the way, not Ricketts, and not Anderson and Goldberger. But the wonderful thing was Anderson and Goldberger's analysis—based on the epidemiology of the disease and the characteristics of the possible insect vectors—of why the disease had to be louse-borne. It is that same reasoning, based on epidemiological facts, that Goldberger later used to conclude that pellagra had to be a nutritional disease.

Goldberger was an experimenter. He applied the experimental approach to a mite-borne disease, a louse-borne disease, and a noninfectious nutritional disease. You have to realize that epidemiology, before it became so observational under the influence of Wade Hampton Frost, was experimental. Epidemiologists came out of a microbiological background, and they experimented on themselves. With pellagra, Goldberger did a whole series of experiments. First of all, he did animal experiments, many of them. Then he did human experiments trying to infect U.S. Public Health Service volunteers, including himself, with the blood, nasopharyngeal secretions, skin lesions, urine, and feces of pellagra patients.

BUCK: It proved that pellagra wasn't infectious.

TERRIS: Nobody got pellagra. Then he did the studies in the orphanages and the insane asylums. He fed the inmates a good diet and pellagra disappeared.

BUCK: Did he have a control group?

TERRIS: He never had a perfect control. Now this really raises the question of whether you always need a perfect control. My answer is no. Although Goldberger did have some lucky breaks: in one orphanage, for example, they went back to the old diet and pellagra reappeared. They reintroduced the experimental diet and the disease disappeared again.

BUCK: In modern parlance, that would be called a very high-level quasi-experiment. Quasi-experiments can come pretty close to experiments.

TERRIS: But that's the danger in all this insistence on refusing to accept evidence except from randomized trials. When the Soviet Union carried out its polio immunization program, millions of people were immunized and polio practically disappeared. That was all the proof needed, as far as I'm concerned. I don't care that there was no control.

BUCK: I know what you mean, so I'm not going to argue.

TERRIS: Going back to Goldberger, his studies on pellagra also dealt with a very difficult methodological problem—the confounding variable. He discovered the connection between pellagra and a lack of meat and milk in the diet of the affected households. The problem was figuring out whether meat or milk was responsible. After all, the two were connected. Which was primary? Which secondary?

Goldberger did a very simple thing. He categorized households that consumed very little meat according to their milk consumption, showing that with a minimum of meat the incidence of pellagra declined as the milk consumption increased. Then he turned around and categorized households with very little milk consumption according to their meat consumption. It turned out that meat, too, was an independent variable. Both variables contributed to the disease. It was a very simple approach to unraveling the confounding variable.

The other approach which I think is very good was used by Doll in his work on cervical cancer. Since age at first marriage and number of pregnancies are both associated with the disease, he adjusted on age at first marriage and the association with number of pregnancies disappeared. Then he adjusted on number of pregnancies and the association with age at first marriage persisted. It was a beautiful demonstration.

There are a number of papers that deal with the issue of confounding variables, illustrating different ways of approaching one of the key problems in noninfectious disease epidemiology. For example, there is the method of multiple regression, and also the method of matching. I did a study on cancer of the mouth, pharynx, larynx, and esophagus. We matched on tobacco and showed a relation to alcohol. Then, when we got through with the study, we thought it could be the other way around, because tobacco and alcohol consumption are very closely related. So we matched on alcohol, and the tobacco relationship held up. They both held up. There are at least four different ways of dealing with confounding variables.

BUCK: To close on this theme, I think we should try to discuss experimental studies, highlighting behavioral change as a means to remove risk factors. Experience has convinced me that in the study of behavioral change the experimental approach is very difficult because of non-compliance and control-group contamination. Bradford Hill once said that you could not do an experiment on the value of breast-feeding.

LLOPIS: The principal characteristic of experimental epidemiology is that it introduces a new variable—intervention. And the only two possible intervention experiments are prophylactic measures and new treatment. These are the only possible experiments in epidemiology.

BUCK: And the fact is, you know, that experimental studies of that sort can run into serious problems with sample size because the randomization is of groups of people rather than individuals. In this type of experiment you have to make allowances for clustering, and that leads to much larger sample sizes.

TERRIS: One of the major experimental studies was the recent Lipid Research Clinic's study where they used a drug, cholestyramine resin, that lowers serum cholesterol by increasing the removal of low-density lipoproteins from the blood, but is not absorbed from the gastrointestinal tract. The study was organized by the U.S. Public Health Service, and showed very clearly that if you lower the serum cholesterol level, you lower the incidence of coronary heart disease. It really clinched it for serum cholesterol.

BUCK: I must say that I'm not convinced that lowering serum cholesterol provides an overall benefit. Coronary disease is just one part of morbidity.

TERRIS: No, I really think that study clinched it. At that point, people stopped arguing about the role of serum cholesterol.

BUCK: We're digressing now, but I think the real problem, now that you put your finger on it, is that since most people are convinced that cholesterol has a role, they feel that these experimental studies are trying to evaluate a preventive program, rather than trying to establish a cause.

TERRIS: No, it turned the tide. People stopped arguing at that point.

BUCK: I would agree with you, if we were talking about the etiological implications.

NAJERA: There was a very well-planned project in northern Nigeria to establish the role, the importance, of every factor involved in causing malaria: social factors, climatic factors, variables in the host, variables in the vector, and so on. I think it was a very well designed experimental study, etio-

logical only in that it tried to find the role that each factor played.

TERRIS: The treatment of syphilis by the U.S. Public Health Service Hospital in Staten Island is, in my opinion, the most interesting one of all. Three cases were treated with penicillin and the disease vanished. It was published in *The American Journal of Public Health.* Now, if you had had one of these picky epidemiologists, they would have said not to publish it because there was no control.

BUCK: Well, Bradford Hill said that you didn't need a randomized clinical trial to show that streptomycin could keep people from dying of tuberculous meningitis. No one had ever recovered, and when certainty is the outcome you sure don't need a randomized trial.

TERRIS: I think this discussion is very important because today there is such a tendency toward cookbook randomization. Clinical epidemiologists are the worst in this respect.

BUCK: Purity to the point of sterility?

NAJERA: It's probably much easier to find and to do experiments in health services than to do etiological experiments, mainly because of the ethical factor.

BUCK: Not from a statistical point of view, because the problem of group randomization so often comes up in health care experiments.

NAJERA: It is the ethical part of the experiments that constitutes the main objection to most experimental epidemiology. Epidemiological experiments like the one on malaria that I mentioned may be the only model for future experimental epidemiology. In other words, one that assesses the importance of factors in a wide variety of conditions, by changing the pattern of those factors. I remember saying in one of our first discussions that we should pay more attention to the past and try to learn from it, especially from those experiments that failed. I think we would learn more from failures than we learn from successes, but the failures are never published. We should try to understand why some studies were not successful and why some were.

BUCK: I think you've raised an interesting point. There is quite a bit that we can learn from the MRFIT experiment, for example. First, it was done too late, in the sense that people

in the control group had also modified their risk factors. If we are going to avoid contamination of control groups, we have to do our experiments before the public comes to believe that a causal relationship has been proven. Timing is important. The other lesson we could learn from the MRFIT study is that it might be better to experiment with one risk factor at a time. If the study had obtained a positive result, it would be difficult to know which pieces of the risk-reduction package had contributed the most.