PANEL ON CAUSATION

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Dr. Remington: What is it that we require in order to judge if a is related to b? What is it that we require in order to judge if, for example, the serum cholesterol level is causally related to the frequency of coronary heart disease? What is it that we would require to judge that measles virus is causally related to clinical measles? What is it that we would require to judge that the lack of automobile safety belts is causally related to fatal automobile accidents, and so on., Its very much the business of epidemiology, I think, to judge the evidence and to make a decision as to when a relationship between two variables--a potential cause and a potential effect--becomes strong enough or becomes consistent enough or believable enough that we will be willing to say there is a causal relationship that a causes b.

The director of the epidemiology branch of the National Cancer Institute, Dr. Robert Miller, takes the view that the epidemiologist should be considered the "etiologist" and should consider himself as a student of etiology. That he is the person, almost uniquely, in medical science who has taken for himself an interest in studying, quite specifically, etiology. Formerly perhaps the microbiologists and others adopted this particular

role in medical science. But today with modern disease problems such as the ones we are concerned with, microbiology is not equal to the task, or is not interested in the task, and perhaps not related to this particular task. On the other hand, the epidemiologist in all his work is investigating relationships, weak ones, strong ones, ones that are or are not eliminated by confounding variables, as are not destroyed by such investigations, such refinements, all the way to the very strongest individual causal links. There is a prevalent view that it is the epidemiologist who is principally concerned with matters of association and causation. I think you can find this underlying theme in virtually every session here at Pioppi. Sometimes it is very close to the surface, sometimes fairly deep.

Let us look at what we would require as individuals--and I think this is a very personal thing--to decide that a relationship and an association between a and b, is or is not causal. I started my remarks with you last Monday by giving two examples. One about the relationship of the size of the stork population and the birth rate in northern Europe--they are quite closely related, perhaps even causally! But with this association our job was to interpret it. I suggested that this might be an instance in which we had cause and effect reversed, possibly. And the other example was women's footprints--the angle at which they place their feet in walking, in which both variables--age and angle--were perhaps due to a third underlying variable. We will disagree among ourselves, and here on this panel, as to the kind of evidence we require to judge that an association

is causal. I regard my function here to shake your confidence in the word "cause," and what it means. My job, I think, is to suggest to you that none of us probably really understands what we mean in rigorous detail by the word "cause." The word "cause" is ambiguous, it is used in different times, in different places, by different speakers, to mean very different things. There are a variety of causal links and the simple, unadorned word "cause" may do as much harm as it does good in our thinking about relationships. At any rate I want to shake your confidence, if I can, in the words cause and causation.

I'm going to give three examples of causal relationships, or potential causal relationships. Let me, in the best sense of Louis Carroll, define the word infection as I'm going to use it here. I will talk about infection with an infectious agent. What I mean when I use the word "infection" is the introduction and growth of an agent within a host. I think that's a fairly common definition in epidemiology. For the first relationship then, let me list cause or potential cause and potential effect, then the nature of this relationship, and then a diagram. The first is infection with polio virus as the cause. Infection with polio virus in the non-immune subject, and the effect, paralytic poliomyelitis. Very few people doubt that there is a causal relationship between infection with polio virus and the production of paralytic polio. However, we know that in the overwhelming majority of cases infection, which can be demonstrated to have occurred, does not produce paralytic polio. That is a cause which we would call a

necessary but not sufficient cause. Given the effect the cause is implied. If we have a case of paralytic polio certainly there was infection with polio virus but not the reverse. To illustrate that by diagram, I say here's a cause and then we introduce, possibly, several effects. One link says that given the effect, that effect came from the cause, but we cannot say that the cause invariably produces a particular effect.

The next example is major reduction in caloric intake as a cause, and weight loss as an effect. I do not think we would argue that there is a causal link between those two entities, but it is a different sort of a causal link. This one turns out to be sufficient, but not necessary in the sense that the cause here implies the effect. On the other hand, weight loss can result from other causes. Given weight loss we cannot say that there must have been a major reduction in caloric intake. The diagram goes in reverse here. We say that this is a sufficient cause of weight loss--major reduction in caloric intake--but not a necessary cause.

The third example is infection with measles virus, again in the susceptible non-immune. I mean "hard" measles, rubiola instead of rubella. Infection with measles virus, and then clinical measles. Clinical measles is the result of the virus infection. This one is a necessary and sufficient cause. Infect a susceptible subject with measles virus produces clinical measles with practically no exceptions, and the same is true in the other direction. Here the effect implies the cause and the cause implies the effect.

Most people when presented these three samples would say "yes, this causes that" in every one of the cases. Most people would feel these causes each produce their own effect, and yet how different is the nature of the cause in the three cases. We use one word to describe all these different relationships! English has one word for "love" while Greek has many, perhaps for different kinds. We use the single word "cause" to mean very different things in English and I think we should be aware and beware of it.

If we took a public opinion poll about the relationship between cigarette smoking and bronchogenic carcinoma most would say, "yes, cigarette smoking is causally related to lung cancer." I take that view, that there is a causal relationship between cigarette smoking and lung cancer. Yet, is cigarette smoking either a necessary or a sufficient cause of lung cancer? Here is a fourth use of the word "cause." I am prepared to argue with you that cigarette smoking is a cause of lung cancer, and yet given a life-time history of cigarette smoking, lung cancer is not inevitably produced. Given lung cancer, does it follow that the individual must have been a cigarette smoker? No. That cause is neither necessary nor sufficient, and yet most of us would feel that smoking is a cause. Finally to shake the case further, let us consider genetic cancer in mice, mammary carcinoma in in-bred mice, bred selectively to produce cancer spontaneously. In this kind of a causal link, a very different sort of thing, the in-breeding is not enough. There has to be a virus infection in the mother's

milk; it requires both the virus and the hereditary susceptibility to produce in a high percentage of offspring of these matings with spontaneous development of this particular tumor. Here is an instance in which several causes are required to act jointly. The interesting thing to me about this one is that there are causes from outside the host and from within the host. As we try to find a working definition of cause, keeping in mind the ambiguities we have discussed, let us consider some definitions of cause that have been used in our field and in related fields.

Some people say that a causes b whenever the probability of b (p for probability), given a, is greater than the probability b not given a. They say that whenever the chance that b occurs is stronger in the presence of a than in the absence of a, that a is a cause of b, causally related to b. The example does not include temporal priority, it does not include a need for a to precede b in time. Secondly, most of the associations we observe in cross-classifications have this property. If we observe an association, however small, this property will tend to be satisfied. So I regard that as a rather weak definition of cause but perhaps it is adequate for some purposes.

I would like to conclude my remarks by reviewing for you just briefly a part of a document you are familiar with, the report of the U. S. Surgeon General's Advisory Committee on Smoking and Health. That committee, you will recall, was convened by the Surgeon General of the U. S. P. H. S. late in 1962 and it met repeatedly through the rest of '62 and all of '63

and made the final report very early in 1964. One of their major conclusions was that cigarette smoking was causally related to lung cancer. They considered criteria for judging an association causal or not. They used five criteria they believed are needed to judge an association as causal. They defended their thesis that lung cancer and smoking are causally linked by applying these criteria. 1) The first of these was consistency. If a is to be causally linked to b then the relationship must be consistent. By that, they meant that the relationship had to hold under a wide variety of circumstances when studied under different populations, different conditions and with different methodology. They found that in the studies, all 29 of the available retrospective studies, and all 7 of the available prospective studies, produced the same relationship though differing in quantitative relationships. The test of consistency they argued, was met. 2) Secondly, strength of the association. If an association is to be causal, then it should be strong. Incidentally, this is one point at which this criterion would break down. There is nothing that says this one has to be much larger than that, only that it be larger. They require that the association must be strong, and again they found that the association was strong. They looked at the frequency of effect among the haves as compared to the frequency among the have-nots, and found a very large difference. Then they looked at grading, or a dose-response relationship: If there is more of a potential cause, does it more frequently produce the effect? If those two things hold, then they judge the relationship strong, and in the evidence

of smoking and lung cancer they felt it was. 3) Third, was the "specificity" of the association. Does it produce chiefly this effect, lung cancer for example, or does it also produce many other effects? There was a problem in applying the criterion of specificity, as Dr. Berkson at Mayo Clinic has pointed out for 15 years. It is not true that cigarette smoking produces only lung cancer, but it produces an excess of virtually all forms of mortality investigated (with some exceptions) and it has a pronounced effect on total mortality. 4) Fourth, a temporal relationship. In order for there to be a causal link between a and b, a should precede b in time. I doubt we would argue much about that. 5) Finally, the coherence of the association. Does it hold together with other facts, or is it inconsistent with other findings? Or does it build a coherent, cohesive body of knowledge. They judged that on these criteria cigarette smoking was causally linked to lung cancer. Those are the criteria they proposed for judging an association as causal.

Dr. Keys: We have little difficulty about the logic involved, it's simply how we use the words. The main reason for this discussion is to force us to use technical words carefully, precisely and in exactly the same fashion every time. The kind of discussion we're having here almost never occurs when we know what we are talking about. It rarely occurs in the physical sciences except where physics merges into metaphysics. And as a philosophical discussion, the kind of thing we are talk-

ing about here is almost peculiar to medical sciences, and particularly to certain aspects of the medical sciences. So we have on the one hand physical sciences, chemistry and physics, and on the other hand social science, and somewhere inbetween, medical science. That's an indication of the complexity of the material we deal with, our inability to separate variables. There is little of this discussion in the social sciences because their skills are so far from dealing with anything tangible or reproducibly measurable that they don't dare think about causes in the sense we are talking about. Many years ago Joe Berkson used to talk about these things. He is one of the most provocative persons in statistics and certain areas of epidemiology. But driven into a corner trying to tie causation down, one can arrive at the position that nothing can be shown about cause and effect unless the effects produced by the cause are found under precisely defined experimental conditions. This rules out some of the most useful and consistent scientific operations. There are two fields one can think of. One is geology. There would be no geology or astronomy if experiment were the only way to proof. Yet many would say that astronomy and geology are more rigorous scientific disciplines than anything we normally deal with in medical science.

One can ask, "Why are you concerned about cause and effect?" I think we are concerned about cause and effect because if we accept the hypothesis that $\underline{x}$ causes $\underline{y}$, we want to apply it. We want to apply this in some kind of a prediction. In a very simple-minded way if we have a

causal relationship it must enable successful prediction and if it does not, it isn't a causal relationship; if it does predict, it is usable. If one puts two chemicals together at such and such a temperature, such and such a compound is formed. If one allows other things to vary it changes the degree to which the reaction takes place. One has to standardize. In the medical sciences by and large we are not very successful in controlling all possible influences. What is the next best? In probablistic terms we say that we have to have a high percentage of success in prediction in the actuarial sense. George Pickering, who was one of the greatest debators of his time, taught me an old debate trick: "Well, if you believe this to be the case, what is the one reason that persuades you. Tell me that one reason so that we can look at it." Of course, rarely is there one reason, one piece of evidence, one which is all-persuasive. This can be in physics and chemistry. But in medical science rarely does a single observation or experiment finish it. We are dealing with an accumulation of facts in coronary heart disease, many pieces of evidence that lead us to believe that blood pressure is contributory, serum cholesterol is contributory, and sex is contributory. There is no one factor that is a major, necessary, or sufficient cause. It is a matter of allowing the evidence to be accumulated and weighing it as a pile of evidence, not as each piece but overall. If we consider the problem in this way it makes one think more sharply and not demand too much.

There is a school of thought which, if it had its way, would stop attempts

in preventive medicine. One could defend the negative view at the expense of everything else. But the history of preventive medicine is the application of not completely proven ideas.

Dr. Remington: There is a real advantage in being first on a panel discussion of this sort. That's why I insist on speaking first every year, that's my price of participation. One can then take a very firm position and can use all the debating tricks at his disposal. Jerry Stamler assures me that he spent the last year reading Charles Darwin and thinking about this question, and I am sure he is well prepared.

Dr. Stamler: I would add or embellish a little bit. I believe it important, the consistency of the data collected by different methodologies. It's not only a matter of consistency and coherence of epidemiologic data, it is also the coherence of the epidemiologic data with clinical data and with animal experimental data. We shoot to see if epidemiological data is coherent in terms of what clinical investigation is telling us, and in terms of what animal work is telling us. We must consider so-called exceptions. Coronary heart disease presents an interesting series of exceptions. The Masai experience has been put forth as an exception, as well as other African tribes and the Swiss mountaineers. One has to ask, "Are the data good, are these valid exceptions and do they refute the general relationship?" Exceptions test the rule rather than prove the rule.

We have to consider exceptions very carefully and whether they are valid exceptions. If they are valid (most of the ones we are talking about here now turn out not to be valid exceptions), but if they are valid when you test the rule against these exceptions. Individually as scientists, or even collectively as a group of scientists, we are always limited in terms of the infinite variety of the world. We are limited by the fact that we live at a given time, we stand on limited knowledge from the past, we are limited in our ability to reflect and analyze the world, and this world is changing. So knowledge is always limited and therefore proof is always limited, never final and absolute. We have to approach the problem of truth as a problem of approaching knowledge at a satisfactory level. What is satisfactory? Complete knowledge is nonascertainable. Complete knowledge is a contradiction in terms as is absolute truth. At what level do we find the data meaningful enough to act on, in terms of the course of action, the complexity of action, the risks and costs of action, etc.

There is a very interesting study in the history of epidemiology that considered two of the most important actions of medical science. The initiation by a British genius, Lind, of giving citrus fruits to British sailors to prevent scurvy was based on a thin reed of information by modern standards, long before there was the science of nutrition and long before any vitamin was dreamt of. Simple observations led to the conclusion that this might work, and it helped make Britain queen of the seas for many decades. Another is small pox, before microbiology in the 1790's, long

before any proof of relationship between viruses and disease, before the data on contagion. Contagion remained a controversial idea until the time of Pasteur. A set of simple observations permitted effective action. The same is true in regard to the origin of public health in the sanitation movement of the mid-19th century. It all began with infectious diseases, chiefly tuberculosis, under the special social conditions in England and newly industrialized countries. Action was proposed and initiated, interestingly enough, by laymen. Bacteria and the theory of infectious disease had not yet developed. This concept of proof is very important.

A businessman, Mr. Harley, who was put on a diet to lower his cholesterol because he had a very high cholesterol, made a point that has always stuck in my mind, that if in the competitive world of big business one waited before instituting a new product, a new manufacturing process, for 90% or 99% certainty we would be destroyed in the competitive effort. Business is content to proceed on the basis of, say, 70% certainty.

How much proof is proof. Obviously this is a very important question of judgment. Does one always need a trial to prove something? Berkson's idea is also erroneous. It is even erroneous to say that even if trials are possible, one should never act in the public health area without trials. It is a question of judgment and a very complicated one. We now face it in regard to mild hypertension, in the case of high risk of coronary disease and all the rest. None of us feels entirely secure in our judgments. Many are proposing public health efforts and trials at the same time. At one

point in discussions on the diet-heart report a distinguished colleague categorically said, "We don't know anything about diet and coronary disease. Until we can do a trial, it is correct to say we don't know anything." That is an obvious absurdity. The only reason a trial is being proposed on diet and coronary disease is the vast amount of information indicating that this is possibly or even probably a key or necessary causative factor. To make the statement that because we have not this "final proof" we must say we don't know anything, is an absurdity. There's a kind of rigidity in this thinking either yes or no, and it is absurd in terms of the realities of life and proof. It acts as a major obstruction to progress. The same individual made the statement at the Second National Conference of Cardiovascular Diseases, that we shouldn't act now in the public arena on diet, but give the laboratory investigators five more years and we'll clarify the question, then it'll be appropriate to act. Those five years have now gone by.

There is great concern among American scientists about making the false positive error. The assertion that something is causal when it really isn't. The inference of causality breeds action in the history of medicine, and is strewn with wreckages of terrible notions of positive relationships leading to therapies that not only didn't work but hurt people, such as bleeding and purging. So the conservatism of medicine in this regard is understandable. Skepticism, caution, and conservatism is indicated. We have had a grim experience in coronary disease with the drug MER-29,

triparonal, in terms of too ready acceptance of the value of something. But there also is a major error of the other kind, the avoidance of the false negative error. To stand and say persistently, "I want more proof, there isn't enough proof, it isn't enough proof, I will do nothing until I have more proof," deviates from objectivity as much as the other error. I think it is very important that scientists appreciate that there are two kinds of error. The statement is glibly made by many people, who think they are being very objective, that what we have is a lot of associations with atherosclerosis but we have no proof that any of these associations mean anything. We really don't know anything about this disease. My experience with such individuals is that if you stop to ask them "Well, okay, you don't think there is any meaningful relationship demonstrated, so what is proof for you," most have never seriously given thought to what proof really is, in science in general and biology in particular. I think it is important for everyone to wrestle with these questions of proof because they have a big meaning. First and foremost and chiefly, they have meaning in application. If you are not prepared to accept something as proof, ask yourself cold-bloodedly what are the criteria for proof. Why were the ideas of Darwin accepted rather rapidly by most scientists in the middle of the 19th century. The whole essence of the concept of evolution and the origin of species could not be put to experimental proof. Two billion years of evolution couldn't be put to experimental proof. The climate was right intellectually in the mid-19th century. I won't go

into why it was right--it was right. In a sense we have a similar situation in diet and coronary disease today.

Many of us in speaking of diet and coronary disease are repeating things said in the 1920s. But the climate is different today. Among other things the disease is a much bigger problem. The second reason is that Darwin accumulated a huge amount of information. Unlike any of his predecessors he presented such a wealth of data that it was almost impossible to ignore the information that lead to the conclusion that there must be evolution, and origin of new species from previous ones. Third, he had a reasonable pathogenetic mechanism. The mechanism whereby the species evolved in natural selection. None of his predecessors had that. These were his two great contributions. The fact is that proof was established at a sufficient level to make this the background of theoretical biology and much of practical biology without any possibility of trials. So the Berkson thesis, I think, is all wrong.

Finally, on coronary disease I give my views on this in terms of classical epidemiology. Can one name, of the multiple causes, one that can be regarded as a sufficient cause of coronary disease? I don't think so. Diet? No. Why? There are people who are genetically disturbed metabolically, who develop severe hyperlipidemia and premature atherosclerosis even on a diet that might be viewed as protective. Therefore, a sufficient cause in regard to individuals, and in classical epidemiological formulations from infectious disease, breaks down. And there is no

necessary cause. Let's formulate the question a little differently and see if we can come out of this dilemma. I think we can, if we ask "Is there a cause without which there would not be epidemic premature coronary disease?" Let us move causation now from the individual to the population. Here I think we can speak about necessary, sufficient, and contributory causes. My own view is that there will never be, and has never been the mass occurrence of coronary disease in a population eating a diet low in animal saturated fat and cholesterol. This is an essential, a primary, a necessary cause for mass disease in populations, in premature form. But not a sufficient cause, because some individuals eat this way, have low serum cholesterols, and escape. Similarly, populations can smoke cigarettes for decades, particularly populations eating differently, and not get coronary disease. Much hypertension occurs in populations without much coronary disease, if they are eating differently. Therefore I think hypertension and smoking can be ruled out as primary, essential or necessary causes and considered contributory causes. The point is not to accept my ideas but to get a classical concept in epidemiology, which can be reformulated and used very fruitfully to clarify concepts of chronic disease and multi-factorial etiology, from the population point of view rather than the individual point of view. Many people are puzzled--is it a cause, isn't it a cause. If it is a cause why doesn't it function all the time. Lots of people get coronaries who are not hypertensives. Lots of people get coronaries who don't smoke. Some people get coronary disease

without a high fat diet. But if we formulate it on the basis of population problems, and problems of epidemic disease, we can use these fruitful concepts of classical epidemiology today. Period. End of report.

Dr. Rose: Could I take as a jumping off point a contradiction in what Dr. Stamler said, which you may have noticed. He starts off by saying that evidence of causation should include a reasonable hypothesis of the mechanism by which the cause might operate. He said that, and then he said quite the opposite. He pointed to the historical examples of controlling disease. Various epidemics--scurvy and so on--which managed to get along without any laboratory work or tenable theory at all. But I don't think we should be ashamed when we find a paradox. I think it's true to say that the great majority of medical research into the causation of disease, in terms of men and money, has gone on in the laboratory, and much of it has been useless; hardly anything has come out of it so far that has led to increase in our power to control disease. The laboratory service which has been helpful has so far been almost entirely from the drug firms. And the reason for this, I think, is that laboratory work is concerned with pursuing intellectual curiosity without regard to the usefulness and application of the findings in the control of disease. The drug firm, of course, is interested in selling its products and that gives it a direction. Well, the successful epidemiologist is concerned with the usefulness of this research to what application it can be put.

I have a very simple definition of "What is a cause?" along these lines. I would define a cause of disease as a factor or habit, whose reduction leads to reduction in incidence of disease. Something which when you use it, does some good. This is very simple and maybe it doesn't always work out. But I think it slants us in the right direction--a useful direction. I'd like to add three practical points: The first two of the three are the significance of the evidence for causation in a statistical sense and secondly our estimate of the magnitude of the effect. And I think if there is one point which has come up repeatedly in our thinking during the last days which is helpful is the statistical significance of the results and the estimate of how big the effect is, which may or may not be shown to be significant. I'd like to suggest that we should ban the word "proof." I don't think it is a useful word. Another point we've touched on repeatedly is that you can never be certain: we are not certain that cigarettes cause lung cancer. It may be that we've just never thought of noticing that cigarette smokers do something else, like wiggling a finger, that's the cause of lung cancer. But we're not worried about this. The evidence is good enough to get going. We shouldn't speak of proof but the confidence of results may be high or low. How sure have you to be of the evidence before you do something. It's a complex question which takes us beyond purely scientific deliberations. Next, we need to know something about the magnitude of causation. I really think it is of very little use to demonstrate that a is a cause of b unless we know how much of

a cause it is and how common the effect on b is. We must keep in mind the size of causation and things that are only trivially important. The other point, the magnitude of causal effect, is the difference between "relative" and "absolute" association, relative risk and absolute risk. If a particular factor has a small relative effect on a very common disease that may be a more important cause than a factor which has a large effect on a rare disease. We have to remember that in coronary disease we are dealing with an enormously common thing and causes that have a small relative effect can lead to a large absolute effect. Cigarettes, for example, have only to add a relatively small percent to the bulk of coronary heart disease to have an enormous effect, far bigger than the total of their effects on lung cancer. This goes for all the common cardiovascular diseases.

My final point is that we need to know about the technical significance, the level of confidence we have in evidence of causation. We need to know estimates of the size of the causal effect. Lastly, as applied scientists, we are interested in whether the problem is reversable. We are interested chiefly in identifying forces that are controllable. I think, for example, there is a lot of evidence that winter is a cause of CHD mortality. Any you may say, "All right, but that's not an interesting or useful observation because we can't do anything much about the winter." We can't stop people aging but we may be interested, nevertheless, in comparing let us say age and the cause of coronary heart disease because we may be

able to protect individuals against effects of aging.

I'm sure you all know about the doctor in London named John Snow, facing an epidemic of cholera. He made epidemiological observations which led to the belief that people who got their water from a particular pump on Broad Street had a high risk of disease and those everywhere else were at a low risk. He went along to his council and said "Look at my evidence. You do something, get rid of that pump." I'm sure that if they were acquainted with modern terms they would have said, "But Dr. Snow, your evidence is purely statistical." They rejected his evidence and said that it wasn't good enough. He went along that night under the cover of darkness and removed the pump handle and the epidemic stopped, based only on statistical evidence.

Dr. Labarthe: I would like to raise a question in reference to the Broad Street pump experience. There were a number of apparent exceptions to the hypothesis that the common water supply accounted for the distribution of mortality from cholera. By very close studies of the apparent exceptions, some of which were very serious, helped the hypothesis. Snow was able to clarify the nature of the exceptions and it turned out to add a great deal of strength to the hypothesis rather than challenge it.

Dr. Blackburn: I think we've already mentioned this question of the difference between proof and causation. I've heard many epidemiologists say, including several in this room, that one can never obtain proof with

epidemiological methods, but only confirm hypotheses, get clues, and so forth. I think that is somewhat contradictory to the tone of the discussion here today and I'd like to consider whether we might stop saying that sort of thing and speak more intelligently about degrees and types of causation.

Dr. Stamler: I agree. Epidemiologists are very perfectionistic in regard to the false positive error in saying "We can't prove anything." And yet they accept the notion that people working with animals, by their nature different from man, can prove things. I think there's an element of the intellectually absurd about that. There are ways of taking associations and exploring them by a variety of carefully designed studies that permit you to approach a high level of probability the notion that the relationships present are caused and therefore permit you to approach proof. Although I agree with Geoffrey that there is no such thing as final or absolute proof, in that sense nothing has ever been proved. After all, Newton gave way to Einstein and now Einstein's concepts of the world are giving way to others. Nothing is final or absolute. I think there is a place for the word "proof" and I think epidemiologists can, in that sense, prove things at high levels of probability. I don't think we should continue to go around and say "Oh, all we ever look at is associations and nothing that we do leads us further down the road of proof."

Dr. Keys: Well, I agree with Dr. Rose. As soon as you start talking about proof with high levels of probability. Well is it or isn't it? I don't think that is particularly useful. I do think, though, that we may pursue

the idea of probability and get some place.

Dr. Remington: I want to comment on the remarks of the businessman and proof. I was struck by the first application of hypothesis testing in the business and industrial world, industrial sampling lot inspection. Sampling in which a plant produces manufactured goods in a lot, and then they sample from that lot and decide whether to release it or not. They inspect it--a sample of manufactured articles and make a decision whether or not to release the lot. If they test the hypothesis that the lot is okay, that it's up to standards, then this testing is in fact the Type I error, which is the level of significance, and in that context is called the "producer's risk." And the Type II error--the error of falsely accepting a hypothesis--that is called the "consumer's risk." The reasoning is clear, the risk of the producer is to reject a good lot. If these samples test the hypothesis that the lot is really all up to standard, and if he rejects it falsely, he's in trouble. Not only does he have to store these things, possibly, or do a full inspection of them, he may have to flush them down the drain depending on what they are. I want to underscore what Professor Keys mentioned in a very strong point. We build probability statements, and we build them into great long chains. We take an action on the basis of incomplete information and go one step further with some probability that we take the wrong action, that the information is wrong. And then we go the next step. Again with the possibility of fallibility. And as these chains get very very long, as Professor

Keys is showing here, these probabilities can get very, very large, unless each step is controlled well. Now, obviously, if you control it too well you're up against the other side, that you never can detect anything. You can just sit there and quiver, as it were, and say "I can't do anything. I just can't decide. I can't move. It's too dangerous. Life is too formidable and it's full of all these traps that statisticians keep talking about, so I'm just going to sit and shake a little and not come to grips with the issue." That's a dreadful thing as well. On the question of proof, my former teachers, Professors Dixon and Massey, now at the University of California, Los Angeles, distinguish in their well-known textbook types of proof. I don't know if this is a way out of this dilemma; they make a distinction between at least two types of proof. They talk about deductive proof and inductive proof and they say that the type of proof that we all deal with as scientists is inductive proof, based on incomplete information, with the probability of an incorrect decision. And that the kind of proof that we're used to if we've studied logic or mathematics is deductive proof in which we adopt a set of axioms and postulates and a set of rules of the game, and within that very restrictive framework make infallible proofs. So long as you accept the rules of the game and the rules of combination then you are forced to accept the conclusion as a proof, as being proven within those rules. I have found this a useful distinction between two kinds of proof. I think most of the pure mathematicians have come to the conclusion that pure mathe-

matics and mathematical proof have very little to do with real life or with science. We just don't prove things that way within those structures. And yet is it useless? Are the concepts useless? No. I think those principles of logical thinking and the study of those mechanisms may help us to order our approach to the real world, which is much more complex, contains components of chance, contains the possibility of risk, of hazard. So, I find some attraction in the notion that proof, as a term, should be ruled out because of this ambiguity.

Dr. Labarthe: It seems to me that one of the factors that determines the level of assurance required for acting is the urgency of the problem. If one accepts a false hypothesis and thereby determines the course of action to prevent disease, one conceivably may produce some undesirable effects. But this must be compared to the undesirable effects of taking no action, by rejecting all hypotheses. The question is, which is the more serious error? Is more harm likely to be done by preventive programs which have relatively little effect. Or is greater harm done on the other hand by taking no action at all. I think this is the coronary heart disease problem, which makes us more willing in this situation than we might be in some others to take action because of the urgency of the problem, and the relatively small risk of the programs proposed.

Dr. Stamler: Should there by an adoption by the general population of a change in diet? The proposition was put to the person at the Second National Conference who said "no" that "therefore you contend that the

best medical judgment is that the diet now being consumed is the best which we can advise people to eat, that's the implication of the 'no' answer." This made that individual extremely uncomfortable. He didn't want to be driven into that position, that by saying "no" to a change he was saying that given a series of diet proposals, we regard the present one as the best one. But that is the logic of the negative answer.

Dr. Rose: I don't think it is. I think that although you can argue that faced with the choice either to do something or do nothing, that doing nothing is a positive decision. But I don't think it is equivalent, in nature, to a decision to alter things. I think in medicine we can run into disastrous trouble if new drugs, new treatment are introduced as soon as initial and inadequate evidence suggests that they are better than the old way of doing nothing, or very little. And I think the same is true in the public health area. I think that we need a greater weight of evidence that a change will do good and we need a weight of evidence to make us content for the time being to do nothing.

Dr. Stamler: That's true if redirection is high in risk. All experience tells us that with drugs given in longterm consumption particularly, have to be given with great conservatism. But it doesn't apply when the intervention is almost certainly of minimal risk. And all the evidence on a proposed dietary change--evidence from peoples eating different ways for generations--indicate that a change would not be risky: therefore you can say to the person who says "Keep the present diet" that operating on

this concept is indeed believing that doing nothing is preferable. I'm with you on drugs, I'm very conservative about drugs because the risk is unknown and potentially sizeable. I'm also that way about exercise, because I think that there is a risk and too casual an attitude about the risk of exercise in developed countries among middle-aged men. But on smoking, and on diet I think there's no reason to believe that there's any risk. Therefore you have to drive a person to the wall who says "do nothing," who says the status quo is preferable. I find it hard to escape that conclusion and its attendant social responsibility. I'll tell you what the answer I get is: The change involves all kinds of socio-economic, not health, problems, and they are legitimate problems about which you can't be cavalier. It would be a big thing, for example, to make a major shift in the diet of peoples even though it took place over 10, 20, or 30 years. It would mean things for American agriculture, for American industry, and one just can't go around making proposals based on the present level of proof. I think the proposal to recommend high intakes of unsaturated fatty acid is wrong. So I wouldn't recommend that. I propose that people eat the way the populations are eating in many countries. No population has for any time ever ingested 15 per cent calories from oil. I think there is potential danger, and there's no real need for it in my opinion. One can accomplish the same thing with reducing saturated fats, reducing dietary cholesterol, and using oil and polyunsaturates in moderation.

Dr. Rose: One of our starting points in this seminar was the fact

that the physician of the bedside is required by his patient to appear to be very confident of his recommendations and his opinions. If he is honest he will recognize that the evidence does not permit any degree of confidence. As Public Health research workers, we have also something between certainty and uncertainty. Whereas the public--our patient--puts the same pressure on us as the individual patient on his physician, to be sure of our recommendations.

Dr. Remington: I heard the senator from New Jersey speak at a National Air Pollution Conference one time and he indicted all of us scientists strongly. He said, "I come to one of these conferences after another and I hear of the need for more research. We have to know what the automobile is putting into the atmosphere in more detail. In order to be sure the consequences are dreadful, and not being certain that an intervention scheme will work." "We, in legislatures in the Congress, who have to work in areas of public policy and help formulate public policy couldn't care less about this. In our minds the evidence is so clear and so overwhelming now from the case that you've built that as far as some of us are concerned not to take action at the present time is the most severe problem." And I think that, in a sense, was a refreshing view, coming from that source, and I think we often make that mistake in science. We are working in a stream--an almost infinitely long stream--pushing knowledge ahead toward complete knowledge which we'll never reach, there's always another step for us to take. We seem unwilling

to step ashore from that stream and take some sort of public action or become involved. We're uneasy. We're not trained in this action and don't feel qualified. But when you come right down to it, who is? Who's better qualified?

Dr. Stamler: I heard Dr. Paul White speak on this in Geneva to the International Cardiology Foundation. He made the point that when the National Heart Institute was first set up in the United States with an advisory council and he was asked to serve on this council, it was a very alien and hostile and threatening proposal to him. He'd never had anything to do with government. His attitude had always been that as a professional he was separate, apart from government. He was finally convinced to do it. It was a very rich and rewarding experience and he learned a lot from it. He also came to feel that professional people must be involved in these kinds of things. And I personally agree with that. I also agree one of the worst things that happens in research is that year after year we say "We need more evidence! We need more evidence!" At the Second National Conference on Cardiovascular Diseases, if you read the section on atherosclerosis research, written by a distinguished colleague and friend, you come to the conclusion that a) we know nothing and b) everything needs to be researched and c) there isn't the vaguest notion of what's more important than something else. Therefore the task is endless and therefore hopeless. It was an endless list. It was a very comprehensive list of things that might be looked at, in such completeness, but with no sense of where we've come from and what

is fairly well clarified, and what isn't clarified and without priorities. I don't think this serves a useful purpose. It's no accident, in my opinion, that that particular document has become a piece of paper in the archives gathering dust. It has not been used at all, because it is a practically useless document. And the public which gives money to research will not endlessly tolerate the posture of twenty years ago, that the main energy at this point must go into research. If you say that year after year after year, and go to the public with that same theme and not present a picture of what you've accomplished and what you haven't accomplished and how your accomplishments can be applied, or honest proof that we don't know enough yet to apply, the public will run out of interest. And the goose that lays the golden egg will be killed--is killed. There is that cavalier attitude of politicians in our country to research at the present time that the research boys are now people who are easy to kick around. And nobody seems to care very much about it. Part of it is due to this attitude in medicine. That's not the only reason, but that's part of it. We are not transmitting a message of concern for the problems of the people, of progress in their solution, of dedication to the solution and therefore justification of further social investment of capital.

Dr. Remington: This is a problem of epidemiology and statistics. That as we do our job here, we run the risk of making people so critical that they will see it as the U.S. has, and quiver. I'm an activist in terms of getting on with the job and applying the results of accumulated

research. I think the criticism you apply gently to the discipline of statistics and of epidemiology is often a valid one. I don't think it's unique to statistics but I think it's a phenomenon. I think it's encouraging that large numbers of statisticians nowadays are aware of this problem. You see, there's a risk on the other side too. If standards of "proof" become dropped low, then an uncritical approach might be taken up. And we're in a sense balancing on a kind of a knife edge here--no action and appropriate action under certain circumstances. I think the main thing is that our statisticians nowadays, and our epidemiologists, should be forced to stick their heads outdoors now and then, because there's a great big world out there and it's fun.

Dr. Peterson: I think often we are dealing with causal chains with several links, and what we've talked about may be an over-simplification. If we're fortunate enough to be dealing with a reasonably long chain then we have the potential of breaking a link and breaking the chain. Thinking in those terms may be useful in some of the chronic diseases.

Dr. Stamler: One of the most interesting aspects of the coronary disease question is the 5 per cent of the population which eats the usual Western diet and walks around with cholesterol level under 175. The lack of knowledge on this is very intriguing. If we could master this question and perhaps transfer everyone into people like this, the urgency of diet change would be much less.

Dr. Keys: Just to give an example, I do not think we have anything like

a reasonable case to oppose cigarette smoking for the purpose of controlling coronary heart disease. You can see it because it goes back to the days when it was immoral to smoke. And now you've got a big argument that it is a promoter of lung cancer and certainly, if maintained long enough, does all kinds of unpleasant things to the bronchial tree. And actually, there isn't anything good in it.

Dr. Blackburn: So would you say the logical conclusion of that is that non-action should result?

Dr. Keys: No. I said the only reason that most of us would accept the idea and say "Look, let's get rid of the thing" is not because we believe the case in coronary disease is all that strong; I think the case is weak.

Dr. Rose: I suppose we don't have time and it probably wouldn't be opportune to pursue this one, but could I just put on record a different opinion. We have broadly consistent evidence that cigarette smoking is a risk factor; there is evidence that the degree of risk is related to the quantity of smoking. We have evidence that those in the population who choose to give up the habit enjoy progressively improving disease rates over a period of years. I think it is very suggestive that the association is real, that it is probably causal, and that it is large enough to be very important. If it is real and causal then if we succeed in altering smoking habits the reduction in coronary mortality would be considerable and finally, in our experience, I think it is the most promising of the various

bad habits that we are concerned with--the most promising from the point of view of changing public habits. I can imagine that if we tried hard, in 15 years' time we could make a greater impact on smoking than we could on diet at a national level.

Dr. Stamler: I think perhaps the very interesting things that are coming out of the International Study of Dr. Keys, which all of us will look forward to studying and thinking about, lead us to underestimate the data that are there from previous studies. The pooling project has eliminated confounding factors with considerable care and the association is still there with at least three factors considered, weight, cholesterol and blood pressure. With these three controlled the relationship with smoking is still strong.

Dr. Keys: As far as I can see around the world there certainly are plenty of examples of populations that smoke like chimneys and have no appreciable coronary heart disease.

Dr. Stamler: That's a different question, intellectually, totally different.

Dr. Keys: All right, but you see if you're insisting that there is an hierarchic causal relationship, I'd like to have some type of explanation of why smoking doesn't work universally. It works only in a couple of populations, only in the English-speaking people as far as we can make out. There's something wrong.

Dr. Stamler: Well, I can hypothesize why it doesn't work in less

developed countries. It's like why hypertension does not produce atherosclerosis in rabbits, chickens, guinea pigs, dogs or monkeys. You need a certain lipid metabolic and nutritional setup, before a contributory cause like either hypertension or smoking will result in more atherosclerotic disease. I think it is in that sense that smoking is a classic contributory cause and not a primary cause. To try to produce atherosclerosis with smoking alone, you'd never do it. Just like you could never produce atherosclerosis with hypertension alone. I think it's in that sense a contributory cause. But once you have people eating a certain way, then at least for the American and English populations, there is powerful evidence. There may not be such evidence for Finland, and then you have to explain the exception. Or maybe the exception calls for re-examination of the American and British data. But the American and British data sit there and they're pretty powerful data. In fact, the Japanese, when they have low cholesterol levels and a low fat diet, don't get coronary disease from cigarette smoking. This doesn't disturb me at all, intellectually, that's all right. The bigger problem is when you have a population eating a high fat diet. If it would turn out to be that way for the Norwegians, the Swedes, the Danes, then it would be a much different problem. The fact that the less developed countries with low fat intakes and low cholesterol intakes and low lipid levels in the blood are not bothered by smoking doesn't trouble me.