Causal Models in Epidemiology: The Need for Some New Thinking

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It is a great honor to be invited to give the Wade Hampton Frost Lecture. This is especially so when one considers the names of the other 38 people who have previously been honored in this way. The very first winner was a man who had a profound effect on my thinking and who, in many ways, shaped my approach to research in the field of epidemiology. In 1972, Dr. Abraham Lilienfeld gave the first Frost Lecture. I met him ten years before that event took place. In 1960, I became Executive Secretary of the very first Epidemiology Study Section ever created at the National Institutes of Health. Dr. Lilienfeld was the first person who was appointed to serve on the Study Section. In those days we were not permitted to call our new review group the Epidemiology Study Section because, I was told, the word "Epidemiology" was reserved for the study of infectious diseases only. The charge we were given for the new Study Section was to review research grant proposals dealing not only with a wide range of infectious diseases but, if can you believe it, such diseases as coronary heart disease, cancer, and even mental health! Since we could not use the word Epidemiology, we called the new Study Section "Human Ecology" and that name persisted for

5 years. After I left NIH to do other work, the Study Section was finally re-named the Epidemiology Study Section.

That Study Section was successful in creating a new field and Dr. Lilienfeld was the most important and influential member of that group. Here is why. In those days, the Study Section had only a few research grant applications to review each round. Sometimes five, sometimes ten. In spite of our light workload, the new Study Section had the dubious distinction of having the lowest approval rate at NIH. We found fault with everything. Nothing was good enough to gain our approval! The variety of disciplines represented in the review group was impressive and that almost guaranteed that we could rarely reach agreement. We had on the Study Section a geneticist, a nutritionist, a sociologist, a virologist, a physician, a dentist, a demographer, an epidemiologist, among others.

About one year after we were in existence, Dr. Lilienfeld spoke up about our poor approval rate and his comments changed everything. He pointed out to all of us that the Study Section's low approval rate was, in effect, destroying the new field of epidemiology rather than building it. Nature, he said, presented us with some very difficult and nasty research challenges. Could we not, he asked, at least be kind to one another? Could we not find a way to encourage the growth of this new discipline instead of finding fault with everything and insuring its failure? His speech had a major impact on all of us and was an important influence in changing our approach and in actually allowing us to award research grants to investigators to do work in this field. Abraham Lilienfeld, the first recipient of the Wade Hampton Frost Lecture, was a hero to me at that time, and he still is.

A second very early recipient of the Frost Lectureship Award was another hero of mine. I have a large picture of him in my office. John Cassel gave the Fourth Wade Hampton Frost Lecture in the 1975. The title of his talk was "The Contribution of the Social Environment To Host Resistance." His lecture was subsequently published in 1976 in the American Journal of Epidemiology and I still assign that article to students every year. It is, to me, one of the classic papers in Epidemiology. That paper also shaped my thinking at the time and it still does. In that paper, Dr. Cassel noted that while disease agents are ubiquitous in our environment, only some of us get sick only some of the time. For this reason, he emphasized the crucial importance of better studies of the factors that influence host resistance. He particularly urged the study of a range of social factors that had not previously been studied sufficiently. In 1979, three years later, I co-authored a paper with Lisa Berkman that also was published in the American Journal of Epidemiology. Our paper was titled "Social Networks, Host Resistance and Mortality." And it was the first paper ever written on the importance of social support for health. This paper was, of course, directly influenced by John Cassel's Frost Lecture.

John Cassel was influential in my career in another important way. In 1967, a colleague and I organized a conference to discuss the research that was then beginning to deal with the social epidemiology of coronary heart disease. We wanted a meeting to bring together all of the investigators in the country who were working on this problem so that we could compare notes. We scoured the country and were able to find only 28 people! But

John Cassel was one of them, and his contribution to that meeting made the whole event worthwhile.

So you can see that I come to this Frost Lecture, some 35 years later, in awe and with a sense of the seriousness of this event. This, for me, is not just another talk. My purpose today will be to reflect back on those early days, discuss some events that I see as significant in our current work, and then offer some thoughts about the future. Specifically, I will offer some thoughts on our need to develop a more appropriate causal model in Epidemiology.

My first point today deals with my thought that we are looking at causality in a way that has lead to confusing and misleading results. Consider the case of coronary heart disease. We say that risk factors for this disease include serum cholesterol, hypertension, cigarette smoking, and several other factors such as obesity, diabetes, and physical inactivity. Without taking into account host or environment. This way of looking at the problem causes puzzling outcomes. It turns out that all of the risk factors for coronary heart disease that we know, considered *together*, account for less than half of the disease that occurs. And it is not as if we have missed one or two important risk factors. Those missing risk factors would have to be of enormous significance in order to account for the 50% of disease not accounted for. It is not likely we would miss risk factors of such importance.

And the case for coronary heart disease is not unique. The same problem exists for many other diseases as well. I am aware of the controversy that

exists regarding the 50% statistic and I am prepared to debate this issue with those who think the percentage explained is higher than I have claimed.

I suggest the solution to this problem comes from research that is now being done on the *social* determinants of health. This research has presented its own set of challenging problems. For example, how can we explain the fact that people in lower social class positions have higher rates of not just one, two, or three diseases but for virtually every disease we know about? On the face of it, this does not make biologic sense. It is difficult to explain how one such risk factor can be related to so many diseases. The same phenomenon exists for the concept of social support. A recent review of the literature on social support examined 148 studies involving 308,000 people. That review found that those people who had poor social connections had mortality rates that were 50% higher over 7 years of follow-up than people with better connections. That finding involved not just one two diseases, but a wide *range* of diseases. And these observations held after account was taken of age, gender and health status at baseline. The same finding is true for many other psychosocial risk factors.

So, on the one hand, we have a set of disease-specific risk factors that do not satisfactorily explain the diseases they are intended to explain and, on the other hand, a set of psychosocial risk factors that inexplicably are related to virtually all diseases. This puzzle can be explained if we look at disease causation in a new way. In a more appropriate way. In a two-step model framework. Thus, the argument would go as follows: psychosocial risk factors are related to host susceptibility. The effect of harmful psychosocial risk factors would be to compromise the body's immune system and make

us more vulnerable to disease but it would not predict which diseases we get: These psychosocial risk factors would not increase the risk of any specific diseases but they would make us vulnerable to disease in general. The specific disease that one would get would be attributable to the particular disease agents that one was exposed to: the viruses, the bacteria, the cigarette smoke, the high fat diets, the air pollution, the stress, and so on.

A colleague of mine at Berkeley, Dr. Emily Jacobs, recently showed me some remarkable early data that is supportive of this way of thinking. She studied 113 people of varying racial and ethnic backgrounds, and from several social class groups, and she showed that several important psychosocial variables were related to immune functioning in a very significant way. Specifically, she found that interleukin 6 responses varied in exactly the ways we would have expected with selected psychosocial factors. For those unfamiliar with this protein, interleukin 6 is importantly involved in the immune functioning of the body and it is related to several diseases including diabetes, coronary heart disease, rheumatoid arthritis, depression, and prostate cancer. I look forward to her publication of these findings so that we can discuss their implications for the development of a two-step model of disease etiology. The recent research on telomere length is pointing in the same direction.

As I have thought about this issue over the years, I have come to the conclusion that we epidemiologists who study such non-infectious diseases as coronary heart disease, cancer, asthma, and arthritis are using an inappropriate model of disease causation in our work. Infectious disease epidemiologists have it right. They know that disease agents must be

considered in relation to both host susceptibility and environmental circumstances. We epidemiologists who study non-infectious diseases tend to study the relationship between risk factors and disease while taking relatively little notice of either host susceptibility or environmental circumstances.

So that's point one. A two-stage model of disease causation has important implications for the way we understand disease etiology. And this leads me to point two. We in epidemiology tend to study individual diseases using categories that are clearly useful in clinical medicine - disease categories that clinicians find useful in diagnosing and treating patients. Heart disease, cancer, arthritis. When we epidemiologists use these same categories in our research, it makes it difficult for us to study the fundamental determinants of health in the population. I introduce this idea to beginning students at Berkeley by telling them a made-up story. I tell of a curvy road in the mountains where, at one point, cars fall off a cliff at a very high rate. And these cars crash at the bottom causing very serious damage. Head injuries. Spinal cord injuries. And, in my story, the medical care at the bottom is not good. As a consequence, people have to be transported long distances, usually by helicopter or ambulance, to get help. Not good.

In my story, I suggest that we develop a state of the art health promotion and injury prevention program for this road. First, we will develop a hazard assessment and barrier program that will prohibit certain groups from driving on this road. Certain old people or people with vision and physical problems will be directed to take an alternative road. Those drivers who are permitted to proceed will have to submit to a behavioral intervention: a safe

driving course. But we will also develop an environmental intervention by getting car manufacturers to reinforce and strengthen the cars before they can proceed. And we will build a state-of-the-art medical facility at the bottom of the cliff. This new facility will have the best medical staff imaginable – neurosurgeons, orthopedic people, and other specialists. And we will remove all economic barriers for care so that everyone has universal access. And we will insure that everyone gets culturally appropriate medical treatment with language translation help when necessary. In short, we will do everything that it is now being recommended in first-rate health promotion and disease preventions programs.

In my classes, someone will eventually raise their hand and quietly ask, "How about fixing the road?" I then attack that person by asking how they can permit the diversion of funds from critically injured and bleeding people to do a highway construction project? Eventually, someone will tentatively suggest that if we don't do the highway work, people will keep falling off the road. We eventually agree that a truly effective health promotion program must take account of the fundamental forces that cause our problems in the first place.

But this is difficult because our attention is inevitably drawn to the suffering people lying on the ground and it is difficult to talk about some vague future prevention programs that will be of possible value far off in the future. None of this is to suggest that we ignore those injured people lying on the ground. They clearly need the best clinical care they can get. But we epidemiologists have a different mission. Our job is to identify risk factors

for disease that will result in the prevention of disease programs in the population. And that job cannot be done by studying individual diseases.

I really struggled with this concept even when I began my research on coronary heart disease in 1958. At that time, we knew that mortality rates of CHD were much higher on the East Coast and West Coast of the country as well as in the Detroit/Chicago industrial area but that CHD mortality rates were much lower in the rest of the country.

After several years of research on this phenomenon, I observed a very strange and upsetting thing. It turned out that States with high coronary heart disease mortality rates also had high *all-cause* mortality rates. And States with low coronary mortality rates also had low *all-cause* mortality rates. So States with high rates of CHD were distinctive *not for that reason* but because they had high *death* rates. And low-rate States were remarkable not because of their low CHD rates but because of their low *death* rates. Coronary heart disease mortality rates accounted for about 38% of all deaths in *all* the States. I did that analysis in 1965.

For purposes of my talk today, I re-did those analyses using current data and found the same proportionate mortality story as I found over 40 years earlier. Death rates from coronary disease are, of course, much lower now than they were in 1965, but the *proportion* that coronary heart disease rates, relative to all cause of death, is still about the same in all States –whether the rates are high or low in that State. Instead of about 38%, the proportionate rate of

coronary heart disease now averages about 26% for men and about 24% for women.

What is the meaning of these statistics? The meaning to me is that by focusing our attention on such clinical disease categories as coronary heart disease, we are prevented from seeing the larger picture. Why do certain States have high or low *death* rates? It seemed to me in 1965, and it seems to me now, that our continued focus on one or another particular disease was preventing us from seeing the larger picture. Our focus on trees was limiting our ability to see the forest.

I told the story of the curvy road to emphasize the importance of searching for fundamental underlying causes. I suggested that was a more appropriate way to proceed, a more appropriate way than focusing our attention on one or another disease that is merely a *consequence* of those underlying forces. The curvy road story was a made-up story. Here is a real story illustrating this same point. We have been studying 2,000 bus drivers for many years now. The project started when a former student of mine became the Director of Health for San Francisco city employees and, as part of her job, supervised the physical exam for the bus drivers when they got their driving license renewed. She called me one day to say that she thought the prevalence of hypertension was too high in this group and would I come and have a look. I did. And she was right. Among drivers over the age of 60, the prevalence of hypertension was 90%! So we applied for a research grant to study this problem in detail. We did all the things you would imagine and wrote several journal articles about the problem. Then we began to develop an intervention program to help the drivers.

Then we noticed that the drivers were complaining about a lot of back pain. We got another grant to study this problem and we wrote several journal articles about that. And we brought in some ergonomic experts to help with the redesign of the driver's seats and so on. Then we noticed that the drivers had high rates of gastrointestinal problems and respiratory difficulties. And later we observed that they have high rates of alcohol problems (after work – not while they are driving!). And we got research grants for everything and we designed interventions for all of these problems and, while what we are doing was not a waste of time, it certainly was not going to solve the problem for the drivers. For example, even if we did a wonderful job on the blood pressures and the back pain and the stomach problems and the breathing difficulties and the drinking issue, as new drivers came to work for the bus company, they would soon exhibit the same disease profile as the old drivers because none of our work is addressd the fundamental problem. The fundamental problem was the job itself. We got so focused on the various specific disease problems of the drivers that we did not recognize the problem common to all the complaints: the job.

We therefore began a new project to see if we could figure out what it is about the job of bus driving that is problematic. It didn't take long to discover the problem. It is the schedule. In San Francisco, drivers must keep to the schedule but it cannot be done. For example, if you were to look at the schedule, you would see that you had to get from Mission and Army Street to Mission and Geneva Street in 2 minutes. It cannot be done. Even if you drove your Ferrari on Sunday morning with no traffic to contend with, it would take much longer than 2 minutes.

I always thought that a bus schedule was developed by driving a bus from stop to stop and seeing how long it took. That would be OK if you had lots of buses available. There is a shortage of buses in San Francisco and the schedule is therefore made by a computer that simply allocates times depending on the number of buses that are available. But then, drivers are penalized when they are late in arriving at the bus stop. The drivers compensate for this by giving up their rest stops at the end of the line. They just keep driving and hope to minimize their lateness in this way. They dash into a MacDonald's when they need to use the bathroom and when they need food.

And since they are almost always late, passengers are almost always mad at them. The drivers feel that they are being unjustifiably blamed for a situation that is not in their control and they sometimes behave impolitely to passengers who then get upset with the driver.

Most drivers have a terrible shift arrangement. They must come to work very early for the morning rush hour and they must be at work for the evening rush hour but they have nothing to do in the hours between these two intervals. There is generally not enough time to go home so the drivers generally hang around and do little. At the end of their very long day, they are usually completely worn out and many go to the local tavern to wind down. By the time they get home, they are often not in good shape for social interaction. They go to bed and get up at 4 AM to begin another grueling day.

Yes, they have hypertension and back pain and stomach and breathing and alcohol problems and they should be helped with those problems. But the job needs to be fixed. Once again, work in infectious diseases is instructive. The fundamental disease classification scheme used in the consideration of infectious diseases include such categories as water-borne diseases, air-borne diseases, vector-borne diseases and food-borne diseases. Classifying diseases in this way is not helpful to clinicians in the diagnosis and treatment of sick people but it is entirely relevant if we are interested in the prevention of these diseases. These categories tell us where disease is coming from and where to direct intervention efforts. This system of disease categorization is exactly appropriate to the public health mission. The clinical categories are not.

In the study of non-infectious diseases, we do not have a good a set of categories equivalent to water, air, food and vector-borne diseases. Several years ago, we applied for a grant from the Centers for Disease Control and Prevention to study 5th grade children in a low-income community near Berkeley. The CDC had invited grant applications that would focus on cigarette smoking and other drug use, violence, poor school performance, inappropriate sexual behavior, and so on. But when we sent in our application, we said that we had decided not to study any of those things they cared about. This is not a strategy I recommend to others.

We decided, instead, to focus on the fundamental issues underlying all of these problems. We decided to focus on hope. We based this decision on our interviews with many of these young people in which they told us they didn't think they would live beyond the age of 20! Our view was that if these

children, mostly from minority groups and mostly from very poor families, had no hope for the future, what difference would it make if they smoked or used drugs or missed school or engaged in violent behavior? So we decided to work on hope and to help these children see that they could have a future. CDC received over 400 proposals from all over the country and I was amazed that they rated our proposal number 1 in the country. Even though we broke the rules. So it can be done.

In our work with these children, we decided, over a three-year period, to teach them ways of implementing their dreams. How to make things work for their benefit. How to select a problem and succeed in solving it. How to develop strategies for getting done what they want to get done. For having control over their destiny.

These children are not very interested in talking about smoking or drugs or violence – our topics _ but they can become interested in their future. The people we chose to work with them are high school students from their community along with selected undergraduates from the University at Berkeley. We did a wonderful job with these kids for 3 years. I would love to follow them into the future but where would I get money to do this? The Centers of Disease Control has moved on to other interests and most other funding agencies remain interested in specific disease and individual risk factors such as obesity and diabetes, not a topic like hope.

To this point I have suggested that our causal model in epidemiology is deficient because we have not recognized that a two-step model is necessary in our work – a model that focuses not only on disease-specific risk factors

but one that recognizes host susceptibility as well. That was point 1. Then I suggested, point 2, that to truly understand host susceptibility, we need to recognize the need for a new way, a more appropriate way, of classifying diseases. A classification for non-infectious diseases equivalent to the one used in the study and prevention of infectious diseases. What would that classification look like?

I can think of a category of disease that might be termed "poverty diseases". Or another that might be referred to as "nutritional deficiency diseases". Or how about a category called "discrimination diseases"? If one were to actually use such a classification scheme, to which Institute at the NIH would your proposal be sent? The reality is that NIH would not know what to do with your proposal. There has until now been no institute of at the National Institutes of Health that can easily accommodate such categories. Even such Institutes as the National Institute of Mental Health, or the National Institute of Child Growth and Human Development, or the National Institute of Aging, or the National Institute of Environmental Health Sciences, tend to be focused on very specific clinical problems in their area of concern. Our proposal would not easily fit into any of these Institutes. Until very recently, the NIH has been organized around clinical diseases and not around epidemiologically relevant, and prevention-oriented, categories.

Actually, things are not as bad as I am suggesting. Things are now getting better. NIH is moving towards a more interdisciplinary stance and the new Institute of Minority Health and Health Disparities is a major step forward in this regard. In addition to these changes at NIH, the Robert Wood Johnson Foundation has established a post-doctoral training program called Health

and Society that is explicitly aimed at transcending disciplinary silos. They only support 18 Fellows a year but it is a beginning.

And Canada is providing a good example as well. A few years ago, the Canadian government was considering the establishment of an NIH for Canada. Many of us warned them that if they patterned *their* NIH along the lines of *our* NIH, it would be a major setback for the cause of disease prevention. They *did* establish a Canadian Institute for Health Research and they *did* set up a whole series of Institutes focusing, as we do, on heart disease and cancer and arthritis but they also established institutes of Population Health, Gender, and Aboriginal Health. I served for 5 years on the Population Health Advisory Board and it is hard to communicate the difference it makes when one can concentrate on population health without the restraint of having to relate everything to one or another disease. We must somehow come to recognize that the clinical, individually oriented tradition runs strong in this country and that it limits our ability to think in population terms.

Another step forward. We recently applied for a large grant from the Robert Wood Johnson Foundation to develop an intervention to improve the level of social capital in a very low-income community with high rates of virtually all diseases. The goal of this project is help people connect with one another, to realize that they have interests in common, and to help them work together for the common good. The Foundation wanted to know what our disease outcomes would be. Or, if we were not going to look at disease outcomes, whether we would be studying changes in such health related behaviors as smoking and obesity.

These are, of course, entirely reasonable questions. Our response to the Foundation was that we would be examining none of these traditional outcomes. We would, instead, monitor such things as changes in trust, engagement, and civic participation. We would be assessing changes in the fundamental social forces that underlie the poor health statistics and the high-risk behavior. Our argument to them was that if we merely focused on one or another disease, or one or another health-related behavior, and if we neglected the community social forces that were causing the health problems in the first place, we would not be helping to improve the circumstance of people in this community. And we were successful in getting that grant. Of course, the grant was not awarded through the normal Foundation divisions but under the category of "Pioneering Grants". So while I am complaining about the current status of Epidemiology funding, there are signs that things are improving.

To summarize the two points I have tried to make so far: I have suggested that our causal model in epidemiology is deficient because we have not recognized that a two-step model is necessary in our work – a model that focuses not only on disease-specific risk factors but one that recognizes host susceptibility as well. Then I suggested that to truly understand host susceptibility, we needed to recognize the need for a new way, a more appropriate way, of classifying diseases. A classification for non-infectious diseases equivalent to the one used in the study and prevention of infectious diseases.

I would now like to introduce a third point that will be useful in developing a more appropriate causal model in epidemiology: the need for a better understanding of biological processes. A colleague recently suggested to me that our work in social epidemiology was doomed to failure. And I think his point is relevant for other sub-disciplines in epidemiology as well. He said that we study a concept such as social class without knowing what we mean by this term and without knowing how to measure it. Then the disease outcome we study has taken years to develop and is the result of many influences that are far beyond our intellectual grasp. He said that the same problem exists for such other mysterious concepts as social support, social capital, and hostility. He wondered how we could possibly build a science on such a shaky foundation.

His suggestion was that we stop focusing on disease outcomes and instead look at biological markers for those diseases, markers that are more proximally related to the predictor variables. By looking at the relationship between these markers and predictors, we will be able to use the markers as criterion variables that will help us better refine our understanding and measurement of the predictors. This is not to suggest that we focus on the biological markers in their own right. The suggestion is that we use these markers only to help us better define what we mean by words like "hope" and "social support" and "social class". By identifying the important elements involved in these concepts in this way, we will be better able to develop interventions aimed at them.

Mycolleague, Dr. Laura Gottleib, has criticized my suggestion that we do a better job of understanding biological process. She said that she understands

my intention to not focus attention on the biological markers per se but that we instead use them only to help us better understand social factors. But she argues that it probably won't work out that way. She said that the identification of a biological marker such as interleukin 6 will probably set us *back* in our efforts to develop a more appropriate prevention agenda. She fears that a finding such as interleukin 6 will simply provide the drug companies with a perfect opportunity to develop a *drug* to fix the problem and *that* will be the result of this important research. I responded by saying that we cannot censor our research because of what bad guys *might* do. But I have not slept easily since she made these comments and her point is something I think we should all think about and take more seriously than we have to date.

I would like to now add a fourth suggestion to my list of ideas that will lead to a more relevant causal model for epidemiology. This fourth suggestion comes from a recent article by Professor Lisa Berkman in the Annual Review of Public Health. In that article, Berkman noted that there is a discrepancy between the results we obtain in our epidemiologic research and the success we have in interventions based on that research. For example, we note in our research that people with poor social connections have higher rates of certain diseases. We then design an intervention to improve social connections to show that those in the experimental group will have better health outcomes than those in the control group. More often than not, our interventions fail to show the results we had hoped for. Berkman suggests that many of these failures have occurred because we have not paid sufficient attention to critical periods in the life cycle. We intervene on risk factors at one time in people's lives even though those risk factors may have

been established and set in place many years earlier. She suggests that more attention needs to be devoted to (*a*) identifying the correct etiologic period within a life-course perspective and (*b*) understanding the dynamic interplay between interventions and the social, economic, and environmental contexts in which interventions are delivered. This is good advice.

All of these suggestions – the need to recognize the importance of host susceptibility in the etiology of disease, the need to develop a more appropriate disease classification scheme that will be a more relevant for prevention, the need for a better understanding of biological processes to help us better define predictor variables, and the need to be cognizant of critical periods in the life span – all of these will help us develop a more useful causal model for Epidemiology – a more useful model for understanding disease causation and disease prevention.

Nothing I have said, of course, is to suggest that we stop studying diseases, one at a time. Of course we need to continue that work. But I *am* suggesting that we also pay more attention to the cause of causes.

These suggestions are made with a sense of urgency. Beginning this year, the baby boomer population is beginning to enter the over-65 year old population in the United States. By the year 2030, the number of people over the age of 65 in the country will almost be double what it is today. If we think our medical care resources are strained now, we ain't seen nothin' yet. It is hard to imagine the expansion of medical care resources that will be needed to care for this greatly enlarged and needy population. To deal with this crisis, it seems clear to me that we will need to help people enter

the over 65 population in a healthier condition than is now the case. And to do that, we will need to improve our approach to disease prevention and health promotion. And to do that, we will require an epidemiology that is more appropriately attuned to the fundamental forces that affect health. A continued focus on individual behavior and individual risk factors will not do the job.

Public Health has a long and distinguished history of cleaning our water, protecting our food, cleaning our air, and controlling mosquitoes and other disease vectors. We now need to expand that mission by learning better ways of influencing a broader set of determinants of health and disease.

Since I began work in this field 50 years ago, the improvements we have made in our approach to these issues are astonishing. In the days of the Human Ecology Study Section, we never saw work of the quality that is in evidence today. I am optimistic that work in the next 50 years will be even more impressive. Especially if we can free ourselves to think more imaginatively about causal models. I wish us all the best in this important mission.