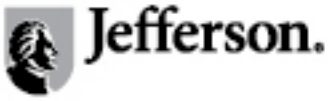

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Causes and Mechanisms, an Interview with Dr. Jeremiah Stamler

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Causes and Mechanisms, an Interview with Dr. Jeremiah Stamler

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Dr. Jeremiah Stamler began his career in New York City and moved to Chicago in 1947 with his wife Rose, to accept a basic research position with Dr. Louis N. Katz. Early animal studies convinced him of the role of dietary factors, particularly cholesterol and salt, in the etiology of atherosclerotic vascular disease. Because of a strong interest in public health, he began the first of many population based cohort studies in the 1950s that subsequently defined the role of health behaviors (adverse nutrition choices, tobacco use, low physical activity) and associated measurable biologic traits, now called risk factors, in the causation of the cardiovascular disease epidemic then at its peak in the United States.

He began his professional work in preventive medicine with the City of Chicago Health Department and subsequently developed the Department of Preventive Medicine at Northwestern University Medical School where he now serves as professor emeritus. His research, leadership, and teaching have been critical in defining the contemporary roles of both the American Heart Association (AHA) and the National Heart, Lung, and Blood Institute. He remains an active investigator at age 85. I interviewed Dr. Stamler at his home.

Causes and Mechanisms, The Theory

SSG: A mark of your career has been the integration of your hypotheses across all levels of investigation, from basic science to clinical trials to population studies. Was that an early idea?

JS: It probably began in college, reading about the philosophy of science, and how you establish that "A" causes "B," particularly in complex biological systems. I learned that methods were subordinate to the goal of trying to unravel the key question, which is causation, not mechanisms. One approach was to assume the exposure, as the epidemiologists call it, and then study mechanisms. Take it as a given that smoking is bad for people, so how does it produce disease? As methods for elucidating mechanisms became more and more exquisite, you collect more exquisite data. But the fundamental issue is, without the exposure you don't have the disease, or it's very rare. So exposures are key.

Virchow, in the middle of the 19th century, spoke about mass diseases as caused by disturbances (he used the plural) of human culture. We study these diseases by every means at hand: clinical and autopsy work, animal experimentation, anthropology, sociology, and of course epidemiology. The main strength of epidemiology is the ability to elucidate causation. Clinical trials may sometimes be crucial, they may not be. You use every method as a means to an end, not an end in itself. Judgments on etiology must be based on assessment of the totality of the data, accumulated by all methods. Some people become a master of a method and then look around and say "what can I use it for?"

Causes of the Cardiovascular Epidemic

SSG: Are there examples in today's research?

JS: Yes! The idea has been resurrected that arteriosclerosis is an inflammatory disease. Like almost everything, there's an element of truth. Part of the process is an inflammatory process. It comes back to the concept of cause or mechanism. First and foremost is mass exposure to adverse life styles---specifically adverse eating patterns, sedentary habits, and smoking. Virchow considered mass diseases disturbances (I emphasize the plural) of human culture. Once you have those exposures, elevations of blood lipid and glucose levels, blood pressure, and weight, are more common. Lipids are more likely to get into the vessel wall and there is an inflammatory reaction. Is inflammation a component of atherogenesis? Of course. All you've got to do is look under the microscope. There are inflammatory cells and a fibrous reaction etc., etc. up to and including calcification and bone formation, all well known for more than a hundred years. The human body has a limited set of ways for reacting to and attempting to combat adverse exposures, infectious and non-infectious. Inflammation is a key reaction. So, inflammation is a part of the atherosclerotic process. But from an etiologic point of view, is it central and critical? No way. We've got a society that has all of these adverse exposures, nutritional, smoking, sedentary lifestyle, etc. and therefore the process is set in motion on a mass scale. The basic answer is primordial prevention. Get rid of the exposures. That's the fundamental answer. Dubbing this disease inflammatory obfuscates the fact that atherosclerosis is a nutritional-metabolic disease.

SSG: The distinction between causation and mechanism is critical. If you look at current obesity work it seems people forget that eating too much and not exercising are the causes and everything else is the mechanism.

JS: Correct. It's very interesting. The people whose orientation focuses on the individual and biomedical aspects look for leptin and they look for this and they look for that. But the central question is not "why does a particular individual have a propensity to become obese?" The problem is a mass phenomenon. That's a bad word to use when talking about obesity. But the epidemic of obesity is unprecedented in history. It hasn't happened before. Why has it happened? Once you put that question on the table, it really isn't very hard to figure it out. You have automobiles. You have television. You have work that is sedentary. I began research in the Peoples Gas Company labor force in Chicago in the late fifties and I looked for employees at various levels of physical activity at work; I looked for heavy activity workers. I was told "there are none." The last such ceased to be such five years previous when the coking ovens closed. Once that happened almost all work there was sedentary or light. There were a few people whom you could call medium-activity workers. And then you have the abundance of "rich" food. I remember when in the sixties a leading cardiologist and epidemiologist, Risteard Mulcahy, a wonderful guy from Ireland came to visit the United States. We sat down and had dinner at our house. He said "Food! It's everywhere. You go on the subway. There are places with vending machines and kiosks that sell food. You walk out on the street, there's an ice cream parlor, a hamburger place, a fried chicken place. In Ireland, we sit down to the table three times a day. When the kids come home from school, they don't raid the refrigerator. It's an entirely different culture!" It never quite occurred to me until

that moment, you know. You have an epidemic of obesity beginning with children now. It's sad, very sad. To correct that, no matter how skilled people are, you also must have a societal approach, a societal effort. It's not enough to have just an individual one-on-one clinical approach.

SSG: Suppose, in the original research approach, there had been emphasis on what keeps you healthy rather than what gives you heart disease. How would the world be different?

JS: It's valuable to be able to detect people at high risk. They become the focus for prevention. But even though the concept "risk factor" related to the likelihood of getting the disease, we were also concerned from the beginning with the other side of the coin. For example, in the late fifties we began the Chicago Coronary Prevention Evaluation Programs, working with higher-risk middle-aged men (having two or more of the major risk factors: cholesterol, blood pressure, smoking), Of course, all of them were American and most therefore had adverse eating habits, were sedentary, and overweight. I had a chart to show the effect on cardiac risk of this adverse pattern. "This is where you're at risk." I then turned the page over and showed what could happen if they improved, it predicted low risk.

What we didn't have then, and this is what's important about the advance in the last decade, was actual data on people who are low risk. I could estimate how much better off you could be with a cholesterol of 180 rather than 250 or a systolic of 116 instead of 148. But we just had estimates. Why? Because there were very few low risk people! But then 10 years ago or so, in the nineties, we began to have enough low risk people, with long-term follow up of the MRFIT cohort (about 350,000 men) and our Chicago Heart cohort

(about 40,000 men and women). The low risk strata - well under 10% of these cohorts - are very impressive. The epidemic disappears. The disease becomes endemic. Coronary artery disease, instead of accounting for one-third of all deaths, is about one-tenth of all deaths. All cardiovascular disease, instead of being a majority of deaths as it was at the peak of the epidemic, is maybe 15% of all deaths.

Looked at clinically, 90+% of people with acute coronary events have one or more of these etiologically significant, readily measured risk factors -- elevated serum cholesterol, elevated blood pressure, obesity, diabetes, cigarette smoking. These data, published in JAMA in 1999 and 2003, (REFS?) laid to rest the assertion that the major risk factors account for no more than 50% of coronary events. They account for most, even though measured only once (with the limitation that imposes) even though the equation does not include the key "disturbances of human culture", of adverse eating and sedentary habits. Such data, of decisive importance for public health and medical practice, dot the i and cross the t of the concept that *causes*, not *mechanisms* must be the focus.

Based on these facts, all we have to do, that's a big "ALL" to end the epidemic is progressively increase the percent of the population at low risk until it constitutes the vast majority, beginning with primordial prevention. When does primordial prevention begin? I used to say "with weaning." Then Barker and others published about effects in utero. So now I say from conception.

SSG: One of the interesting things is the numbers you give for low risk. They generally define the 75th to 90th percentile for children, though the obesity epidemic is changing

things. If a child can keep his or her risk factors the same with aging and never smoke you have that low risk population.

JS: Good point. If you look at National Health and Nutrition Examination Survey data, you will find that the average systolic at age 18 to 25, is about 118-120 in both Blacks and Whites. And the average diastolic is about 80. And "all" we have to do is keep it that way. In isolated populations we and others have studied, blood pressure does not change over the decades of adulthood; they have low salt intakes, are physically active, and lean.

All that poses another historical matter related to causation. Two questions were clear 50 years ago: 1. Why the high average levels of blood cholesterol and why the rise during the adult decades? 2. The same for blood pressure. Early on, a tremendous amount of work was done, including very useful animal and metabolic ward nutrition studies, on what influences blood cholesterol. Dietary cholesterol, saturated fats, and *trans* fats raise it. Low fiber intake is associated with higher levels, as is weight gain on an American diet. These were mostly delineated in the sixties. But the question what influences blood pressure was—at least until the 1980s -- neglected by all of us. Then our INTERSALT data showed that with 100 millimoles a day higher sodium intake, blood pressure is significantly higher; high body mass, heavy drinking, and inadequate potassium intake likewise.

Another important aspect may be early life programming. In Holland, studies have compared lower vs. higher sodium intake during the first six months of life, that is the approximate equivalents of breast vs. cow's milk (which is 3 to 4 times higher in salt). With higher salt, blood pressure was significantly higher at 6 months of life, and at 15

year follow-up they still had lower blood pressure. You know, it's all got to do with disturbances of human culture.

SSG: And now we have DASH to prove it.

JS: Exactly. DASH is a wonderful study. One of the great trials.

Attacking the Causes of an Epidemic

SSG: You are not someone who has sat calmly on the sidelines. You have tried to influence public policy, to create your own disturbances of human culture towards better health.

JS: No mass public health problem has ever been solved without societal measures. The AHA, since 1960, has said the main causes are clear, all you've got to do is get rid of them, and even government has accepted that, despite all that special interests (the meat, dairy, egg, sugar, salt, alcohol, and tobacco industries) have tried to do to obfuscate. For example, there's no reason why only three cereals should be without added sugar and low in salt (puffed wheat, puffed rice and shredded wheat).

An example of positive government leadership is the Hill-Burton project. Well, Lister Hill was a senator from Alabama, and Burton was a congressman from Ohio. and they developed a program in the Congress, I think in the 1930's, in the depth of the Depression, when the country's hospital system was inadequate. Hill and Burton led congressional support for government financed and subsidized hospital construction. That program went on for a long time, and many of the hospitals in our country, the network of community hospitals, are the result of Hill-Burton money. Why can't we

similarly encourage good nutrition behavior with government support for healthy food super markets and fast food emporia?

Advertising is important too. Back in the 1960s and 70s "equal time" public service announcements were very effective against tobacco

SSG: So what I'm hearing you say is that with the collection of data comes responsibility for the public health?

JS: Yes. By definition, public health is a public thing. In the late 1950's, we began to press the AHA to adopt a policy of support to improve lifestyles: no smoking, better nutrition. It took some doing. The AHA was initially reluctant and was under pressure from industry. The AHA prepared its first statement on smoking in 1959, and its first statement on diet in 1960, I had the privilege of working with many distinguished colleagues on the latter - first class statesmen like Paul Dudley White. The first World Health Organization statement did not come out until the 1980s.

A key issue was: should one await the results of clinical trials or make recommendations for the general public based on the best current available knowledge indicating the probability of prevention? With very rare exceptions, trials begin relatively late in the course of the disease, especially if you want to use hard end points, heart attacks, strokes. What were we going to do? Randomize two groups at birth, one smoking and one not, to see how things turn out? The AHA initial statement was very carefully worded. We made the fundamental decision to recommend public policy for the whole population and to recommend trials at the same time. The FDA in those years took a contrary stance, pressed by industry.

With mass disease problems and their causes, “disturbances in human culture”, the one-on-one approach of clinical medicine is not enough. In fact, in order for a one-on-one approach to be fully effective, the social message must be in place. As a physician, one needs to make recommendations that won’t leave the patient thinking he is peculiar, has to do things that are socially “funny”. Prevention should be a norm of human behavior. In the 50’s, a majority of doctors were still smoking. You went on an airplane you were given a tray with a couple of cigarettes, that was the norm of human behavior

The task of science is to make discoveries and seek to apply them to benefit mankind. Think of Bacon who was a modernist in his time. The essence of the Baconian approach is that the truth is objective, and objective truth leads to conclusions, and those conclusions lead to applications, This philosophy was undermined in the 20th Century by the atomic bomb. Dismayed by that application of science, many scientists developed the view that we’ll do research, and then what the policymakers do with our product is their business - we don’t have any responsibility for the social application. That view is still around: stay in the ivory tower collecting data and do nothing about application for the public good -- it saves getting trouble with industry. Scientists have a responsibility, not only to reveal the truth, but to educate and advocate about its implications, and to fight for action on those implications. For example, I have witnessed the average adult blood cholesterol level in this country go from a median of about 240 to 200, one of the few national public health goals that has been achieved. People don’t talk about it much. A result of years long multifaceted public policy efforts.

SSG: Lew Kuller said that when he started his career, intervention was part of epidemiology. For example, when there was a polio epidemic, a key effort became polio immunization; what were the best strategies to protect the public from the virus. That emphasis seems to be muted now.

JS: What is epidemiology? It's the science of disease patterns in populations, comparative evaluation of them, and elucidation of their causes; it's the scientific foundation of prevention and control. Accordingly it is an important tool for assessment of what's going on in prevention and control, for promoting prevention and control. The second half of that definition is, in fact, less practiced---often missing.