UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

UNITED STATES OF AMERICA, Plaintiff, v. PHILIP MORRIS USA INC., f/k/a PHILIP MORRIS INC., *et al.*, Defendants.	)	Civil No. 99-CV-02496 (GK)

UNITED STATES' WRITTEN DIRECT EXAMINATION OF

DR. IRA S. OCKENE

SUBMITTED PURSUANT TO ORDER #471

Q: Will you please state your full name for the record?

A: Ira S. Ockene.

Q: Dr. Ockene, what is your current professional position?

A: I am the David and Barbara Milliken Professor of Preventive Cardiology, Director of the Preventive Cardiology Program, and Associate Director of the Division of Cardiovascular Medicine at the University of Massachusetts Medical School.

Q: Do you have a medical degree?

A: I do.

Q: Dr. Ockene, will you take us through your educational background?

A: I was born and raised in the Bronx in New York City and attended high school at the Bronx High School of Science. I was then a premedical student at the City College of New York, following which I attended medical school at the Albert Einstein College of Medicine in New York City. I received my B.S. from City College in 1962 and my M.D. from the Albert Einstein College of Medicine in 1966.

Q: What did you do professionally following medical school?

A: I was an intern in Internal Medicine at Bellevue Hospital in Manhattan, and then completed a residency in internal medicine at the Bronx Municipal Hospital Center, which is the primary teaching hospital of the Albert Einstein Medical School. Following this I did one-year of cardiology training at the Mount Sinai Hospital.

Q: When did you complete the year of cardiology training at Mt. Sinai?

A: I finished my year at Mt. Sinai in 1970. At the end of this year I entered the Army, and spent two years at Fort Carson, Colorado where I served as the post cardiologist, leaving the service with the rank of Major in 1972.

Q: And continuing your professional chronology, what did you do upon leaving the Army?

A: I then came to Boston, Massachusetts where I served an additional two years of cardiology fellowship at the Peter Bent Brigham Hospital, one of Harvard Medical School's primary teaching institutions. Following the completion of my fellowship I stayed on staff at the Brigham for an additional year, at the end of which time, 1975, I was recruited to join the new Department of Cardiovascular Medicine at the University of Massachusetts Medical School, where their new hospital was just opening. I was the director of the cardiac catheterization laboratories, and entirely developed the service, ordering all the equipment, organizing the catheterization service, hiring and training staff, and overseeing the rapid increase in volume that occurred over the next decade.

Q: Have you been at the University of Massachusetts Medical School continuously since 1975?

A: Yes, I have. As I mentioned, I originally came to UMass to develop and run the cardiac catheterization laboratories; I did that for some 10 years, but became progressively more interested in the prevention of heart disease and in 1985 applied for and received one of the National Heart Lung and Blood Institute's Preventive Cardiology Academic Awards. At that

point I gave up being the administrator of the catheterization laboratories, although I have continued to do cardiac catheterizations until the present time.

Q: You indicated that you are currently the David and Barbara Milliken Professor of Preventive Cardiology. Can you provide the Court an explanation of what preventive cardiology is?

A: Yes. Preventive cardiology is that field of cardiovascular medicine that is devoted to preventing episodes of cardiovascular disease. This includes not only coronary heart disease but also other forms of heart disease and vascular disease occurring elsewhere in the body, such as those causing strokes and peripheral vascular disease. Prevention of such episodes can also be divided into "primary" and "secondary" prevention. Primary prevention refers to reducing risk factors in people who are well and have never suffered a cardiovascular event, whereas secondary prevention refers to the prevention of further clinical episodes in individuals who have already suffered some form of clinical cardiovascular event such as a myocardial infarction.

Q: How large is the Division of Cardiovascular Medicine at the University of Massachusetts Medical School?

A: The Division of Cardiovascular Medicine comprises a very large and busy group, with 23 cardiologists located within the division itself, and an equally large number of outside cardiologists who take an active role in the department both in terms of teaching and clinical responsibilities. There are five catheterization laboratories and an electrophysiology laboratory, and almost 6000 such procedures were carried out last year, making us the second busiest catheterization service in Massachusetts, second only to the Massachusetts General Hospital.

Q: What are your professional responsibilities in your positions at the medical school?

A: I spend approximately 50% of my time in clinical activities, 45% in research and some 5% in administrative activities. Teaching is continuously interwoven into these activities. Although over the course of the year I give a number of lectures to the medical students, house staff, and others, the majority of teaching is combined with clinical activity, overseeing students and house staff and making rounds.

Q: I'd like to explore each of these areas – clinical, research and administrative. Can you describe your clinical work?

A: My clinical activity is divided between several different types of patient care. Tuesday is my day in the cardiac catheterization laboratory, Wednesday and Thursday mornings I see patients in the Preventive Cardiology Clinic, and I take two week blocks of time as the attending on the coronary care unit, the ward service, and the cardiology consultant service. I have been doing this type of service at the University of Massachusetts medical school since 1975, when I came to UMass from the Peter Bent Brigham Hospital in Boston.

Q: Dr. Ockene, what role does cigarette smoking play in your clinical work, if any?

A: To practice clinical cardiology is to constantly see the ravages of cigarette smoking. All of us are constantly aware of the damage that smoking does to the cardiovascular system and a day does not pass without multiple reminders of the toll that smoking takes in unnecessary illness and premature death and disability. The large majority of the patients that I see – in the clinic, on the coronary care unit, on the wards, and in the cardiac catheterization laboratories – have coronary artery disease, with progressive narrowing of the coronary arteries related to multiple

risk factors but particularly exacerbated by exposure to cigarette smoking. I spend a great deal of time counseling patients about the importance of smoking cessation and, equally importantly, counseling them and their families about the value of smoking cessation for all. Needless to say, although as a cardiologist I tend to concentrate on the cardiac effects of cigarette smoking, I also see the chronic lung disease and attendant shortness of breath and the lost limbs secondary to gangrene and severe peripheral vascular disease, especially in diabetics, which has been markedly accelerated by smoking.

Q: Can you describe your research work for the Court?

A: Yes. I have been active in writing and research throughout my career, but as I mentioned I devoted more of my early career at UMass to developing the clinical service in the new medical center. In 1985, I became NHLBI funded, and have been continuously funded by the NIH since that time. My research has been devoted to the treatment of risk factors for coronary heart disease, with a particular emphasis on counseling methodologies that can be easily incorporated into physician practice. Nutrition for the prevention of heart disease has been another important theme in my work.

Q: Can you describe your research devoted to the treatment of risk factors for coronary heart disease in more detail?

A: Yes. I became interested in carrying out research related to the treatment of risk factors in the late 1970s and early 1980s. Initially my work revolved around smoking and smoking cessation, and in particular we carried out a study looking at methods to help patients with known coronary disease stop smoking (Smoking Cessation in Patients with Cardiovascular Disease,

NHLBI supported).

In that study we demonstrated that in contrast to smoking cessation in individuals who are well, which occurs at the rate of approximately 5% per year, when patients have suffered a cardiac event such as a myocardial infarction, the immediate and long-term smoking cessation rate approximates 50%, and with very modest intervention such as in-hospital counseling and telephone follow-up that permanent cessation rate approaches 70%. A study done at Stanford University showed similar results.

Q: Did this initial work revolving around smoking and smoking cessation result in any peer-reviewed publications?

A: Yes, it did. Those publications included Ockene JK, Nutall R, Benfari RC, Hurwitz I, Ockene IS. A psychosocial model of smoking cessation and maintenance of cessation. Prev Med 1981; 10:623-38; Ockene JK, Benfari RC, Nuttall RL, Hurwitz I, Ockene IS. Relationship of psychosocial factors to smoking behavior change in an intervention program. Prev Med 1982; 11:13-28; Ockene JK, Hosmer DW, Williams JW, Goldberg RJ, Ockene IS, Raia TJ, 3rd. Factors related to patient smoking status. Am J Public Health 1987; 77:356-7; Ockene J, Hosmer D, Williams J, et al. The relationship of patient characteristics to physician delivery of advice to stop smoking. J Gen Int Med 1987; 2:337-340; and Frid D, Ockene IS, Ockene JK, et al. Severity of angiographically proven coronary artery disease predicts smoking cessation. Am J Prev Med 1991; 7:131-5.

Q: Did you continue your work related to the treatment of risk factors for coronary heart disease?

A: Yes. Our work expanded from this to look at the larger question of how people make behavioral change, a question that affects multiple risk factors including smoking, hyperlipidemia, diabetes, and hypertension, and how physicians could be provided the skills necessary to help their patients make such changes. From this work came the publication of a book on the prevention of coronary heart disease (Ockene IS, Ockene JK (Eds), *The Prevention of Coronary Heart Disease*, Little, Brown & Co., Boston, 1992). Other publications resulting from this work were Ockene J, Sorensen G, Kabat-Zinn J, Ockene I, Donnelly G. Benefits and costs of lifestyle change to reduce risk of chronic disease. Prev Med 1988; 17:224-234; and Ockene J, Ockene I, Kabat-Zinn J. Teaching Risk Factor Counseling Skills to Medical Students, House Staff, and Fellows. Amer J Prev Med 1990; (suppl.):34-42.

Q: Can you describe the focus of these two papers?

A: Yes, I can. The first is a paper describing how the costs of lifestyle change are balanced by patients against what they perceive as the benefits. The costs are not literal dollar costs, but are more often lifestyle costs such as the requirement to eat or prepare foods that are different from those eaten by your family and friends or the need to separate yourself from your peer group of smokers. The second is a paper describing the methodology that we use to teach risk factor counseling skills to students, house staff, and fellows. The methodology described in the paper came out of the research we had done and is now a standard part of the medical school curriculum at UMass and elsewhere.

Q: Did you continue to work with preventive interventions?

A: I did. Following this work I became especially interested in the area of nutrition, and in addition to a number of studies looking at specific areas of nutrition such as the value of soy products, we began a series of larger scale studies looking at methods by which the efforts of physicians and other providers to provide nutritional counseling could be facilitated. In the NHLBI-funded Worcester-Area Trial for Counseling in Hyperlipidemia (WATCH), we studied three groups of internists (15 per group) and their patients in the Fallon clinic HMO in Central Massachusetts. Two of these groups of internists were trained in patient-centered counseling, a methodology that we developed and described that uses an interactive approach to patient counseling and is designed to take only seven to nine minutes of a physician's time. One of the two training groups received in addition to the training a modest amount of office support which included documents that came with the patient that reminded the physician to attend to the patient's diet and cholesterol level, to carry out the patient-centered counseling they had been taught, and also included a reminder algorithm of the steps involved in such counseling. During several years of follow-up, including patient exit interviews, we learned that training alone was of no value, as the physicians who received training but no reminders did no better than the control group of physicians, whereas the group that received prompts and reminders did carry out the counseling intervention and their patients lost weight and reduced their cholesterol levels.

From this we went on to carry out an additional NHLBI-supported study that now layered on to the physician intervention a computer-driven system that ensured that repeat cholesterol measurements and appropriate referral to dietitians would be carried out in a timely manner. The results of this study will be available in the near future.

Q: Please continue describing your work with preventive interventions.

A: Adherence to prescribed regimens for risk factor control has been a persistent problem, as many patients neither follow recommendations for behavioral changes such as smoking cessation, weight loss, exercise, or diet change, nor in fact do they often take their medications appropriately, either stopping antihypertensive or lipid-lowering therapy altogether or taking these medications erratically. Our most recent study, Improving Adherence To Pharmacological Treatment (NHLBI), looks at this issue in a group of patients admitted to the hospital with coronary disease. The intervention in this study is pharmacist driven, as in the intervention group (there is also a control group), the pharmacist meets with the patients in the hospital to go over all their medications with them and then carries out a series of follow-up phone calls designed to facilitate proper medication taking behavior and explore barriers such as misunderstanding, side effects, or cost.

This year we have received funding from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) to carry out a community-based intervention for the prevention of diabetes in an entirely Latino population in Lawrence, Massachusetts, the poorest city in the Commonwealth. In this study we will be identifying individuals at high risk for diabetes and using culturally appropriate and community-based interventions to improve diet and physical activity to reduce the prevalence of obesity and prevent the development of diabetes. We have also received funding from NIDDK to evaluate the relationship between certain types of diets and the likelihood of developing diabetes, using data collected in a previous study sponsored by NHLBI, the Seasonal Variation of Cholesterol Study.

It may seem unusual that a cardiologist is receiving funding from NIDDK, but coronary artery disease is the primary cause of death in patients with diabetes.

Q: Can you describe additional research activities you participate in?

A: I have devoted considerable time to mentoring and working with others. It has been a great pleasure to assist young physicians and scientists in the development of their careers. This year one of my mentees was awarded a "K" award (an NIH career development award) that provides 75% funding for five years to carry out research on the effectiveness of cardiac rehabilitation programs and explores why they are not utilized more frequently. Another received funding to carry out a study of nutrition and diabetes, and a third received NIH funding to investigate the relationship between diet and exercise and blood markers of inflammation thought to be related to risk of coronary disease.

Q: Dr. Ockene, I'd like you to take a look at the document marked as U.S. Exhibit 78,548. Is this a copy of your curriculum vitae?

A: Yes, it is.

Q: Does this accurately reflect your hospital and academic appointments, committees, extramural activities, societies, editorial and reviewer positions, grant support, board certification, military service and publications, including journal articles, books, book chapters, abstracts, letters and collaborative works?

A: Yes, it does.

Q: Dr. Ockene, would it be fair to say that you are one of the world's leading experts in preventive cardiology?

A: Yes.

Q: What are your other areas of expertise?

A: As a cardiologist with a great deal of experience, I consider myself expert in all of those areas appropriate to my work in cardiology: the physiology of the heart, the pathophysiology of cardiac disease, the assessment and care of patients with heart disease, and the role of the cardiac catheterization laboratory and other diagnostic and therapeutic modalities. Within the area of prevention, I have a special interest in the overall topic of adherence, or why people do or do not adhere to recommendations for lifestyle change or medication-taking behavior and what we can do to improve such adherence.

Q: I'd like to start addressing the substance of your testimony by asking you a few preliminary questions, then we will turn to a discussion of cigarette smoking as a cause of cardiovascular disease, with a particular emphasis on the benefits of cessation. First, what are the medical conditions encompassed within cardiovascular disease?

A: I think it is probably best to break cardiovascular disease down into coronary heart disease, myocardial infarction, angina pectoris and sudden cardiac death.

Q: Let's take those one by one. What is coronary heart disease?

A: Coronary heart disease is the narrowing and ultimate occlusion of coronary arteries resulting from the progressive deposition of cholesterol-laden lipids on and in the arteries of the heart. This process occurs over many years and as time passes lipid infiltrates into the vessel wall and a process of progressive fibrosis and inflammation occurs, with eventual narrowing of the lumen (the opening) of the artery.

Q: And what is myocardial infarction?

A: The inflammation that occurs as part of the process I just described creates a situation where the plaque, as the atherosclerotic lesion is referred to, can suddenly rupture and have clot deposited on it, which is the body's response to an injury. In this case, however, the deposition of a clot on top of a plaque can suddenly entirely block the artery, resulting in a situation where no blood reaches the muscle that that artery supplied, causing the death of that part of the muscular wall of the heart. This is a myocardial infarction, or as popularly termed, a "heart attack." What then happens is a function of how large an area of the heart muscle is affected, what the state of the rest of the heart is (whether there has been prior damage to the heart, or whether the heart has been weakened by high blood pressure or other disorders), and whether or not the muscular damage occurs in a particularly critical location within the heart, such as in the supporting structure of a valve or in a major electrical pathway within the heart.

Q: What is the prognosis for a person who suffers a heart attack?

A: Approximately half of all myocardial infarctions result in sudden death and the affected individual never survives to make it to the hospital. Of those who do make it to the hospital the large majority survive, with a mortality rate that is now less than 10%. In our institution – UMass – almost all patients with acute myocardial infarction are taken to the cardiac catheterization laboratory where the blockages in their arteries are defined, and a decision made as to whether the patient requires only further medical therapy, the placement of stents (wire mesh devices that hold the artery open), or referral for bypass surgery if the disease is too extensive to be otherwise managed. We have learned that if an artery can be opened up within a

relatively brief time after the onset of the infarction (within six to 12 hours) the size of the infarct will be reduced from what it would otherwise have been and the patient's outcome will be better. The sooner that the artery is opened up the better, although some benefit is derived up to 24 hours later.

Q: Are catheterization laboratories readily accessible to most patients?

A The issue here is not access to catheterization laboratories, but rather access to catheterization laboratories that have the capability to carry out percutaneous interventions with balloons and stents in order to open blocked arteries. Many catheterization laboratories can carry out only diagnostic procedures and then transfer patients for further interventions. It is estimated by those in the interventional field that some 40% of the United States' population has timely access to catheterization laboratories that have the necessary facilities to carry out such interventions.

Q: How is a patient treated when a catheterization laboratory is not available?

A: In situations where access to a catheterization laboratory is not easily available, clot dissolving drugs ("fibrinolytic" agents) are used instead. These drugs are also of major benefit in rapidly opening a blocked artery. The key is to open the artery as rapidly as possible.

Q: What type of follow-up treatment does a patient require after the immediate treatment you've described?

A: Following the immediate therapy, continuing medical therapy is directed towards preventing the morbid consequences of an infarct, such as congestive heart failure and abnormal heart rhythms, and towards controlling risk factors that contributed to the infarct occurring in the

first place and equally contribute towards the occurrence of further such episodes. Thus in the absence of contraindications patients are begun on aspirin (for its clot-inhibiting effects), ACE inhibitors (drugs that lower blood pressure and have other beneficial cardiac and kidney effects that prevent heart failure), beta-blockers (drugs that slow the pulse rate and reduce the work of the heart, shown in many studies to reduce death rates and improve long-term survival), lipid-lowering drugs (to reduce cholesterol levels), omega-three fatty acids ("fish oil" - stabilize cell membranes and reduce the likelihood of a lethal arrhythmia) and other medications to treat high blood pressure or diabetes if present. In addition, every effort is made to assist patients who smoke to discontinue smoking forever, as it is very well known that even after an infarct has already occurred there is a dramatic benefit to be derived from smoking cessation. For most patients it will also be suggested that they join a cardiac rehabilitation program where more intensive efforts can be made towards risk factor control and an appropriate exercise program is developed for the patient, and it is generally also advised that after an appropriate interval, usually four to six weeks, a stress test is carried out to look for residual ischemia ("ischemia" is the term used for insufficient blood being supplied to living muscle in the heart).

Q: Continuing our discussion of cardiovascular disease, what is angina pectoris?

A: In situations where one or more coronary arteries are narrowed but enough blood flow is going to the heart muscle such that at rest sufficient oxygen and nutrients are being supplied to the muscle to keep it alive, patients may develop angina, which is a condition where typically the patient is pain-free at rest but with exertion will develop chest discomfort, which then abates when the exertion is discontinued. In essence, what is happening here is that there is sufficient

blood flow to the muscle at rest, but insufficient blood is supplied during exercise when much more blood flow is required and the narrowed artery cannot supply it. This is in many ways similar to an automobile with a clogged fuel line such that the car idles without difficulty, but runs very poorly when a speed is reached where insufficient fuel can pass through the narrowed line. Angina can presage a myocardial infarction, and angina can also be seen in patients who have already had an infarct.

Q: And finally, what is the clinical definition of sudden cardiac death?

A: The sudden cessation of blood flow to an area of heart muscle will often trigger cardiac arrhythmias (abnormal heart rhythms). The most serious of these arrhythmias, ventricular tachycardia and ventricular fibrillation, can cause a dramatic reduction or complete cessation of cardiac function, with the consequence that blood flow either fails entirely or is inadequate to supply the brain and other organs. This can very rapidly cause death and is what is commonly referred to as a cardiac arrest.

Q: Is this the same as myocardial infarction?

A: Not entirely. Although most commonly associated with a myocardial infarction, sudden death can also occur in individuals who have underlying severe cardiac dysfunction, either on the basis of prior coronary disease or sometimes related to other disorders causing the heart muscle to weaken, such as hypertensive heart disease or cardiomyopathy (weakness of the heart muscle from other causes). Cardiac arrest can be treated by the use of electronic defibrillators, and for several years now cardiologists have been placing implantable defibrillators, similar to pacemakers, into patients who are at high risk for sudden death.

Q: Dr. Ockene, can you explain for the Court what cerebrovascular disease is?

A: Cerebrovascular disease refers to disease of the arteries supplying the brain with blood. Abnormalities of these arteries can lead to insufficient blood flow to parts of the brain, causing stroke. In the United States cerebrovascular disease is most commonly related either to atherosclerosis of the carotid arteries and arteries within the brain, or sometimes to long-standing hypertension. Although hypertension contributes to the more rapid progression of atherosclerosis, it can also lead to hemorrhage of the arteries within the brain, causing a so-called hemorrhagic stroke, a variety of stroke which is much more common in Asia. As the most common form of cerebrovascular disease in the United States is atherosclerosis, cerebrovascular disease and cardiovascular coronary disease are closely related, with a common mechanism and common risk factors. Tobacco use is a potent risk factor for stroke.

Q: You mentioned atherosclerosis. What causes the development of atherosclerosis?

A: The development of progressive atherosclerosis requires that a certain level of cholesterol be present in the blood. This minimum level is approximately 130 mg/dl, a level lower than that seen in the overwhelming majority of Americans, where the average cholesterol level is 205 mg/dl. Given a level of cholesterol sufficient to deposit in the arterial wall, multiple other risk factors play a role in accelerating this process. Those risk factors as already mentioned include tobacco use, hypertension, diabetes, obesity, and sedentary lifestyle. In addition, it is useful to think of atherosclerotic disease as a two-stage process. The first stage is the slow and progressive deposition of lipids within the arterial wall, a process that begins in childhood and progresses over a period of many years. The second stage is the series of rapidly occurring

changes that leads to an acute clinical event such as a myocardial infarction. This process involves abnormalities of platelet function, abnormalities of function of the lining of the vessel wall (the endothelium), and abnormalities of clotting functions, such that an atherosclerotic plaque abruptly ruptures, often accompanied by spasm of the vessel wall, and this internal injury leads to the deposition of a clot which abruptly occludes the vessel.

Q: What risk factors play a part in this process?

A: As I mentioned, multiple risk factors take part in this process. Risk factors are not simply additive, but are rather multiplicative, such that an individual with a high level of one risk factor, such as a high cholesterol reading but no other risk factors, is actually at much lower risk than someone with multiple risk factors each of which is at a more modest level, such as an individual with a modestly elevated cholesterol who also smokes a half a pack of cigarettes a day and has moderately elevated blood pressure. The reverse of this is that an individual with multiple risk factors benefits greatly from removing a risk factor such as smoking.

Q: Dr. Ockene, how are the causes of cardiovascular disease and cerebrovascular disease identified?

A: Conclusions about causality are made in different ways. There are some causal relationships that are so strong and obvious that that they are accepted by all without the need for formal scientific investigation. Thus no one requires a study in which a group of people jump out of airplanes, half wearing parachutes and half not, in order to demonstrate the efficacy of such devices. But in medicine, most of the causal relationships that we deal with are much less obvious. Even where there is a direct one to one relationship between causal factor and illness,

that relationship may not be immediately evident. Thus for thousands of years of human existence diseases such as tuberculosis and scurvy were attributed to the anger of supernatural beings or other events beyond human control. It was only careful observation and experimentation that led to the realization that scurvy was a deficiency of vitamin C and could be prevented or cured by the administration of the juice of citrus fruits, or that tuberculosis was caused by a specific bacterial organism. In 1882 Koch described his classic investigation into the cause of tuberculosis, and outlined the criteria for defining such a causal relationship. It is important to understand that Koch's postulates were developed in the context of infectious disease, and do not necessarily apply well to more complex illnesses. Thus in a disease such as tuberculosis it is always necessary to have the tubercle bacillus present in the body to have tuberculosis, although even in this illness the presence of the bacillus is not necessarily alone sufficient to cause illness, as it is well known that many millions of people are infected but never become clinically ill.

Q: Are the criteria applicable to heart disease?

A: No, they are not. More complex illnesses, of which the atherosclerotic diseases such as coronary heart disease are prime examples, are multifactorial in etiology. Thus, the presence of diabetes markedly increases the risk of coronary disease, and coronary heart disease is the prime cause of death in diabetics. Yet the presence of diabetes is neither necessary nor sufficient – there are many diabetics who never develop coronary disease, and of course many nondiabetics who do. Similarly, smoking is an extraordinarily potent risk factor for coronary and other atherosclerotic diseases, yet coronary disease occurs in nonsmokers and there are smokers who

do not develop coronary disease. In sum, such biological processes have multiple etiologies, where disease represents the net effect of many actions and counteractions.

An example from everyday life that would perhaps illustrate this well would be speeding on the highway. It is clear that routinely driving one's car more than 30 miles an hour above the speed limit has a causal relationship to accidents and highway deaths. Yet it is neither necessary nor sufficient: there are speeders who never crash, and individuals driving within the speed limit who nonetheless suffer fatal accidents because of other risk factors related to their own behavior (such as drinking coffee or talking on a cell phone) or a flaw in the machinery of the car itself.

Q: Does smoking cause cardiovascular disease and cerebrovascular disease?

A: Yes, it does. Smoking is a cause of cardiovascular disease, including coronary heart disease, myocardial infarction and sudden cardiac death. Smoking has also been shown to have a clear relationship to cerebrovascular disease and subsequent disability and death. As with myocardial infarction, smoking increases the risk of clinical cerebrovascular events (strokes) and smoking cessation rapidly decreases such risk.

Q: I'd like to discuss the impact of myocardial infarction on persons who suffer from it. Can you describe the course of treatment for a typical patient?

A: Yes. Treatment of myocardial infarction today is a complex combination of drugs designed to dissolve clots, urgent cardiac catheterization to define the narrowed or occluded arteries and, if at all possible, to open them with balloon angioplasty and stent placement (or coronary artery bypass surgery if the extent of the blockages/narrowings is sufficient to warrant this approach). Treatment also involves the use of multiple drugs designed to prevent clot

formation, reduce the work of the heart, control blood pressure and cholesterol levels, and reduce the risk of recurrent events or arrhythmias. In addition, treatment involves patient counseling, often in the context of a cardiac rehabilitation program, to alter those behavioral factors that led to the first event and increase the risk of recurrent events: smoking, high saturated fat diet, obesity, sedentary life style, poor adherence to medication, and stress.

Q: I'd like to explore some of these areas in greater depth. What drugs are administered to dissolve clots?

A: These are fibrinolytic agents, generally referred to as clot-busters. Some examples include streptokinase and tissue plasminogen activator (TPA).

Q: Are there side effects from any of these drugs?

A: Yes. These drugs are designed to dissolve clots. But their action is not specific to clots in the coronary arteries and as a consequence they increase the risk of bleeding anywhere in the body. For example, the stress of a severe illness can precipitate a gastric ulcer which is much more likely to bleed in the presence of these agents. Likewise, bleeding related to the cardiac catheterization is much more common when these drugs have been used.

Q: What is involved in urgent cardiac catheterization?

A: The patient is taken urgently to the cardiac catheterization laboratory after appropriate consent is obtained, which includes telling the patient that there is a small but real risk of serious complications such as bleeding, myocardial infarction, stroke, or even death. The patient is generally premedicated with a combination of drugs to reduce anxiety and decrease pain, but remains awake through the procedure. The procedure itself is carried out in a cardiac

catheterization laboratory, which is a room containing x-ray equipment and computer facilities specifically designed for this type of investigation. Using local anesthesia a catheter is introduced into the femoral artery in the groin (the large artery that goes to the leg) and then advanced under fluoroscopy into the arteries of the heart (the coronary arteries). Specifically designed catheters are used for each of the two coronary arteries. A contrast agent (generally referred to as "dye" although it is a colorless fluid) which is opaque to x-rays is injected into the arteries so that the course of the arteries and any blockages within them can be visualized and a permanent record made either on x-ray film or more commonly today using digital imaging techniques. A separate catheter is often used to go into the left ventricle where contrast is again injected in order to visualize the left ventricle throughout the cardiac cycle, looking specifically for abnormalities of contraction in one or more areas of the heart muscle.

Following the diagnostic portion of the catheterization a decision is made as to whether or not the blockage or blockages within the coronary arteries are amenable to intervention. If the decision is made to proceed with an intervention a separate catheter specifically designed for this purpose (a "guide" catheter) is introduced into the appropriate coronary artery and through this a fine wire is passed through the blocked portion of the artery and either a balloon catheter or a stent device (or both) is introduced over the wire and the blocked portion of the artery expanded. Up until a few years ago only angioplasty balloons were used to dilate the narrowed portion of the artery but in approximately 30% of these procedures the narrowing returned, often requiring a repeat procedure. The stents, which are small wire mesh devices, are expanded within the narrowed area to keep it expanded and prevent restenosis. Early stents were bare metal and also

had a significant restenosis rate, but the present generation of stents is specifically coated with medications that markedly diminish the risk of restenosis, which is now down to approximately 5%.

Q: What is the long-term impact of these treatments on a patient?

A: Any patient with the new onset of clinical coronary disease experiences an abrupt change in the course of his or her life. An individual who previously saw himself as healthy now finds himself threatened by serious disability or death, undergoing serious and potentially dangerous procedures, and is now required to take many medications, some with potential side effects. Work status may change, and disability may ensue, particularly for individuals who have physically active or stressful occupations. Even for patients who are declared to have successfully survived their acute event and are now thought to be asymptomatic, every twinge of chest discomfort will bring on anxiety. The need to take multiple medications will constantly remind the patient of his illness and the need to make lifelong changes, and in general a person who previously may have been carefree will now be weighed down by recurrent concerns about his or her health. From a physiologic point of view the long-term impact of a myocardial infarction depends on the amount of muscle that has been damaged and the specific location of the damage, i.e., whether it affects the function of the valves or the electrical system of the heart. If a large amount of myocardium is no longer able to contract properly or if the function of one or more valves is compromised the remaining muscle may be unable to pump a sufficient amount of blood to sustain normal activity. This results in a condition commonly referred to as "heart failure." When heart failure develops the patient can experience multiple undesirable

consequences, including shortness of breath with exertion (or at rest if the condition is sufficiently advanced), decreased energy level, excessive fatigue, impaired cognitive function, and ultimately dysfunction of many other organs including kidneys, digestive system, and the neuromuscular system. A common measure of the overall function of the heart is the "ejection fraction" which is the percentage of blood present in the heart at end diastole that is ejected during systole. In a normal heart the ejection fraction is greater than 50% and more commonly 60 or 70%. When the ejection fraction falls below 30% heart failure becomes increasingly likely.

Q: You also mentioned the use of multiple drugs designed to prevent clot formation, reduce the work of the heart, control blood pressure and cholesterol levels, and reduce the risk of recurrent events or arrhythmias. First, what drugs are currently used in this type of treatment?

A: Following a myocardial infarction a series of drugs are used. These fall into a number of different categories:

- Beta-blockers - medications in this class work by decreasing the contractile force of the cardiac muscle and slowing the heart rate. Both of these effects decrease the work of the heart and reduce the likelihood of a fatal arrhythmia. We now also know that these medications decrease the risk of heart failure. These medications are usually continued lifelong.
- ACE inhibitors (angiotensin-converting enzyme inhibitors) - these medications lower blood pressure, reduce the likelihood of heart failure, and seem to have other desirable

effects that improve cardiac function and reduce mortality. These medications are usually continued lifelong.

- Antiplatelet agents - unless there is a contraindication, essentially all patients with known coronary disease should take a daily aspirin, which reduces the activity of platelets, which are a type of cell in the blood that promotes clotting. In addition, most patients who undergo balloon or stent procedures are placed on clopidogrel, another agent that reduces the likelihood of clotting. Aspirin is usually continued lifelong. Clopidogrel is usually given for a shorter period of time, generally less than one year.
- Lipid-lowering agents – most patients with known coronary disease require lipid-lowering therapy. The most recent revision of the National Cholesterol Program guidelines suggests that at a minimum LDL-cholesterol levels should be lowered to less than 100 mg/dl, and strongly suggests that a goal of lowering LDL-cholesterol to less than 70 mg/dl may be appropriate in many patients. To reach these goals lipid-lowering pharmacologic therapy is required in the overwhelming majority of patients. The most common class of drugs used to lower blood lipid levels is the statins (e.g., atorvastatin, simvastatin), and in our institution essentially all patients with coronary disease are treated with these medications. Other classes of lipid-lowering medications are also used, including niacin, which has a greater effect to raise HDL (the "good cholesterol") levels, and ezitimibe, which is a medication that specifically blocks the absorption of cholesterol in the intestines. These medications are usually continued lifelong.

- Antihypertensive agents - in addition to the use of ACE inhibitors, patients who remain hypertensive may require one or more additional medications to control their blood pressure. These medications can also come from several different categories, including diuretics and medications that block adrenaline-like effects on the heart and blood vessels.
- Antidiabetic agents - patients with diabetes should have their diabetes as well-controlled as possible and many of our patients with coronary disease are diabetic and require such control. It is not uncommon for these patients to be on two or three antidiabetic drugs.

In addition to the medications listed above, it is also common for these patients to be on additional medications, including medications for acid reflux and for anxiety and depression. It is not uncommon for patients to be on as many as 10 medications and a large majority of patients will be (and should be) on at least four or five.

Q: As a follow-up question, how much do statins lower the risk of a heart attack in patients who take them?

A: Statins lower the risk by approximately 30%.

Q: Do the drugs have side effects?

A: Yes. While most of these classes of drugs are generally safe and the side effects are reversible, they can be at times distressing and interfere with medication adherence. The statins used to lower cholesterol can cause muscle aches and stomach distress and in very rare cases can cause more serious disorders including rhabdomyolysis (muscle breakdown) and liver damage. Beta-blockers can cause fatigue, impaired exercise performance, cognitive dysfunction, and

impotence. ACE inhibitors cause a cough in about 10% of patients. All antihypertensive agents can at times cause excessive drops in blood pressure. Aspirin can cause bleeding as can other anti-clotting agents.

Q: Do they otherwise impact patient's lives?

A: Having to take many medications certainly has an effect on patient's lives. At the very least the patient is constantly reminded that he has a medical problem, and the need to take medications, especially if medications need to be taken several times daily, can intrude on normal activities. Many patients fail to adhere to medication regimens, with the consequence that the desired effect does not occur. In addition, certain classes of medications, including beta-blockers, antihypertensives, and niacin can have undesirable and at times dangerous rebound effects if the medication is taken erratically.

Q: What determines treatment outcomes?

A: The outcome for any individual patient depends on a number of factors, including the presence or absence of other chronic illnesses, age, the rapidity with which the patient reaches the hospital, the size of the myocardial infarction, and ultimately, behavioral factors relating to the patient's ability to adhere to lifestyle change and pharmaceutical recommendations. There is also a large subset of patients who come in with chest pain and either have smaller myocardial infarctions or in fact have what is generally referred to as unstable angina, a situation where a myocardial infarction is threatened but has not yet occurred. In such a situation the therapy is not much different than that for an infarct itself: the risk factors are the same and need to be treated

the same, cardiac catheterization is indicated to define and treat arterial narrowing and prevent sudden blockages, and the lifestyle and pharmaceutical interventions are similar.

Q: What do you advise patients with coronary heart disease who are smokers, if anything?

A: I advise patients in the strongest possible terms that quitting smoking is an absolute necessity and that we will support them in every possible way in making this change. I spend considerable time talking about smoking because of its extraordinary importance. I tell my patients that even after a heart attack, quitting smoking has a very powerful beneficial effect, and that quitting smoking is the equivalent of lowering cholesterol 100 points, as reported by the Multiple Risk Factor Intervention Trial.

Q: When did you start providing such advice to patients?

A: I cannot remember a time in my career when I did not advise patients to stop smoking. As you can see from my *curriculum vitae*, as early as 1980 I was involved in papers describing counseling for smoking cessation in patients at risk for coronary disease. But well before then, even as a trainee in internal medicine and in cardiology, I counseled patients to stop smoking, as it was certainly clear in the early 1970s that smoking was quite harmful.

Q: In your opinion, was there sufficient evidence establishing smoking as a cause of cardiovascular disease at that time to warrant the advice that patients stop smoking?

A: Yes**.**

Q: What types of scientific evidence support your opinion?

A: By the 1960s substantial evidence was already accumulating that there was a connection

between cigarette smoking and coronary disease. From 1950-1960 statements based upon the accumulated evidence were issued by a number of organizations. These included the British Medical Research Council; the cancer societies of Denmark, Norway, Sweden, Finland, and the Netherlands; the American Cancer Society; the American Heart Association; the Joint Tuberculosis Council of Great Britain; and the Canadian National Department of Health and Welfare. The consensus, publicly declared, was that smoking is an important health hazard, particularly with respect to lung cancer and cardiovascular disease. In 1962 the Royal College of Physicians of London issued a report which concluded that "Cigarette smoking is a cause of lung cancer and bronchitis, and probably contributes to the development of coronary heart disease." The 1964 Surgeon General's report on Smoking and Health reviewed seven prospective studies which had been conducted since 1951. In all seven studies, coronary artery disease is the chief contributor to the excess number of deaths of cigarette smokers over non-smokers, with lung cancer uniformly in second place. For all seven studies combined, coronary artery disease (with a mortality ratio of 1.7) accounts for 45 percent of the excess deaths among cigarette smokers, whereas lung cancer (with a ratio of 10.8) accounts for 16 percent. The seven studies were as follows: (1) British doctors, a questionnaire having been sent to all members of the medical profession in the United Kingdom by Doll and Hill, 1956; (2) white American men in nine states. These men were enrolled by a large number of American Cancer Society volunteers, each of whom was asked to have the questionnaire filled in by 10 white men between the ages of 50 and 69. Hammond and Horn, 1958.; (3) policyholders of U.S. Government Life Insurance policies, available to persons who served in the armed forces between 1917 and 1940. Dorn, 1958; (4)

men aged 35-64 in nine occupations in California who were suspected of being subject to a higher than usual occupational risk of developing lung cancer. Dunn, Linden and Breslow, 1960; (5) California members of the American Legion and their wives. Dunn, Buell and Breslow. 1964; (6) Pensioners of the Canadian Department of Veterans Affairs, i.e., veterans of World Wars I and II and the Korean War. Best, Josie and Walker, 1961; and (7) American men in 25 states, enrolled by volunteer researchers of the American Cancer Society, each of whom was asked to enroll about 10 families containing at least one person over 45. Hammond, 1963.

The 1964 Surgeon General's report took the very conservative approach of stating the following: "Although the causative role of cigarette smoking in deaths from coronary disease is not proven, the Committee considers it more prudent from the public health viewpoint to assume that the established association has causative meaning than to suspend judgment until no uncertainty remains." That uncertainty was gone by the 1979 report, which concluded that "smoking is causally related to coronary heart disease in the common sense of that idea." But for myself and my colleagues, the overwhelming weight of the evidence by the late 1960s (when I began to treat patients as a house officer) was sufficient to lead us to conclude that smoking was a major causal factor in CHD, and to act upon that conviction.

By the 1983 Surgeon General's Report, the following conclusions were well known to anyone who followed the literature:

1. Cigarette smoking is a major cause of coronary heart disease in the United States for both men and women. Because of the number of persons in the population who smoke and the

increased risk that cigarette smoking represents, it should be considered the most important of the known modifiable risk factors for CHD.

2. Overall, cigarette smokers experience a 70 percent greater CHD death rate than do nonsmokers. Heavy smokers, those who consume two or more packs per day, have CHD death rates between two and three times greater than nonsmokers.
3. The risk of developing CHD increases with increasing exposure to cigarette smoke, as measured by the number of cigarettes smoked daily, the total number of years one has smoked, and the degree of inhalation, and with an early age of initiation.
4. Cigarette smokers have a twofold greater incidence of CHD than do nonsmokers, and heavy smokers have an almost fourfold greater incidence.
5. Cigarette smoking is a major independent risk factor for CHD, and it acts synergistically with other risk factors (most notably, elevated serum cholesterol and hypertension) to greatly increase the risk of CHD.
6. Women have lower rates for CHD than do men. In particular, CHD rates for women are lower prior to the menopause. A part of this difference is due to the lower prevalence of smoking in women, and for those women who do smoke, to the tendency to smoke fewer cigarettes per day and to inhale less deeply. Among those women who have smoking patterns comparable to male smoking patterns, the increments in CHD death rates are similar for the two sexes.

7. Cigarette smoking has been found to significantly elevate the risk of sudden death. Overall, smokers experience a two to four times greater risk of sudden death than nonsmokers.
8. Cigarette smoking has been estimated to be responsible for up to 30 percent of all CHD deaths in the United States each year.
9. Cessation of smoking results in a substantial reduction in CHD death rates compared with those of persons who continue to smoke.

Q: Have these conclusions been confirmed in subsequent studies?

A: Yes. Perhaps the most striking of these is the 50 year follow-up of the British Doctors Study that was reported in the British Medical Journal in 2004. This of course was one of the primary studies cited in the 1964 Surgeon General's report, but at that time the follow-up had been relatively limited. Now with an additional 40 years of follow-up the patterns of disease caused by cigarette smoking are even more strongly confirmed. The findings can be summarized as follows:

- The smokers in this study died an average of 10 years earlier than lifelong non-smokers. The long-term follow-up demonstrates that the excess mortality is even greater than previously estimated. In this study the probability of dying in middle age (35 to 69) was 42% in the smokers versus 24% in the nonsmokers. The study suggests that half to two thirds of all persistent cigarette smokers will die prematurely from a disease related to their smoking habit.

- The earlier in life smoking was adopted the greater the burden. Prolonged cigarette smoking from early adult life tripled age-specific mortality rates.
- The benefit of smoking cessation is clear, and the earlier the age at which cessation occurred the greater the benefit. Cessation at age 50 halved the hazard, and cessation at age 30 avoided almost all of the risk.
- Although cessation earlier in life produced greater benefits, cessation at almost any age was of value. Cessation at age 60, 50, 40, or 30 years of age gained, respectively, approximately 3, 6, 9, or 10 years of life expectancy.
- The study also demonstrated that the progressive increase in life expectancy that occurred among nonsmokers over the period of the study was not seen in the smokers, whose life expectancy actually decreased. Thus all the benefits of modern medicine which have produced the progressive increase in life expectancy in the general population were not seen in the smokers.

Doll R, Peto R, Boreham J, Sutherland I. Mortality in relation to smoking: 50 years' observations on male British doctors. BMJ 2004; 328:1519.

Q: When discussing the 1983 Surgeon General's Report, you cited the dramatic benefit to be derived from smoking cessation. Can you explain that further for the Court?

A: As I noted previously, smoking plays a role in both the gradual multi-year atherosclerotic process that leads to plaque development and gradual narrowing of the arteries, as well as in the last-straw phenomena that lead to plaque disruption and arterial clot formation with subsequent occlusion of the artery leading to a myocardial infarction. Because smoking plays such a large

role in those factors that relate to the onset of clinical events, smoking cessation leads to rapid benefit. Very rapidly after stopping smoking platelet function improves, endothelial function improves, and the vascular spasm induced by cigarette smoking disappears. Smoking is also one of the primary causes of sudden death, and this tendency towards lethal arrhythmias also improves very rapidly following smoking cessation. It is worth noting that smoking is the only risk factor that can be totally and essentially instantaneously removed: from the moment of hospitalization the smoker becomes an ex-smoker, at least for the duration of the hospital stay.

Q: Can you explain for the Court how platelet function improves after smoking cessation?

A: Smoking affects many aspects of vascular function in a harmful manner. The mechanisms of action of cigarette smoking on the microcirculation include compromised endothelial-dependent voasorelaxation (the vessel does not dilate appropriately in response to stress), platelet aggregation (the platelets have an increased tendency to clump together, increasing the likelihood of clotting within the vessel), endothelial cell dysfunction (the endothelium is the inner lining of the blood vessel – these cells are crucial in determining whether arteries respond appropriately to stress, and whether or not lipids infiltrate into the vessel wall) and the activation of circulating leukocytes (such activation leads to harmful inflammation within the vessel wall, and thereby also encouraging spasm and clotting). Cigarette smokers, but not former smokers, excrete more thromboxane A2 (TxA2) metabolites in the urine than do lifelong nonsmokers, which suggests chronic activation of their platelets. Within 3 days after quitting smoking, 2,3-dinor (Tx-M) and 11-dehydro (dTx) metabolites of TxA2 drop to stable levels of approximately 300 and 350

pg/mg, respectively from 550 and 600 pg/mg creatinine, respectively at baseline. Cigarette smoking also elicits an increase in platelet activity in the absence of vascular injury which is reversible within the life span of the platelets.

Q: What is the significance of improved platelet function for prevention of cardiovascular disease?

A: Platelets participate in the clotting process whereby plaque rupture leads to abrupt occlusion of an artery as a clot forms and prevents blood flow. Improving platelet function diminishes the likelihood of vascular occlusion by clot.

Q: How does endothelial function improve after smoking cessation?

A: Endothelial function deteriorates with smoking and rapidly improves after smoking cessation. Cigarette smoking is associated with dose-related and potentially reversible impairment of endothelium-dependent dilation in healthy young adults. Refraining from cigarette smoking for a few days results in a significant drop of plasma, serum, and urinary 8-epi-PGF(2alpha) (markers of oxidation within the vascular system, associated with endothelial dysfunction) . Thereafter, a further continuous decrease is seen, reaching a steady state after about 4 weeks after quitting cigarette smoking. These results indicate that exsmokers may rapidly recover from their enhanced in vivo oxidation, as quitting cigarette smoking results in a fast improvement of in vivo oxidation injury (determined via plasma, serum and urinary isoprostane).

Q: Please explain the significance of improved endothelial function for the prevention of cardiovascular disease.

A: Proper functioning of the endothelium is critical to the prevention of vascular disease. If the endothelium does not respond appropriately to stressors, vessel dilatation does not occur and this abnormal response to stress increases the likelihood of plaque rupture and vasospasm. Improvement of endothelial function with smoking cessation reduces the risk of such events by restoring the appropriate blood vessel responses to stressors.

Q: And briefly, can you explain what the significance is of the disappearance of vascular spasm?

A: Vascular spasm can produce a sudden diminution in blood flow, thereby threatening the blood supply to down stream cardiac muscle. In addition, vascular spasm can result in plaque rupture which then results in clot formation and abrupt arterial occlusion. Removing such an abnormal and deleterious factor is beneficial in reducing the likelihood of these harmful effects.

Q: How immediate are the health benefits from smoking cessation, in terms of reduction in risk of cardiovascular disease?

A: The benefit is very rapid, as evidenced by research studying the reduction in risk with cessation of smoking. Numerous studies, cited in Surgeon General's Reports and elsewhere, have repeatedly reached the conclusions that there are significant measurable reductions in excess cardiovascular disease risk upon cessation in both men and women within the first few months after cessation, and within a few years, excess risk attributable to smoking may disappear entirely. These results reinforce the importance of smoking cessation.

There are even studies showing no correlation between the risk of sudden coronary death and the number of years without smoking - in other words, the decline in risk of sudden coronary

death with smoking cessation has been shown to be essentially immediate and not time-dependent. This is particularly interesting in that the vascular factors affected by smoking - endothelial function, vasospasm, platelet function and clotting - also play an important role in causing the abrupt vascular occlusions that are the primary cause of sudden death.

Q: Does the immediate benefit from cessation distinguish smoking and cardiovascular disease from smoking and other disease?

A: It does. For chronic lung disease, for instance, smoking cessation will lead to a reduction in the rate of destruction of lung tissue, but cannot lead to improvements in the permanent anatomic pulmonary destruction that has already occurred. And, at the opposite extreme, even 10 years out from smoking cessation no benefit can be demonstrated with regard to the markedly increased risk of lung cancer that smoking imposes, and it may take as many as 15 to 20 years before benefit can be observed. This may relate to our understanding that once a cell has been damaged and turned potentially cancerous by a toxin such as smoking, that cell or group of cells may lie dormant for many years before developing into a clinically evident cancer.

Q: Do you specifically advise patients to seek smoking cessation therapy?

A: Yes, and we have resources available, both within our institution and within the community.

Q: What types of therapy do you customarily refer them to?

A: I refer patients to various forms of counseling and support, depending on their needs. At UMass we have a superb smoking cessation program and I refer many patients for both

individual and group counseling. The State of Massachusetts also has a state-wide telephone counseling program called "Quitworks," to which we refer many patients.

Q: Dr. Ockene, in your opinion, would the number of smoking-related myocardial infarctions be significantly reduced with a reduction in the number of persons who smoke?

A: Yes. There is simply no doubt about this. There is overwhelming evidence that smoking cessation is of extraordinary value in preventing both fatal and nonfatal myocardial infarctions, and this is true both for primary prevention (patients who do not yet have known heart disease) and secondary prevention (patients who have already suffered a myocardial infarction or other manifestation of coronary disease.)

Q: In your opinion, would the incidence of coronary heart disease be significantly reduced with a reduction in the number of persons who smoke?

A: Yes. Again, the evidence is simply overwhelming, as described in many of the sources that I considered in the preparation of my testimony. The list of sources considered is included as an Appendix to my testimony.

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