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UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

STONEWALL INSURANCE COMPANY, Plaintiff, - against - ASBESTOS CLAIMS MANAGEMENT CORPORATION f/k/a NATIONAL GYPSUM COMPANY, et al., Defendants.	No. 86 Civ 9671 (JMS)

DIRECT EXAMINATION OF J. CARL BARRETT,
ASBESTOS CLAIMS MANAGEMENT CORPORATION'S
EXPERT WITNESS REGARDING THE COMMENCEMENT AND
DEVELOPMENT OF ASBESTOS-RELATED LUNG CANCER AND MESOTHELIOMA

DIRECT EXAMINATION OF
J. CARL BARRETT,

I. Introduction

1. My name is J. Carl Barrett. I have been requested by Asbestos Claims Management Corporation ("ACMC") to provide testimony in this action regarding the commencement and development of asbestos-related lung cancers and mesothelioma.

2. Attached hereto as Exhibit A is a copy of my Curriculum Vitae.

3. By way of general background, I am a research scientist who has a Ph.D. in Biophysical Chemistry and who specializes in the field of molecular biology and molecular carcinogenesis. Molecular carcinogenesis is the study of the development of cancer at a molecular, genetic and cellular level.

4. For the past twenty years, I have been employed by National Institute of Environmental Health Sciences, or NIEHS. Since 1995, I have been the Scientific Director of the Division of Intramural Research for NIEHS. I am also chief of the Laboratory of Molecular Carcinogenesis and head of the Cancer and Research Aging Group. I have overall responsibility for the activities of the 700 NIEHS employees and scientists who are involved in the in-house, or intramural, research component of the institute. I also oversee 10 independent investigators in the Laboratory of Molecular Carcinogenesis and direct the research of approximately 15 scientists in my personal research group.

5. Prior to my current position, I was the Director of the Program of Environmental Carcinogenesis for NIEHS. In that position, I was in charge of the 100 NIEHS employees who were involved in doing research regarding environmental factors which contribute to carcinogenesis. I held that position from 1992 until 1995.

6. Since 1987, I have been the Chief of the Laboratory of Molecular Carcinogenesis. Before that, starting in 1977, I was a group leader in the Environmental Carcinogenesis Group of the Laboratory of Pulmonary Pathobiology.

7. Before starting at NIEHS, I received a Bachelor of Science Degree in Chemistry from the College of William and Mary in 1969 and a Ph.D. in Biophysical Chemistry from the Johns Hopkins University in 1974. I was then a postdoctoral fellow at Johns Hopkins University until I joined NIEHS.

8. I have been investigating the processes by which cancers begin, develop and spread for over 24 years. During that time, I have personally performed and/or overseen hundreds of studies designed to help us understand the environmental, genetic and biological factors that contribute to the development of cancer. I have also published 6 books and over 320 articles, reviewed the studies and publications of other researchers, and taught and chaired and/or participated in numerous conferences and lectures on this subject.

9. I have studied asbestos-related lung cancers and mesothelioma for years. In that time, I have personally conducted and/or overseen numerous studies concerning the mechanisms of asbestos fibers as they relate to development of lung cancers and mesothelioma. I have also written articles, reviewed the work of other researchers and lectured on this subject.

10. I am a member of the American Association for Cancer Research, the American Society for Cell Biology, the Society of Toxicology, the American Chemical Society and the American Association for the Advancement of Science.

II. Testimony and Opinions

A. Characteristics of Cancer

11. I have been requested to provide testimony regarding the commencement and progression of asbestos-related lung cancers and mesothelioma, a cancer of the pleura or lining of

the lungs. My fundamental opinion, which I discuss in greater detail below, is that cancers related to asbestos exposure develop through a continuous, multi-step process that commences shortly after exposure to the asbestos fiber and progresses by the accumulation of multiple mutations in the cell which becomes the cancer and by the proliferation of those mutated cells over decades until the point the cancer is diagnosable by traditional pathological techniques. Mutations are stable, heritable alterations in the genetic material known as deoxyribonucleic acid or DNA, of a cell.

12. Let me begin by defining cancer. Cancer is a generic name for a series of disease processes that share certain common attributes. Specifically, cancer cells are characterized by their ability to grow unchecked and to spread or metastasize to different sites in the body. All cancers that we have studied, including asbestos-related lung cancers and mesothelioma, involve a multi-step process by which multiple mutations in a cell occur over time. The process by which the mutations occur and accumulate takes place on a continuous basis over a period of years.

13. Genes are the units in the genetic material (DNA) that specify different properties of a cell or individual. When altered or mutated, these alterations can be harmless (e.g., blue eyes become brown eyes) or they can be harmful, (e.g., causing cells to lose their growth control and become cancer cells). Among the genes that are mutated during the cancer development process are those that regulate the replication of cells, those that regulate the death of cells , and those that regulate the ability of the cell to invade and metastasize. If unchecked, these mutations will accumulate to the point where the altered cells are replicating at a much greater rate than they are dying, and they will metastasize to distant locations in the individual. A cancer cell requires mutations in multiple genes to reach this point. This process, given sufficient time, will lead to death.

14. Typically, it takes anywhere between 20 and 40 years, and sometimes longer, between the time that the cancer process begins and when the cells have accumulated enough genetic and cellular changes that the cancer can be identified by pathological diagnostic techniques currently available. During these decades, the cells that are accumulating the mutations are replicating themselves and growing in the host body through a process called clonal expansion, which I describe in greater detail below.

15. There are various known causes of cancer. Certain cancers may be caused by inherited mutations. In addition, exposure to various environmental factors, such as radiation, cigarette smoke and certain fibers, can also cause cancer. Since cancers involve multiple steps, all cancers probably have multiple causes.

16. Asbestos is an established carcinogen. As discussed below, exposure to asbestos fibers can contribute to both the early and late stages of lung cancer and mesothelioma.

17. Asbestos-related lung cancers and mesothelioma have the same attributes as other cancers—multiple genetic and cellular changes that occur on a continuous basis over decades, and the proliferation of mutated cells through clonal expansion.

B. Mechanisms By Which Asbestos Cause and Contribute to Cancer

18. There are multiple mechanisms by which asbestos initiates and promotes the development of lung cancer and mesothelioma. Asbestos fibers can (i) interfere with chromosome segregation during cell division causing daughter cells to have too many or too few genes; (ii) stimulate the formation of reactive oxygen species that, in turn, can cause mutation of cells and/or stimulate cell growth; or (iii) cause the release of cytokines that also can lead to stimulated growth. Each of these mechanisms are discussed below.

(1) Interference With Chromosome Segregation

19. I will begin by explaining how asbestos can directly interfere with chromosome segregation. All human cells contain 23 pairs of chromosomes, which are linear structures that contain the DNA that is responsible for determining the characteristics of a person. Cells periodically replicate themselves through cell division, also known as mitosis. During mitosis, the identical pairs of chromosomes separate from each other, forming two new or daughter cells. During normal mitosis, each of the two daughter cells receive an exact copy of their genetic material of the original cell.

20. When an asbestos fiber enters the body, it can penetrate the membrane of, and be taken up into, an individual cell. This is known as phagocytosis and it can occur within 24 hours of when the fiber contacts a cell. Within those 24 hours, the fiber moves to the perinuclear region of the cell, the region surrounding the nucleus where the chromosomes are. As has been shown in studies by myself and others, the asbestos fiber can then interfere with normal mitosis by physically contacting a chromosome. This physical interaction can interfere with the precise segregation of chromosomes, leaving one of the daughter cells with too many chromosomes and the other with too few. The state of a cell having too few or too many chromosomes is known as aneuploidy. The physical interaction of a fiber with a chromosome can also result in the deletion of part of an individual chromosome. In either aneuploidy or chromosome deletion, one or both of the daughter cells have changed, or mutated, from the original parent cell. This mutation may be the first of many that lead to lung cancer or mesothelioma.

21. Some of the studies that have established that asbestos can interfere with the segregation of chromosomes during mitosis are Hesterberg, Thomas W. and Barrett, J. Carl, Carcinogenesis, Vol. 6 no. 3 pp. 473-475, 1985; Oshimura, Mitsuo, Hesterberg, Thomas W., Tsutsui, Takeki and Barrett, J. Carl, Cancer Research 44, 5017-5022, November 1984; Libbus, Bisharah L., Illenye, Sharon A., Craighead, John E, Cancer Research 49, 5713-5718, October 15,

1989; Hesterberg, Thomas W. and Barrett, J. Carl, Cancer Research 44, 2170-2180, May 1984; Oshimura, Mitsuo, Hesterberg, Thomas W. and Barrett, J. Carl, Cancer Genet Cytogenet 22:225-237 (1986); Hesterberg, Thomas W., Butterick, Charles J., Oshimura, Mitsuo, Brody, Arnold R. and Barrett, J. Carl, Cancer Research 46, 5795-5802, November 1986); Brody, Arnold R., Hill, Lila H., Hesterberg, Thomas W., Barrett, J. Carl and Adler, Kenneth B., The Cytoskeleton, Edited by Thomas W. Clarkson, Polly R. Sager, and Tore L.M. Syversen (Plenum Publishing Corporation 1986); Barrett, J. Carl, Cellular and Molecular Aspects of Fiber Carcinogenesis, 1991 Cold Spring Harbor Laboratory Press.

22. Through aneuploidy or chromosome deletion, asbestos can either activate or inactivate mutations certain genes that play a particularly important role in the development of cancer. We refer to these as cancer genes. These genes regulate the rate at which cells divide, die and metastasize, and can be placed in different categories depending on their function. One category consists of oncogenes. When activated, these genes, which include those named RAS and MYC, cause cells to divide at a faster rate. This increased mitotic rate has at least two consequences. First, mutated cells will increase in numbers more quickly than normal cells. Second, the increased mitotic activity increases the possibility for mutation through an increased number of cells at risk, causing yet additional alterations in the cells on the way to them becoming pathologically diagnosable as cancer. Another type of cancer gene, of which p53, Rb, and BRCA1 are examples, is what we refer to as a tumor suppressor gene. These genes retard cell proliferation and/or help maintain the integrity of the DNA. If these genes are inactivated, cells divide at a faster rate, thereby again increasing the number of mutated cells in the body. This increased mitotic rate also increases the chances for mutations.

23. Mutations can either be induced by environmental agents or occur spontaneously. Spontaneous mutations are mutations that occur without a known cause, possibly as a consequence of rare errors in the normal process of cell division. The activation of

oncogenes and the inactivation of tumor suppressor genes increase the rate of cell division, thereby increasing the chances for a spontaneous mutation. Increased chances for spontaneous mutations, in turn, increases the chances for accumulation of mutations of cancer genes that results in the development of cancer. Some of the studies that have discussed oncogenes and tumor suppressor genes are Fearon E.R. and Vogelstein, B. Cell 61:759-767, 1990; Sugimura, T. Science 258:603-607, 1992; Lechner, J.F., Tesfaigzi, J., and Gerwin, B.I. Environmental Health Perspectives 105 (Suppl 5):1061-1067, 1997.

24. The amount of time between when an asbestos fiber enters the body and when it causes mutation through aneuploidy or chromosome deletion can be quite short. Although many of the fibers are cleared from the lungs, those that remain may be phagotasized by the lung cell or mesothelial cell and make their way to the perinuclear area possibly within 24 hours from when the fiber contacts the cell. The time when the fiber actually induces mutations will depend on when the cell goes through mitosis. This, in turn, depends on a number of factors, including, but not limited to, what kind of cell it is, when the cell last divided, whether there are any environmental factors that are accelerating or inhibiting mitosis and whether any of the genes regulating mitosis have already been altered through asbestos exposure or other means. Thus, we do not know precisely when any particular cell will divide. It can be hours, days, weeks or years. Normal lung cells tend to go through mitosis approximately every few days. Studies that support this include The Lung. Structure, Function and Disease by 23 Authors. (International Academy of Pathology Monograph) Thurlbeck, W.M. and Abell, M.R., Eds. Williams & Wilkins:Baltimore, 1978, pp. 143-145. Thus, a normal lung cell that has phagotasized an asbestos fiber but has not been previously altered and is not being influenced by other environmental factors will most likely divide no later than a few weeks after the asbestos fiber enters the body. Generally speaking, normal mesothelial cells divide at a slower rate than lung cells The life span of a pleural mesothelial in the rate is estimated as 33 days. Studies that support this include The Pleura in

Health and Disease. Chretien, J., Bignon, J., and Hirsch, A., Eds. Marcel Dekker:New York/Basel, 1985, pp. 23, 36, 39, 41, 42. Thus, a normal mesothelial cell that has not been previously altered through asbestos exposure or otherwise and which is not subject to other environmental factors will probably divide within a few weeks or months after the asbestos fiber enters the mesothelium, as shown by Adamson, I.Y.R. Environmental Health Perspectives 105 (Suppl 5):1205-1208, 1997.

25. With both lung cells and mesothelial cells, if the cell has already gone through a previous mutation that has activated oncogenes or inactivated tumor suppressor genes, because of asbestos exposure or otherwise, the new mutations caused through this additional asbestos exposure may occur even more quickly.

(2) The Production of Reactive Oxygen Species

26. A second means by which asbestos can initiate or promote cancer is the production of reactive oxygen species. Reactive oxygen species are reactive chemical derivatives of oxygen produced by chemical reactions or by enzymes made by the cells. Asbestos fibers may be phagocytosized, or partially enveloped, by cells called macrophages whose function is to clear foreign substances from the body. To destroy such foreign particles, the macrophages produce reactive oxygen species. Other cells, including lung and mesothelial cells, may also take up fibers and produce reactive oxygen species during this process.

27. Reactive oxygen species that are produced by the interaction of asbestos fibers with macrophages or with lung or mesothelial cells can cause and/or contribute to the development of lung cancer or mesothelioma in two ways. First, the reactive oxygen species can directly cause the mutation of genes by interacting directly with DNA or with cell membranes to produce reactive products that can cause gene mutations. Second, reactive oxygen species can also cause cells to divide at an increased rate by either stimulating production of cytokines and growth facts, discussed below, or by killing cells, which, in turn, causes other cells in the area to

proliferate more rapidly to compensate for the dead ones. As I described before, increased cell proliferation increases the chances for spontaneous mutations, which may contribute to different steps in the development of pathologically diagnosable cancer.

28. In addition to commencing a cancer process, reactive oxygen species can also contribute to the development of a cancer process that has already begun through the same two mechanisms-- by directly causing new mutations in initiated cells or by increasing the rate of division of cells that have already been altered by prior asbestos exposure or through other means to divide at a greater rate. That greater rate of cell division will cause the already mutated cells to increase in number in the host body and will also increase the chances for spontaneous mutations. Asbestos fiber can cause the production of reactive oxygen species within minutes or hours after contact with cells. The reactive oxygen species can cause direct gene mutation in that period of time. Studies that have established this fact are reviewed by Walker C., Everitt, J., and Barrett, J.C. American Journal of Industrial Medicine 21:253-273, 1992; Kane, A.B. In: Mechanisms of Fibre Carcinogenesis; Kane, A.B., Boffetta, P., Saracci, R., and Wilbourn, J.D. (Eds.). IARC Scientific Publications No. 140; International Agency for Research on Cancer, Lyon, 1996, pp. 11-34, Jaurand, M.-C. In: Mechanisms of Fibre Carcinogenesis. Kane, A.B., Boffetta, P., Saracci, R., and Wilbourn, J.D. (Eds.). IARC Scientific Publications No. 140; International Agency for Research on Cancer, Lyon, 1996, pp. 55-71. In addition, the reactive oxygen species can cause increased cell proliferation within hours to days. Studies that have shown this effect are reviewed in Walker C., Everitt, J., and Barrett, J.C. American Journal of Industrial Medicine 21:253-273, 1992; Kane, A.B. In: Mechanisms of Fibre Carcinogenesis. Kane, A.B., Boffetta, P., Saracci, R., and Wilbourn, J.D. (Eds.) IARC Scientific Publications No. 140. International Agency for Research on Cancer, Lyon, 1996, pp. 11-34; Jaurand, M.-C. In: Mechanisms of Fibre Carcinogenesis. Kane, A.B., Boffetta, P., Saracci, R., and Wilbourn, J.D. (Eds.). IARC Scientific Publications No. 140. International Agency for Research on Cancer, Lyon, 1996, pp. 55-71;

Driscoll, K.E. In: Mechanisms of Fibre Carcinogenesis. Kane, A.B., Boffetta, P., Saracci, R., and Wilbourn, J.D. (Eds.). IARC Scientific Publications No. 140. International Agency for Research on Cancer, Lyon, 1996, pp. 73-96.

29. Most oxygen free radicals are short lived and active only for a few seconds or minutes. However, more stable intermediates can be produced by reaction of reactive oxygen species with cell membrane components. This produces reactive intermediates that may induce the same effects as oxygen free radicals themselves.

(3) The Release of Cytokines

30. A third mechanism through which asbestos exposure can cause or contribute to cancer is through the release of cytokines. More specifically, when asbestos fibers are taken up by non-target cells such as macrophages, cytokines are released.[1] These cytokines send chemical signals which call more macrophages to come to the site of a foreign substance to help eliminate it. The release of the cytokines causes the proliferation of target cells, much like reactive oxygen species. Studies that have demonstrated this effect are reviewed in Walker C., Everitt, J., and Barrett, J.C. American Journal of Industrial Medicine 21:253-273, 1992; Kane, A.B. In: Mechanisms of Fibre Carcinogenesis. Kane, A.B., Boffetta, P., Saracci, R., and Wilbourn, J.D. (Eds.). IARC Scientific Publications No. 140. International Agency for Research on Cancer, Lyon, 1996, pp. 11-34; Jaurand, M.-C. In: Mechanisms of Fibre Carcinogenesis. Kane, A.B., Boffetta, R., Saracci, R., and Wilbourn, J.D. (Eds.). IARC Scientific Publications No. 140. International Agency for Research on Cancer, Lyon, 1996, pp. 55-71; Driscoll, K.E. In: Mechanisms of Fibre Carcinogenesis. Kane, A.B., Boffetta, P., Saracci, R., and Wilbourn, J.D.

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[1] Target cells, in this context, are the cells that give rise to the asbestos associated cancer, i.e., the lung epithelial cells for lung cancer and the mesothelial cells for mesotheliomas. Non-target cells are cells that are damaged by the fibers, such as macrophages, but do not develop into cancer cells. As I just discussed, damage to non-target cells may contribute to the development of cancer in the target cells during the cancer process.

(Eds.). IARC Scientific Publications No. 140. International Agency for Research on Cancer, Lyon, 1996, pp. 73-96.

31. Increased proliferation that results from cytokines causes an increased opportunity for spontaneous mutations, which, as discussed, in turn can lead to pathologically diagnosable cancer. In addition, the cytokines can lead to increased proliferation of cells that have already been mutated by prior asbestos exposure or other means. Cytokines start causing this increased cell division within hours or days of when the asbestos fiber enters the host body. Studies that discuss this phenomenon are reviewed in Walker C., Everitt, J., and Barrett, J.C. American Journal of Industrial Medicine 21:253-273, 1992; Kane, A.B. In: Mechanisms of Fibre Carcinogenesis. Kane, A.B., Boffetta, P., Saracci, R., and Wilbourn, J.D. (Eds.). IARC Scientific Publications No. 140. International Agency for Research on Cancer, Lyon, 1996, pp. 11-34; Jaurand, M.-C. In: Mechanisms of Fibre Carcinogenesis. Kane, A.B., Boffetta, R., Saracci, R., and Wilbourn, J.D. (Eds.). IARC Scientific Publications No. 140. International Agency for Research on Cancer, Lyon, 1996, pp. 55-71; Driscoll, K.E. In: Mechanisms of Fibre Carcinogenesis. Kane, A.B., Boffetta, P., Saracci, R., and Wilbourn, J.D. (Eds.). IARC Scientific Publications No. 140. International Agency for Research on Cancer, Lyon, 1996, pp. 73-96.

32. Each of the mechanisms by which asbestos can cause cancer – the direct interference of fibers with mitosis, the direct mutation of genes and the increased proliferation of cells from reactive oxygen species produced by asbestos exposure and the increased proliferation of cells through the release of cytokines—can commence or contribute to the cancer process within hours to days of the asbestos entering the host body. Studies that provide evidence in support of this fact are reviewed in references cited previously.

C. The Development of Asbestos-Related Cancer

33. Based on the work of numerous cancer researchers, it is well established that cancer is a multi-step, continuous process. For a cancer to develop to the point that it is

pathologically diagnosable, cells must accumulate a number of mutations to the critical cancer genes that I discussed previously. These mutations, which cause the activation of oncogenes, thereby stimulating cell proliferation, and the inactivation of tumor suppressor genes, thereby removing the brakes on cell proliferation, occur over time.

34. In my opinion, the cancer process commences with the mechanism that leads to the first cancer gene mutation. That first mutation is passed on to two daughter cells. When the daughter cells divide, they pass the mutation to their daughter cells. These altered cells, each carrying the same mutation, are called a clone and the process by which the mutations are passed on to generations of daughter cells is known as clonal expansion. Eventually, additional mutations occur in the clone of cells carrying the first mutation through any number of possible mechanism, including a) mitosis interference by another asbestos fiber; b) mutation due directly to reactive oxygen species; c) spontaneous mutation resulting from normal cell proliferation; d spontaneous mutation resulting from increased proliferation due to the production of reactive oxygen species or cytokines, or e) some other environmental exposure. The cell that contains the two mutations will then divide, passing on those two mutations to its daughter cells, generating another clone and additional clonal expansion. The cancer process continues on until a third, fourth and possibly many other mutations occur through one of the same mechanisms and is called clonal evolution.

35. Eventually, sufficient mutations occur changing the identifiable characteristics of the cells, and a sufficient number of cells accumulate, containing the multiple mutations, such that the cancerous process can be diagnosed by the pathological methods currently available.

36. It is important to understand that asbestos can contribute to the cancer process and cause additional injury at any stage of the process. It can directly cause the first mutation. It can directly cause the second mutation. It can cause increased cell proliferation that leads to the second mutation, and so forth. In other words, asbestos can play a role at any time from before

the first mutation occurs and the cancer actually begins up until and past when the cancer is pathologically diagnosable.

37. Even when asbestos is not directly leading to or causing new mutations, cells that are already carrying mutations from asbestos exposure that have already accumulated to that point in time are continuing to proliferate, putting more damaged cells into the host body. Further, to the extent that the mutated cells have come into contact with reactive oxygen species and cytokines produced because of asbestos, the mutated cells accumulate in the host at an increased rate. As a consequence, as time goes on, the person has more and more damaged cells being induced and dividing in his or her body.

D. Diagnosis of Asbestos-Related Cancer

38. It takes decades from when asbestos-related lung cancer and mesothelioma begin to become diagnosable by conventional pathological means. Before such a diagnosis can be made, three things typically must happen. First, the cancerous cells must have accumulated multiple mutations to critical cancer genes. Second, the cells that contain the mutations must have proliferated to a sufficient number, typically in the billions, before they can be detected by traditional methods. Third, in the case of lung cancers and mesothelioma, the individual typically must become symptomatic. Because the lungs and the pleura are not easily accessible and because routine medical examinations often do not involve any procedure through which a tumor would be found, the physician usually needs to have a specific reason to go looking for the cancer. This often does not occur until the cancer process has proceeded for many years.

39. Physicians and cancer researchers sometimes use the word "precancerous." "Precancerous" is a term used different ways by different people. Most commonly, it is used to describe a tumor that has not yet begun to metastasize to other locations or acquired the histological characteristics that enable pathologists to predict the ability to metastasize. Although the prefix "pre" may be misleading, physicians and researchers typically do not use the word

"precancerous" to mean that the cancer process has not yet begun. To the contrary, "precancerous" is simply an earlier stage of the continuous process in which some, but not all, of the cell mutations have occurred that are necessary for the cancer to begin to metastasize. "Precancer" starts with the first mutation of a cancer gene.

E. Factors Relating to Whether a Pathologically Diagnosable Cancer Will Develop

40. Not all individuals who have that first cell mutation will eventually develop cancer. A number of factors influence whether such a cancer develops, including the age of the individual, the intensity and duration of the asbestos exposure, and other environmental exposures, such as cigarette smoking.

41. We do not know with certainty all of the roles that age may play in the development of cancer. We do know that because cancer is a multi-step process requiring multiple mutations, the longer one lives, the more time one has for the accumulation of multiple cancer gene mutations to occur. It is also possible that the aging process itself contributes to the cancer process. However, the relationship between the aging process and the cancer process is not clear.

42. As the intensity and duration of asbestos exposure increases, the number of fibers in the lungs of an exposed individual will also increase. This increases the probability of the occurrence of the asbestos-associated changes that lead to cancer in both the early and the late stages of the disease.

43. Other environmental factors, such as cigarette smoking, can influence the cancer process by some of the same mechanisms that asbestos fibers operate-- that is, by inducing mutations or by stimulating proliferation of mutated cells.

44. The critical events in the cancer process are the induction of multiple mutations in cancer genes and the of proliferation of mutated cells. It is through these mechanisms that the precancer progresses to a malignancy.

F. The Timing of Mutations

45. As discussed above, an asbestos-related cancer is typically not diagnosed until late in the cancer process. At that time, it is not possible, given the current state of scientific knowledge, to determine exactly when any of the mutations then existing in the cancer cells occurred.

46. However, based on the current state of scientific knowledge, we do know the following facts pertinent to the timing of asbestos-related cancers:

a. As discussed above, asbestos fibers may cause the first cell mutation, or any subsequent cell mutation, within hours or days of the exposure of the fiber to the cell through the mechanisms discussed above;

b. As also discussed above, normal lung cells that are not subject to any other influence may divide every few days; normal mesothelial cells may divide every few months;

c. As also discussed above, lung cells and mesothelial cells that are subjected to asbestos exposure may proliferate at a much higher rate if cell injury is induced;

d. By the time a cancer is typically detected, it is generally one centimeter or greater in size and consists of billions of cells;

e. By the time a cancer is typically diagnosed, a high fraction (greater than 1%) of the cells in the cancer are dividing every day;

f. To achieve the billions of cells necessary for a diagnosis by traditional pathological means, billions of cell divisions had to have first taken place. This is, in part, because cancerous cells also die at an increased rate through much of the cancer process, as shown by Naik, P., Karrim, J., and Hanahan, D. Genes & Development 10:2105-2116, 1996; Dunn, S.E., Kari, F.W., French, J., Leininger, J.R., Travlos, G., Wilson, R., and Barrett, J.C. Cancer Research 57:4667-4672, 1997; Preston, G.A., Lang, J.E., Maronpot, R.R., and Barrett, J.C. Cancer Research 54: 4214-4223, 1994;

g. Consequently, some mutated cells are probably dividing every few days even at the earliest stages of the cancer process. At a minimum, some mutated cells are dividing at least annually decades before the cancer is clinically diagnosed and, most likely, within the first year or two of the initial asbestos exposure; and

h. The multiple mutations to cancer genes, usually estimated at three to ten, are necessary before a cancer is typically diagnosed by traditional means occur during the decades between the first mutation and diagnosis. There is no evidence that suggests that the accumulation of multiple mutations all occur a short time before diagnosis.

47. Thus, the critical and multiple steps in the cancer process -- the accumulation of multiple mutations and the proliferation of mutated cells -- are occurring continuously during the decades from the first mutation through diagnosis.

G. The So-Called "Latency Period"

48. Historically, some researchers believed that following one or two mutations, the damaged cells became essentially dormant for decades, after which they would become active again and proliferate at an extremely fast rate. More recent studies indicate that the precancer cells are not dormant, but rather, are actively dividing; however, the rate of cell division is approximately equaled by the rate of cell death, so that the number of precancer cells in the body during this period does not appear to expand at a rapid rate. This does not mean that the mutated cells are dormant or that no proliferation of mutated cells is occurring. No evidence exists that mutated cells proliferate at a rate lower than normal cells, which proliferate on a regular basis, and, to the contrary, the studies establish that mutated cells, in fact, proliferate at an increased rate. However, because the mutated are also dying at an increased rate during this period, the overall growth in the number of cells is not apparent, as shown by Shibata, D., Navidi, W., Salovaara, R., Li, Z-H., and Aaltonen, L.A. Nature Medicine 2:676-681, 1996. It is this phenomenon that explains the appearance of a "latency period."

H. New Diagnostic Techniques

49. Lung cancer and mesotheliomas are generally diagnosed today after a detectable lesion has developed, for example by radiographic techniques, or after symptoms associated with the cancers (bleeding, pain, difficulty breathing) are recognized. As discussed above, at this point, the cancer consists of billions of cells with multiple mutations in the cancer genes. New molecular techniques are now available that can detect mutations in cancer genes in even a single cell. Furthermore, significant progress has been made on the identification of cancer genes, particularly over the past 10 years. Knowing the critical genes to study for mutations and having techniques to measure mutations in only a few cells has allowed scientists to detect mutated cells that lead to the cancer at earlier times. This new field of molecular diagnosis holds great promise and is therefore a major focus of cancer research today. The hope is that precancer

cells can be diagnosed early and appropriate intervention taken to prevent the cancer from developing and metastasizing. This new technology should also improve the sensitivity and accuracy of cancer diagnosis. One notable example of this is the case of Hubert Humphrey.

50. As reported by Hruban, et al, at New England Journal of Medicine, Vol. 330, pp. 1276-1278, 1994, Hubert Humphrey, while he was vice president of the United States, was admitted to the Bethesda Navel Hospital for hematuria in 1967. Urine specimens were obtained and cytologic examination and cytoscopy detected chronic proliferative cystitis, and a biopsy revealed only a minute focus of dysplastic change in the cells of the bladder. No cancer was detected by gross examination and a number of pathologists reviewed the urine-cytology slides and disagreed on the diagnosis. Two years later, another biopsy revealed carcinoma in situ but Mr. Humphrey was asymptomatic until 1973. A biopsy at that time revealed "borderline malignancy" and he received therapy. In 1976, malignant cancer was finally diagnosed but it was too late-- he had metastases and died in 1978. Molecular studies performed in 1994 of the specimens taken at different times detected a mutation in the p53 gene in the malignant cancer. When the urine specimen from 1967 was also examined in 1994, cells with this identical mutation were detected. These results clearly show that the mutations leading to the cancer occur in cells long before the cancer can be diagnosed by conventional techniques. Furthermore, this new technology has provided additional evidence for the multi-step, continuous nature of the cancer process.

51. Even with the new techniques of molecular diagnosis, the current state of scientific knowledge does not make it possible to say with certainty the time at which any particular given mutation occurred in an individual who is diagnosed with cancer.

I. Asbestos As a Complete Carcinogen

52. Carcinogenic fibers induce mesotheliomas and lung cancer in humans and animals. Asbestos alone appears to be able to cause mesothelioma and is therefore a complete

carcinogen. Asbestos fibers have the ability to induce mutations, which are associated with the initiation of the cancer process, and to induce cell proliferation, which is associated with the process of tumor promotion. Both of these mechanisms are also important in cancer progression. In the case of lung cancer, asbestos and smoking appear to act synergistically to cause cancer. The mechanisms by which asbestos may influence the cancer process, i.e., induction of mutation and induction of cell proliferation, may act at multiple stages of the cancer process. Cigarette smoke contains a large number of chemicals that may influence the cancer process by both mutagenic mechanisms and by affecting cell proliferation and cell death. Therefore, it is not surprising that these two carcinogenic exposures act synergistically. Given the complexity of the carcinogenic process and the number of different mechanisms by which these two carcinogenic agents operate, it is my opinion that it is impossible to say when in the cancer process either is having an influence.

J. Summary of Conclusions

53. As discussed above, asbestos-related lung cancer and mesothelioma are multi-step, continuous disease processes that develop through the accumulation of mutations and the proliferation of those mutated cells over decades. These cancer processes begin with the first cancer gene mutation, which may occur within hours or days of exposure to the asbestos fibers through any one of a number of mechanisms discussed above. Asbestos fibers may also cause the proliferation of cells containing the first mutation at an increased rate, thereby causing the person to have an ever-growing number of damaged cells in his or her body. Those same mechanisms can also cause subsequent mutations and subsequent proliferation of those additionally mutated cells. Relatively early in the cancer process, and at least within a few years of initial asbestos exposure, damaged cells are proliferating through clonal expansion on at least an annual basis and, eventually, on a daily basis. Although not all individuals whose cells develop a first mutation through asbestos exposure will eventually have a pathologically diagnosable lung cancer or

mesothelioma, it is the case that all individuals who have a pathologically diagnosable lung cancer or mesothelioma developed those cancers through the multi-step, continuous disease process discussed above.

J Carl Barrett
J Carl Barrett

Sworn to and subscribed before me
this 13th day of January, 1998.

M. Ruth McFarland
Notary Public
Durham Co, North Carolina
Commission Expires: March 29, 1998