Professor Henderson's evidence in relation to indivisible diseases and causation

Lorraine Fay Sim v Allianz Australia Limited [2010] NSWDDT 19

Curtis J

170. Professor Henderson holds the opinion that each of Mr Sim's employments: *"made a significant and substantial causal contribution to the development of each of his asbestosis and lung cancer".* In his report of 31 August 2010 he explained the relevant pathology as follows:

> *Current understanding of the patho-biological mechanisms for lung cancer and mesothelioma development indicates that epithelial/mesothelial cells are being initiated, initiated cells promoted, and altered cells proliferating at different times, apparently at least in part as a result of free radical generation, with oncogenes and tumour suppressive genes being activated and inactivated. At some stage, the proliferative airway/mesothelial cells are thought to become resistant to apoptosis* [orderly destruction of defective cells]*. At the same time, fibres are cleared at different rates and, if exposure is continuing, they continue to be deposited in the lung.*
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> *All these processes at a cellular level are probabilistic: i.e. the probability of fibre/cell interaction (or, more accurately, fibre/cells interactions) depends on the number of fibres and the number of cells involved at any point in time and space. Hence, simplistically, the greater the number of asbestos fibres, the more free radicals (generated from the fibres or their interactions with cells such as macrophages) and the greater probability of initiated, promoted or proliferative cells at any given time point.*
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> *From a current understanding of the multistage model for cancer induction by asbestos, it follows that each of all exposures to asbestos - recalled or unrecognised - contributes incrementally and cumulatively to the singular disease outcome lung cancer or mesothelioma (provided that the latency interval between any one exposure and the subsequent diagnosis of the cancer is not too short for a carcinogenic effect).*

171. In evidence Professor Henderson said this:

> *The simple fact is that if one has say four separate asbestos exposures, one cannot fractionate a causal effect or even one stage in the multi step progression to an indivisible outcome like lung cancer, and attribute that stage to one of those four exposures. The point is, … that amphibole fibres* [amosite and crocidolite] *in particular which are known to be the most carcinogenic forms of asbestos, are characterised by bio-persistence, that is once deposited in tissues, they will remain there for year after year after year, and they will interact with cells such as macrophages and they will generate toxic chemicals known as reactive oxygen and reactive nitrogen species,*

which are known then to be injurious to the DNA of various cells, for example, airway epithelial cells in the case of lung cancer.

So that when you have multiple exposures, one cannot say that one stage is related to exposure 1 and that that exposure or its effects then cease and then one goes on to exposure 2, because the fibres are persistent to the tissue year after year and as additional exposures occur, additional fibres are deposited in the tissues, so that there are more fibres interacting with more cells generating more toxic chemicals increasing the toxicity to the DNA of airway epithelial cells and increasing the probability of a set of mutations in what is a chain of necessary causal preliminary events on the pathway to lung cancer which is an indivisible and singular outcome.

Professor David Bryant

172. Professor Bryant is a specialist physician, and the chairman of the Medical Authority of the Dust Diseases Board of NSW. He is also a member of the Board of Directors of the Asbestos Diseases Research Foundation.

173. In a report of 17 May 2010 Professor Bryant said this:

> *It is known that the risk of lung cancer is materially increased in individuals with asbestosis, and that the higher dose of inhaled asbestos the greater is the* [risk of] *development of lung cancer. I am therefore of the view that each of the periods of asbestos exposure sustained by the late Mr David Sim (i.e. when employed at Australian Asbestos, Asbestospray Corporation and Bells Asbestos) is likely to have made a material contribution to his development of lung cancer.*

174. The notion of risk is prospective. Professor Bryant sufficiently clearly expresses the opinion that although the exposure to asbestos created a risk, that risk came home when the cancer developed, and the cause of that cancer was the exposure.

175. In this report Professor Bryant expressly adopted the statement by Professor Henderson in a report of 19 April 2010 that:

> *It is known that asbestos can induce lung cancer, the causal relationship being one of linear dose response effect with no threshold. That is, the greater the inhaled "dose" the greater the risk of lung cancer and the causal contribution by asbestos for lung cancer induction.*

176. Although objection was taken to that evidence being given in this form, it remains an expression of personal opinion within the medical expertise of Professor Bryant, and is admissible.

177. In evidence, Professor Bryant said that the cancer was a response to Mr Sim's total fibre burden, and that:

> *In my view, this man has been exposed in all probability to enough asbestos in each year of his employment to be capable of causing lung cancer if one takes the view that it is likely that he has been exposed to between 20 and 40 fibre/ml years during his total employment, in each year of employment. Therefore in each year that this man was employed, he was exposed to enough asbestos to cause lung cancer in its own right.*

Dr Deborah Yates

178. Dr Yates is a highly qualified Consultant Thoracic Physician with a particular interest in occupational lung diseases. In addition to her qualifications in Thoracic Medicine she has a Masters in Occupational Medicine conferred by the London School of Hygiene and Tropical Medicine, and an MD in Respiratory Medicine from Cambridge University. She publishes regularly in the area of occupational lung disease. In the course of cross examination it relevantly emerged that she also has a first-class honours degree in the study of Pathology.

179. Dr Yates is of the opinion that: *"on the balance of probabilities, each of Mr Sim's employments ... materially contributed to the development of his asbestosis, asbestos related diseases, and lung cancer".*

180. Dr Yates said that: *"my opinion as both a medical researcher and scientist … [and] as a physician, is that every individual exposure contributed towards the development of Mr Sim's lung cancer …"*

181. Dr Yates expressly agreed with Professor Henderson's exposition of the pathology. She also said:

> *"…because asbestos exposure is a necessary pre-requisite towards the development of cancer and is dose related, each of those employments, and also each inflammatory insult produced by asbestos fibre which was related to the durability and the retention within the lung of those fibres, each contributed towards the* [risk of the] *development of the cancer, which then came home* [when] *Mr Sim was diagnosed with lung cancer in 2009"*.

184. The first proposition advanced reflects the factual basis upon which the House of Lords proceeded in *Fairchild v Glenhaven Funeral Services Ltd* [2002] UKHL (20 June 2000) where Lord Bingham said:

> *The mechanism by which a normal mesothelial cell is transformed into a mesothelioma cell is not known. It is believed by the best medical opinion to involve a multistage process, in which six or seven genetic changes occur in a normal cell to render it malignant. Asbestos acts in at least one of those stages and may (but this is uncertain) act in more than one… It is accepted*

that the risk of developing a mesothelioma increases in proportion to the quantity of asbestos dust and fibres inhaled: the greater quantity of dust and fibres inhaled, the greater the risk. But the condition may be caused by a single fibre, a few fibres, or many fibres: medical opinion holds none of these possibilities is more probable than any other, and the condition is not aggravated by further exposure.

185. Professor Henderson is aware of this decision, and says that this view of the medicine *"simply does not hold up in biomedical terms".*

186. As I understand Professor Henderson's evidence, a cell mutates, not because of mechanical impingement upon the cell by an identifiable asbestos fibre, but because of its exposure to free radicals, toxic to DNA. These radicals are released by the response of the immune system, not only to the presence of any particular identifiable fibre or fibres, but to the presence of all retained fibres. Because the ultimate mutation occurs shortly before the development of the cancer, all retained fibres are causally implicated in a cascading chain of mutations.

187. His opinion is encapsulated in an exchange in cross-examination, where Mr Parker sought to isolate a mutant ancestral cell caused by a particular asbestos exposure as the single cause of the cancer.

188. Professor Henderson responded by pointing out that, even if it were accepted that an identifiable ancestral cell was generated in a discrete period of employment, further necessary mutations of that cell are modulated by the totality of reactive oxygen and reactive nitrogen species released in the immune system's continuing response to the presence of all retained asbestos fibres, inhaled both before and after the generation of that particular ancestral cell.

Q. So looking at the ultimate development of the cancer, it is possible to trace it back to a series of finite number of individual events at which first the ancestor cell has become genomically unstable and then further mutations have occurred to its descendant cells until it eventually becomes a cancer cell and then develops into a tumour, correct?

A. Well, I don't know what you mean by the expression a series of finite steps. All I'd say is that when you have a deposition of inhaled asbestos fibres especially amphibole fibres those fibres will interact with otherwise normal cells, macrophages release toxic chemicals which can then impact on otherwise normally replicating bronchial epithelial cells and induce mutations and the more fibres that are inhaled and deposited the greater the number of the toxic chemicals, the greater the number of the mutations, the greater

> *number of epigenetic events, for example, autocrine cell stimulation, which will lead to this expanded population of cells and the point is that all of these factors accumulate in a necessary obligate causal chain of precancerous events finally leading up to the final event which becomes the cancer.*

189. Professor Henderson graphically illustrated his opinion with a diagram, PX 26, depicting the causal effect of retained asbestos fibres at several intermediate stages of the mutations in which healthy cells ultimately become cancerous.

190. Professor Henderson is well qualified to express his opinion. It is an opinion supported by Dr Yates who was also well qualified in medicine and pathology. No defendant calls medical evidence to the contrary.

191. It may be accepted that it is impossible on the current state of scientific knowledge to fully identify the sequence of mutagenic events that caused a lung cancer in an individual. That fact is not decisive. A fact may be proved by medical opinion if that opinion is *substantially* based on specialised knowledge gained from a witness's training study and experience, and as Basten JA said in *Amaba Pty Ltd v Booth* [2010] NSWCA at 116:

> *The civil standard of proof, on the balance of probabilities, permits a yawning gap between complete understanding and sufficient understanding.*

192. The defendants called no medical evidence contrary to the opinions expressed by Professors Bryant and Henderson and Dr Yates.

193. The Court of Appeal has twice held that the Tribunal is entitled to accept Dr Henderson's "cumulative effect" theory of causation, and to reject the defendant's proposition that repeated inhalation of asbestos fibre creates a number of separate and independent possible causes of cancer. See *E.M.Baldwin v Plane* (1998) 17 NSWCCR 434 and *Amaba Pty Ltd v Booth* [2010] NSWCA 344.

The Doubling of Risk

194. The submission that mathematical proof of the doubling of risk is the sole criteria of causation in cancer cases is quite wrong. The cases upon which Mr Parker relies: *McDonald v State Rail Authority* (1998) 7 NSWCCR, *Judd v Amaca Pty Ltd* [2003] NSWDDT 1*, Evans v Queanbeyan Shire Council* and *Amaca Pty Ltd v Ellis* (2010) 240

CLR 111, all concerned the necessity to make a rational election between two competing causes. This is not such a case.

…

198. This submission must fail for several reasons.

199. The first is that epidemiological studies are concerned with risk not cause. Once the cancer has developed medical science may attribute that cancer to a causal factor notwithstanding that, prospectively, that factor was not seen as a probable cause.

…

203. The second reason is that epidemiological evidence cannot prove that exposure to a toxic agent at a certain concentration *did not* cause a corresponding disease in an instant case.

204. Epidemiological predictions hold for the average member of a population, not for all members of that population. As Professor Henderson points out in his report 31 August 2010:

> *The relative risk (or odds ratio) derived as an average across the population cannot be applied simply and automatically to every individual comprising that population. For example, a particular adult human group may have an average height of 175 cm, but this does not mean that each and every individual in that group measures 175 cm in height.*

205. Professor Henderson suggests that because of idiosyncratic considerations such as chance, genetic susceptibility, or differential rates of clearance of fibres, the background risk of Mr Sim contracting lung cancer may have doubled at 13 fibre /ml years of exposure to amosite.

206. A third reason for rejecting the submission is that the incidence of lung cancer rises with increasing doses of asbestos fibre. That circumstance gives rise to an inference that all contributions are causative. Mr Parker cannot advance any scientific basis upon which a particular period of exposure may be exculpated.

207. Professor Henderson said in evidence that he agreed with a comment by Professor Geoffrey Berry, the eminent biostatistician qualified by Allianz, that:

> *In the absence of quantitative exposure information it would be invalid to conclude that the lung cancer was caused only by the exposure while employed by Australian Asbestos. There were three other periods of exposure that would have made a contribution to the excess in risk, and there is no*

scientific basis for saying that only one of these four periods of employment [caused] the lung cancer.

208. Professor Henderson explained:

> *If one has an exposure which has contributed say, 60% to the total fibre pool and there are two other exposures, each of which has contributed 20% I don't think one can say that the cancer which has developed is the outcome, even on a probability basis, from the 60%. It is the total 100%-the 60+20+20-which is the cumulative exposure which has been brought home in terms of the development of the cancer.*

209. It is significant that no defendant calls expert evidence on the issue of causation. Allianz obtained a report from Professor Geoffrey Berry. WorkCover arranged for Associate Professor A.B.X. Breslin, a highly regarded respiratory physician with extensive experience in asbestos related diseases, to examine Mr Sim. Neither expert is called, and I draw the inference that neither would have advanced the case argued by the defendants.

210. I find that inhalation of asbestos fibres in the employment of each defendant materially contributed to the cause of Mr Sim's lung cancer.

Allianz Australia Ltd v Sim; WorkCover Authority (NSW) v Sim; Wallaby Grip (BAE) Pty Ltd (In liq) v Sim [2012] NSWCA 68

Allsop P

14. In Professor Henderson's later report of 19 April 2010, he expressed the conclusion that the exposures in each of the employment periods made a significant and substantial causal contribution to the development of his lung cancer. He said:

> Joint Blue Book Vol 5 of 5 pp 2105-2106
> "It is known that asbestos can induce lung cancer, the causal relationship being one of a linear dose-response effect with no threshold. That is, the greater the inhaled 'dose' the greater the risk of lung cancer and the causal contribution by asbestos for lung cancer induction. Lung cancer differs qualitatively from asbestosis and falls into the class of malignant neoplastic diseases. It is considered to be a 'singular' injury, in that once it has come into being, further exposure to its causal factors (e.g., cigarette smoke; asbestos) cannot significantly worsen the injury (cancer) and, conversely, withdrawal of the causal factors cannot reverse the cancer.
>
> ...

> Because asbestosis itself represents a dose-response outcome of asbestos exposure, it follows that each of Mr Sim's asbestos exposures related to each of his employments with Australian Asbestos, Asbestospray Corporation and Bells Asbestos made a significant and substantial causal contribution to the development and severity of his asbestosis, as a matter of high probability.
>
> ...
>
> Because the likelihood and pathogenesis of lung cancer are governed by a dose-response relationship, it also follows on a probabilistic basis that each of Mr Sim's asbestos exposures related to each of his employments with Australian Asbestos, Asbestospray Corporation and Bells Asbestos made a significant and substantial causal contribution to the development of his lung cancer.
>
> The basis for my opinions expressed above is covered in the review published in 2004."
> …

16. Professor Henderson wrote a later report dated 31 August 2010 in response to the views of Professor Berry (whose report was exchanged, but who was not called). The report is to be read as a defence by Professor Henderson of his opinions as to the causal relationship of all the exposures of Mr Sim by the three appellants, a matter contested in the report of Professor Berry. The whole section entitled "Causation in a claimant" on pp 7-10 of Professor Henderson's report is directly relevant. (See Joint Blue Book Vol 5 of 5 pp 2177-2180.) In it, Professor Henderson seeks to explain why differentiation between employers, such that one can be and another not be causally responsible, cannot be done. He explained that this was the case because, if lung cancer occurs because of exposure to asbestos (as on the probabilities it did here), the induction of asbestos fibres into the lung and respiratory structure that were there retained all played a necessary, cumulative and incremental part in the development of the disease. At the risk of unnecessary lengthening of these reasons I set out the following from this report:

> Joint Blue Bok Vol 5 of 5 pp 2178-2180
> "The point is that lung cancer is considered to develop by way of a multi-stage model of carcinogenesis, analogous to that which applies to the development of mesothelioma when caused by asbestos, but in most cases of asbestos-related lung cancer cigarette smoking is an important causal co-factor.

In this context, it is worth noting the following:

Because of the apparent capacity of asbestos fibres to participate at several stages of cancer (*lung cancer; mesothelioma*) induction (please see the attached document *MM_Overview_Schematic*, reproduced from reference 24), **all exposures to asbestos in an individual patient must be considered cumulatively to play some part in causation of the cancer in question.**

Current understanding of the pathobiological mechanisms for lung cancer and mesothelioma development indicates that epithelial/mesothelial cells are being initiated, initiated cells promoted, and altered cells proliferating at different times, apparently and at least in part as a result of free radical generation, with oncogenes and tumour suppressor genes being activated and inactivated. At some stage, the proliferative airway/mesothelial cells are thought to become resistant to apoptosis. At the same time, fibres are cleared at different rates and, if exposure is continuing, they continue to be deposited in the lung. [At this point he gave a reference for a detailed exposition of the mechanisms of mesothelioma induction.]

All these processes at a cellular level are probabilistic: i.e., the probability of fibre/cell interaction (or, more accurately, fibres/cells interactions) depends on the number of fibres and the number of cells involved at any point in time and space. Hence, simplistically, the greater the number of asbestos fibres, the more free radicals (generated from the fibres or their interactions with cells such as macrophages) and the greater probability of initiated, promoted or proliferative cells at any given time point.

From a current understanding of the multistage model for cancer induction by asbestos, it follows that each of all exposures to asbestos - recalled or unrecognised - contributes incrementally and cumulatively to the singular disease outcome lung cancer or mesothelioma (provided that the latency interval between any one exposure and the subsequent diagnosis of the cancer is not too short for a carcinogenic effect).

From the preceding discussion it is evident that the risk and causal contributory effects of asbestos towards lung cancer or mesothelioma induction are dependent upon the cumulative exposure to asbestos, modified by asbestos fibre types, and in years following commencement of the exposures. Provided that the latency interval is appropriate (i.e. more than 10 years following the beginning of any exposure), each of any identified above-

background exposure makes a causal contribution towards the induction of the lung cancer or mesothelioma, the proportional causal contribution being modified by the three factors mentioned in the preceding sentence. **Therefore, it follows that when there are multiple exposures with an appropriate latency interval, each one of those exposures makes a causal contribution towards lung cancer induction. It also follows that one cannot point to any one exposure as being responsible for the lung cancer entirely, with exculpation of the others. Furthermore, one cannot point to any one exposure and exculpate it and to blame all of the others. All exposures contribute to the final outcome (i.e., the lung cancer).**

I agree with Prof. Berry that **not all asbestos fibres initially inhaled actually participate directly in lung cancer induction. When airborne asbestos fibres are inhaled, a proportion will be filtered out by the upper nasal passages (although humans frequently convert from nose breathing to mouth breathing when exerting themselves). A proportion of the fibres which successfully bypass the upper respiratory passages will be deposited in the bronchial walls, and amphibole fibres such as crocidolite and/or amosite will tend to persist, although some will translocate away from bronchial walls and others will reach the pleura. Nonetheless, those that remain within the airway structures and eventually induce the lung cancer represent a proportional fraction of those fibres first inhaled, and the more fibres that are deposited (when there were multiple exposures over time), the greater the probability of induction of chemical messengers such as reactive oxygen species *and the amounts of such reactive chemicals*, which can damage the DNA of the cells. Put simplistically, the more fibres deposited in airways, the greater the probability of key interactions with airway epithelial cells and the greater amounts of chemical messengers produced by the cells-fibres interactions, with the greater probability that different asbestos fibres interacting with cells over multiple generations of cells, eventually and cumulatively lead to the production of a lung cancer. To reiterate: these cells-fibres effects do not occur between a single asbestos fibre and a single airway epithelial cell: rather, the situation is one of multiple asbestos fibres interacting with multiple airway epithelial cells over multiple generations of those cells (please see preceding discussion and the analogous situation for mesothelioma induction by asbestos, as discussed by Hammar et al).**

In other words because tobacco smoke and asbestos fibres are thought to participate at multiple different points in the causal chain leading to the development of lung cancer, the cancer itself is thought to be the outcome of reactions between a proportion of the inhaled and deposited fibres, and the greater the numbers of those

deposited fibres the greater is the likelihood of lung cancer induction."
(Endnotes omitted; emphasis added.)

…

19. In relation to his rejection of Professor Berry's opinion, Professor Henderson stated:

Joint Black Book Vol 1of 2 p 245
"A - The simple fact is that if one has say four separate asbestos exposures, one cannot fractionate a causal effect or even one stage in the multi step progression to an indivisible outcome like lung cancer, and attribute that stage to one of those four exposures. The point is, and a point that I think is overlooked in the quoted passage of text, that -

Q. From Professor Berry. A - That's right, is that amphibole fibres in particular which are known to be the most carcinogenic forms of asbestos, are characterised by biopersistence, that is once deposited in tissues, they will remain there for year after year after year, and they will interact with cells such as macrophages and they will generate toxic chemicals known as reactive oxygen and reactive nitrogen species, which are known then to be injurious to the DNA of various cells, for example, airway epithelial cells in the case of lung cancer. **So that when you have multiple exposures, one cannot say that one stage is related to exposure 1 and that that exposure or its effects then cease and then one goes on to exposure 2, because the fibres are persistent to the tissue year after year and as additional exposures occur, additional fibres are deposited in the tissues, so that there are more fibres interacting with more cells generating more toxic chemicals increasing the toxicity to the DNA of airway epithelial cells and increasing the probability of a set of mutations in what is a chain of necessary causal preliminary events on the pathway to lung cancer which is an indivisible and singular outcome.** So my problem there is that the quoted passage of text involves speculation on pathogenesis which is at variance with what we know about the biopersistence of asbestos fibres in tissues, and also the multi step model of lung carcinogenesis.

...

Ibid pp 246-247
Q. ... A - ... **So the difference is between the non-necessity for this causal chain in the throwing of the darts, but the dire necessity - in fact, it is essential - that one moves from one mutational event to another, ultimately striking the right sequence or combination of mutational and other events necessary to lead to a lung cancer. So there is a necessary causal chain.**

HIS HONOUR

Q. So if we do not look at darts, but 99 to 100 fibres, every fibre does its part . A - **Every deposited fibre potentially does its part, yes.**

MR SEMMLER

Q. Going on to the next page, at the top of page 8 you use the expression, 'The hundred darts do not constitute an obligate chain of events essential for the score of a triple 20.' Does the exposure in four separate periods, as in Mr Sim's case, to asbestos, with four separate employers - does each exposure constitute an obligate chain of events essential for the ultimate development of the cancer. A - **Well, in the development of that particular cancer my answer is in the affirmative; but, yes, that each of those exposures will increase the likelihood that a cancer will develop, but the fibres from the first exposure remain throughout the other periods of exposure and are added to by the fibres inhaled and deposited by the subsequent exposures, so that each has incrementally increased the likelihood that a lung cancer will develop, and in this case that likelihood has been translated into the actual development of lung cancer.**

Q. **When the lung cancer develops and the risk expressed as a likelihood has come home, is it possible then to exclude any of the four periods of exposure to asbestos with each for the employers in the explanation for the reality of the cancer. A - Well, the answer to that is no, one cannot exclude any one and blame all of the others. The point is that all of them have contributed to the load of inhaled and deposited asbestos fibres in lung tissue, or a fraction of those fibres have interacted with the cells to produce the toxic chemicals involved in producing mutations. Those mutations have increased in number as a result of the fact that asbestos fibres can interact with cells at multiple different points along the causal chain, leading up to the development of the lung cancer.** ,... **one cannot point to one and blame it and exculpate the others; and equally, one can't point to one and exculpate it and then blame all of the other three exposures. The point is that all of them have contributed to the fibre burden in lung tissue, all have contributed to the risk which is then translated into the actual occurrence of the lung cancer.**

Q. Yes. And when you say it is translated into the actual occurrence of the lung cancer, you mean that once the risk comes home each of them has caused that cancer. A - That's right, yes."

...

24. It was then put to Professor Henderson that that was "all that science tells us relevantly." (Joint Black Vol 1 of 2 p 257 X.) Professor Henderson did not accept this. He said:

> Ibid p 258
> "A. **Well, I think it goes beyond that because a number of the steps in a mutational pathway towards cancer have been established, and there is now a - although the process is incompletely understood, there is now good evidence for a number of the mutational steps and one can name individual genes involved.**
>
> Q. Well, can we include all of that as falling within the general statement in the fourth proposition. A - Right.
>
> Q. **Now, understanding the propositions in those broad terms, is what I put to you correct, that those four propositions exhaust what science can tell us about the relationship. A - I don't think they exhaust it**."

24. Meticulous cross-examination then followed in aid of the propositions as to the limits of science identified. This included the following exchange:

> Ibid pp 263-264
> "Q. Now the creation of genomically unstable cells is something that happens even without asbestos exposure, correct. A - Yes, people develop mutations spontaneously.
>
> Q. So it can happen spontaneously, correct. A - Yes.
>
> Q. Or other carcinogens can be involved. A - Yes.
>
> Q. Such as ionising radiation. A - Yes.
>
> Q. Or cigarette smoke. A - Yes.
>
> Q. And that may happen either at the initial stage when the first, and I call it, the ancestor cell which is the first genomically unstable cell was created or at any of the descendant stages. A - Well, yes, just as the asbestos fibres interact either at the first and as they accumulate the subsequent stages in cancer development.
>
> Q. So you could have one genomically unstable cell that had been started by ionising radiation and then another at later generations that could accumulate a further mutation and that might be the produce of an asbestos fibre. A - **Yes, but all the asbestos fibres then are doing is adding on to a previous mutation and furthering the**

development of the necessary causal chain of the mutations necessary for cancer development.

...

Ibid p 264
Q. So looking at the ultimate development of the cancer, it is possible to trace it back to a series of finite number of individual events at which first the ancestor cell has become genomically unstable and then further mutations have occurred to its descendant cells until it eventually becomes a cancer cell and then develops into a tumour, correct. A - **Well, I don't know what you mean by the expression a series of finite steps. All I'd say is that when you have a deposition of inhaled asbestos fibres especially amphibole fibres those fibres will interact with otherwise normal cells, macrophages release toxic chemicals which can then impact on otherwise normally replicating bronchial epithelial cells and induce mutations and the more fibres that are inhaled and deposited the greater the number of the toxic chemicals, the greater the number of the mutations, the greater number of epigenetic events, for example, autocrine cell stimulation, which will lead to this expanded population of cells and the point is that all of these factors accumulate in a necessary obligate causal chain of precancerous events finally leading up to the final event which becomes the cancer.**

...

Ibid p 271
Q. The proposition is that when one reads this report as a whole it is clear that the words on a probability basis and the sentence to which I have drawn attention connote an exercise for an individual in the application of a formula RR equals 1 plus K times E. A - **Well, I just do not agree with that proposition. I would not use that equation. I would think that the attribution in an individual patient is based on a variety of considerations and including - and a work history of substantial to heavy exposure as in this case or asbestosis however diagnosed and I don't think one needs to invoke the equation RR equals 1 plus K times E. I don't see the relevance of that to this particular exercise.**

...

Ibid p 274
Q. Now, I asked you some questions earlier about the biochemical processes which are thought to lead to the development of cancer. You will agree with me, will you not, that not all of the fibres which lodge in the lung and produce the adverse effects that you are

referring to actually contribute to the chain of causal events which lead to the generation of the particular cancer which may later develop**. A - I agree that not all of the inhaled fibres will actually participate in the process of carcinogenesis, that some of the fibres will migrate away and be translocated to pleura. But what I can say is that a proportion which is likely to be proportionate to the dose of each episode of exposure will participate in the process of carcinogenesis, so one is looking at a fraction, a proportion of the inhaled and deposited fibres which will participate in carcinogenesis.**

...

Q. Well, we do not now how many steps there are or may be, how many mutative steps there are or may be between the original unstable - and I am sorry, I have forgotten your phrase - the ancestor unstable cell. A - Well, we don't know the precise number of steps."

...

Ibid pp 276-279
Q. Would you agree with me that the model that you have described involves an assumption that there is a continued accumulation through the generations of further mutations which, if the cell does not automatically die or undergo apoptosis or be eliminated by the body's defence mechanisms, eventually results in accumulating enough mutations that the cell then becomes a cancer cell capable of replicating itself and then the cancer grows from that cell. A - Well, that's a fair representation of the process, as we discussed this morning; and again, the more a person smokes cigarettes the greater the likelihood that the carcinogens in the cigarette smoke will lead to an outcome, yet not everybody who is even a heavy smoker will develop lung cancer. It is increasing the probability that the required chain of sequential causal mutational and epigenetic events will actually occur that lead to the cancer; and the point is, the more that one smokes, the more that one is exposed to asbestos, the greater the probability that this chain of events will come to its fruition, if you like. And the point is that each of the, if you like, cigarette smoke or asbestos exposures will contribute to the pool of asbestos fibres, from the first, second, third and fourth exposures, and as the fibre numbers increase the probability that a cancer will develop increases. Each adds to the likelihood that a cancer will develop and eventually that is translated, or comes home, or comes into being as a cancer.

Q. When it does, in your language, the fibre in question - that is, the fibre that has been inhaled as a whole - in your language has made a material causal contribution to the cancer which ultimately results. A - What I am saying is that -

Q. That is the sense in which you have used this phrase, 'material contribution or cause,' is it not. A - I don't think I've used the word 'material,' but if I have it has been a mistake on my part.

HIS HONOUR ...

Q. Doctor, can you reply. A **- Well, I try not to use the word 'material,' your Honour. To me that is a legal term, the expressions I use are 'significant and substantial causal contribution', and the point that I am simply trying to make is that the more fibres that are inhaled, the greater the probability that the cancer will develop. So that each of - when you say there were four exposures, each of the exposures will increase the likelihood of a cancer developing. They each increase the likelihood on top of those that have gone before, so that the total likelihood at the end, when it's translated into a cancer, is the total cumulative exposure that has come home to fruition in terms of a cancer.**

Q. In that each additional fibre adds to the chemical soup which is toxic. A - That's correct. Each of the exposures is adding to all of the events and chemicals and mutations which ultimately lead to the cancer, so that when you see a cancer in reality, as expressed in an individual patient, you're looking at the end result of all the risks or likelihoods imposed by each of multiple exposures.

... HIS HONOUR

Q. So that does each exposure create some additional mutations. A - Well, I don't think one can put it quite so precisely, your Honour, because if you have, say, somebody with four exposures to asbestos over, say a period of two or three years each, then the amphibole fibres from the first exposure, a proportion of those will be present in bronchial walls and lung tissue. They will persist. The second exposure takes place and that adds to that pool of asbestos fibres. So does the third and so does the fourth. But the first exposure fibres are still resident, so that the chemical soup and the mutational events are the end result of the cumulative exposure imposed by each of multiple exposures when there is more than one.

Q. So that each exposure creates some additional mutations. A - The likelihood is that each does, that each additional exposure, because it increases the number of fibres, increases the likelihood that the chemical messengers will induce one of the required mutations for the development of a lung cancer. I mean, I can only requote Professor Berry when he says, 'It would be invalid to conclude a lung

cancer is caused only by one exposure. There were three other periods of exposure that would have made a contribution to the excess in risk, and there is no scientific basis for saying that only one of those periods caused the cancer.'

... WITNESS

If one has an exposure which has contributed, say, 60% to the total fibre pool and there are two other exposures, each of which has contributed 20%, I don't think one can say that the cancer which has developed is the outcome, even on a probability basis, from the 60%. It is the total 100% - the 60 plus 20 plus 20 - which is the cumulative exposure which has been brought home in terms of the development of the cancer.

MR PARKER

Q. That is the way you analyse it. A - Well, yes, it is.

Q. And you have said now many times that an additional exposure - or an individual episode of exposure - increases the risk of a cancer ultimately developing. A - Yes.

Q. **But that particular exposure may not in fact play any role in the development of the particular cancer that in fact develops; correct. A - I think - well, I wouldn't say - I don't believe that is correct, because I think it falls into the realm of far-fetched speculation beyond what is available in the biological and scientific evidence. I think that is entirely speculative.**

Q. **Well, most of the cells which develop these mutations ultimately do not go on to grow into a cancer, they either die out or are eliminated by the natural processes that we have discussed; correct. A - Well, that's correct.**

Q. So it's only a fraction of those cells or indeed usually only one that will actually lead to a line which endures down the generations enough and develops the necessary mutations to turn into a cancer. That is right, is it not. A - Well, yes. The majority of the cells will either die out, the mutations will be irrelevant or they will not progress to cancer for a variety of reasons and it requires a complex series of sequential causal steps to cause the cancer but the point is that the likelihood that those essential causal steps in this casual chain will be achieved is increased by the additional asbestos exposures so that one can't point to any one exposure and say well this one on a probably basis has not contributed. That to me is speculation.

Q. Nor can one point to any particular individual one and say on a probability basis this one did contribute. A - Well, as I say **one cannot point to one of, say, four exposures and say that is the exposure responsible, the other three played no role. One cannot equally point to one exposure and say well that played no role it's the other three. The point is, it's all of the exposures in an individual which are ultimately translated into the development of a lung cancer.**

Ibid p 279
Q. You have expressed yourself in your report and in your evidence a number of times as saying all the exposures make a substantial contribution to any cancer which ultimately develops or you have said all the exposures cumulatively cause the cancer which ultimately develops. A. And this is in accordance with current theories on carcinogenesis.

Q. That is the way you have expressed yourself and in expressing yourself you mean that all of the exposures increase the risk in the way that you have described in your evidence to me. A. That's correct.

Q. **And nothing more. A - Well, I think it means more when the cancer has finally developed because the risk has come home in the form of a cancer.**

HIS HONOUR

Q. But does every additional exposure increase the number of mutations. A - We can't count them because in humans one can't come back and look at the mutations. **The point here is, your Honour, that even the first exposure will produce a series of ongoing mutations. The next exposure will increase the number of mutations and increase the likelihood that one of those mutations is relevant to the development of cancer and so would a third and so would a fourth. One can't neatly fractionate mutations according to each of, say, four exposures because the mutations - the fibres are long resident in lung, new fibres are added and the mutations are ongoing process over 20 to 30 years**."

(Emphasis added.)

Basten JA

94. Professor Henderson provided some further explanations of his opinions in his evidence in chief. He had stated in his third supplementary report that it was "impossible to fractionate or partition various stages in a multi-stage process into

the exposure from one particular employer as opposed to another": at p 7. He was asked to explain why he considered that impossible and stated (Tcpt, 07/09/10, p 240):

> "The simple fact is that if one has say four separate asbestos exposures, one cannot fractionate a causal effect or even one stage in the multi-step progression to an indivisible outcome like lung cancer, and attribute that stage to one of those four exposures. The point is, and a point that I think is overlooked in the quoted passage of text [from Professor Berry] ... is that amphibole fibres in particular which are known to be the most carcinogenic forms of asbestos, are characterised by bio-persistence, that is once deposited in tissues, they will remain there for year after year after year, and they will interact with cells such as macrophages and they will generate toxic chemicals known as reactive oxygen and reactive nitrogen species, which are known then to be injurious to the DNA of various cells, for example, airway epithelial cells in the case of lung cancer. So that when you have multiple exposures, one cannot say that one stage is related to exposure one and that that exposure or its effects then cease and then one goes on to exposure two, because the fibres are persistent to the tissue year after year and as additional exposures occur, additional fibres are deposited in the tissues, so that there are more fibres interacting with more cells generating more toxic chemicals increasing the toxicity to the DNA of airway epithelial cells and increasing the probability of a set of mutations in what is a chain of necessary causal preliminary events on the pathway to lung cancer which is an indivisible and singular outcome."

95. With respect to the translation of risk into causative effect, he gave the following further evidence (p 241):

> "Q. ... Does the exposure in four separate periods, as in Mr Sim's case, to asbestos, with four separate employers - does each exposure constitute an obligate chain of events essential for the ultimate development of the cancer?
>
> A. Well, in the development of that particular cancer my answer is in the affirmative; but, yes, that each of those exposures will increase the likelihood that a cancer will develop but the fibres from the first exposure remain throughout the other periods of exposure and are added to by the fibres inhaled and deposited by the subsequent exposures, so that each has incrementally increased the likelihood that a lung cancer will develop, and in this case that likelihood has been translated into the actual development of the lung cancer.

Q. When the lung cancer develops and the risk expressed as a likelihood has come home, is it possible then to exclude any of the four periods of exposure to asbestos with each of the employers in the explanation for the reality of the cancer?

A. Well, the answer to that is no, one cannot exclude anyone and blame all of the others. The point is that all of them have contributed to the load inhaled and deposited asbestos fibres in lung tissue, or a fraction of those fibres have interacted with the cells to produce the toxic chemicals involved in producing mutations. Those mutations have increased in number as a result of the fact that asbestos fibres can interact with cells at multiple different points along the causal chain, leading up to the development of the lung cancer. ... In other words, one cannot point to one and blame it and exculpate the others; and equally, one can't point to one and exculpate it and then blame all of the other three exposures. The point is that all of them have contributed to the fibre burden in lung tissue, all have contributed to the risk which is then translated into the actual occurrence of the lung cancer."