IN THE CAMBRIDGE COUNTY COURT 7 AF 01190

LESLIE GEORGE THOMAS Claimant

and

MERCK SHARP AND DOHME LIMITED Defendant

Trial heard before H. H. Judge O'Brien on 29th and 30th September and 1st October 2008.

JUDGMENT

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1. Mr Leslie Thomas ("C") claims damages for personal injury arising from a contract not requiring any proof of negligence. C took part in a drugs trial carried out by Merck Sharp and Dohme Ltd ("D"). During the trial he suffered ulcerative colitis. D disputes C's case that the drug trial caused the ulcerative colitis.

2. The Court ordered the trial of the preliminary issue: "Whether C's ulcerative colitis, as set out in his Amended Particulars of Claim was caused by the Rofecoxib ingested during the drug trial as defined in the Amended Particulars of Claim."

3. C was born on 27 October 1933. He is a retired college lecturer. He lives with his wife who is a retired health care assistant and about a year younger than him. They have been married for about 40 years. In September 2003 he was a better than averagely fit man, a serious walker and played badminton weekly.

4. In about 1974 he suffered from diverticulitis for a few days. He was referred for hospital investigation but no further treatment was required. It is not suggested that it has any relevance to this case.

5. In about September 2003 C was invited by his G.P., Dr Katrina Young, to participate in a trial of a drug – Rofecoxib. Rofecoxib is a non-steroidal anti inflammatory drug ("NSAID"). The trial was to establish whether it could decrease the risk of prostate cancer. Dr Young was the local instigator for the trial.

6. On 14 October 2003, C and his wife saw Dr Young to discuss the trial. C was provided with an information sheet, version 3 effective 7th April 2003, which read: "It is unlikely that you will have a serious side effect . . . if you do you will be covered by MSD's compensation scheme. This scheme follows the guidelines (produced by the Association of the British Pharmaceutical Industry -ATBI.)"

7. On 30 October 2003, before embarking on the trial, C was given a full medical check by Dr Young, including blood and stool tests. He signed the consent form for the drug trial. In the course of the next fortnight his tests came back and were normal.

8. On 8 December 2003 C took his first dose of Rofecoxib under Dr Young's supervision. He was not aware whether he was taking the drug or a placebo. Thereafter he took Rofecoxib daily.

9. On 23 December 2003 C saw Dr Young and made no complaint of any adverse effect. Further blood tests were carried out.

10. On 12 February 2004 Dr Young carried out a review by telephone. There is no note of any problem.

11. C gives evidence that he began to feel lethargic or fatigued in about March to April 2004. However, when he saw Dr Young on 23 March 2004 he reported himself as very well and made no complaint of any adverse effects.

12. However, after some fairly short (6 – 7 mile) walks over unchallenging Norfolk terrain, on or about 11 April 2004, an 8 mile walk around Sandringham left him feeling completely drained. He reports that from that date his fitness deteriorated rapidly.

13. On 27 April 2004 C and his wife moved home from Ely to live temporarily at Hunstanton. Before the move C and his wife suffered a bout of diarrhoea, the exact cause of which has never been identified, but possibly from something they ate. Although his wife recovered, he did not. C's wife bought some immodium or the like from the chemists for C but it did not stop his diarrhoea.

14. C's wife gave evidence that the diarrhoea started a good 2 to 3 weeks before the move to Hunstanton. That gives a bracket of 6 to 13 April 2004. However, C does not complain of diarrhoea at the time of the Sandringham walk on 11 April. On balance it would seem that it began on about 13 April 2004.

15. On 17 May 2004, after the move to Hunstanton, C and his wife asked a chemist about medication for C's diarrhoea. When they explained that it had been going on for 2 to 3 weeks, the pharmacist told them that C should consult his doctor immediately.

16. C immediately telephoned C's G.P. practice and spoke to Dr Douglas. He told Dr Douglas he had had diarrhoea for 2 weeks. I find that this was a slight under estimate. He queried whether this was caused by the drug trial and explained that he had stopped taking the Rofecoxib in the last 2 days. Dr Douglas took the view that this was unlikely as he'd been taking it for 2 months (it was actually more like 5 months) and advised him to keep taking it.

17. On 19 May 2004, C saw Dr Douglas. He had restarted the Rofecoxib, as advised. C gave evidence that he explained that he was going to the lavatory as much as 7 times per day, that he was sometimes incontinent and that he faeces were bloody and foul smelling. Dr Douglas has noted him as going twice per day. He sent a stool sample off for analysis. Dr Douglas prescribed codeine phosphate. C gave evidence that the tablets did nothing to stop the diarrhoea but caused him to vomit violently. He gave them up after 2 days on Dr Douglas' advice.

18. On 25 May 2004, C saw Dr Young. She has recorded him as "slightly better," bowels open 3 times per day, "very smelly," ? gastro intestinal bleed, poor appetite. She took blood for testing. C's recollection is that by this time he was actually feeling worse and going to the lavatory up to 10 times per day. He accepts that he may well have been minimising the picture to Dr Young.

19. Having seen C and his wife give evidence and be cross examined, it seems to me that the reason for these discrepancies is partly a tendency of C to understate problems at the time and partly because they are not very precise historians of exactly when the problem reached a particular state. I accept that there were times when C was going to the lavatory many times per day and occasions when he was caught short and messed his clothing.

20. On 28 May 2004 C again saw Dr Young. She has recorded him as looking and feeling better, bowels still loose, opened twice yesterday. She appears to record him as anaemic. C says this is not a fair picture. He was going downhill. Dr Young does note that he is to stay off the trial drug.

21. C describes his condition from late May as anally incontinent, losing weight, physically exhausted and unable to eat. He could barely walk and had to remain within a few feet of the lavatory.

22. On Monday 7 June C telephoned Dr Young. She has recorded: "diarrhoea – bowels open 3 – 4 times per day – poor appetite. She advised C to try a bottle of Guinness. She also arranged for him to get some Fybogel.

23. Next day C and his wife travelled from Hunstanton to their daughter's home in Cambridge. They had to keep stopping for C to open his bowels in lay bys and bushes. He did drink a bottle of Guinness.

24. On 9 June 2004 while at his daughter's home C was overcome with extremely severe shaking. He was rushed by ambulance to Addenbrookes hospital where he was found to be tachycardic, febrile, hypotensive, dehydrated, anorexic and suffering from septicaemia. He had lost 2 stone from his usual weight. His temperature was noted at 40.5%C. The treating Doctor established that C had actually been taking Rofecoxib. He was given intravenous antibiotics and steroids and various samples were taken.

25. On 14 June 2004 C underwent a sigmoidoscopy which confirmed a diagnosis of ulcerative colitis. He remained in hospital until 29 June 2004 when he was discharged to his daughter's home.

26. On 30 June 2004 C went to see Dr Young in Ely. Dr Young paid for the taxi fares from Cambridge. C says that she was very upset and apologetic. She told them that they could claim compensation from D. She arranged a fortnight's recuperation for C and his wife in the University Arms Hotel at an approximate cost of £1,900 at D's expense.

27. In September 2004 C and his wife moved into their new home in Ely.

28. C says that he was virtually an invalid for 9 months after leaving hospital and has still not recovered his previous state of robust good health. However, he claims that since his recovery he has not suffered any recurrence of the symptoms of ulcerative colitis. No doctor has suggested that he has suffered from ulcerative colitis since he left hospital on 29 June 2004.

29. On 30 September 2004 Rofecoxib was withdrawn from sale and drug trials. It had been authorised by the United Kingdom Regulatory Authority since 1994 for anti inflammatory use. It was not withdrawn as a result of this case or any problems like it but because it was found to cause cardio vascular problems.

30. The issue before the court is essentially one to be decided on the basis of the expert medical evidence.

31. Dr Ainley, instructed on behalf of C, is a well qualified and experienced Consultant Physician and Gastroenterologist. Although he maintains an interest in inflammatory bowel disease and, in particular, the aetiology of Crohn's disease, his main field of practice and research is the pancreas – pancreatico-biliary disease.

32. He saw and examined C and reported on 5 December 2005. He concluded that C developed ulcerative colitis in April 2004 as a result of Rofecoxib.

33. Professor Forbes, instructed on behalf of D, is Professor of gastroenterology and clinical nutrition at University College and Hospital, London. He has a special interest in inflammatory bowel disease on which he has written a text book now in its second edition. He is a member of the Guidelines Committee for the European Crohn's and Colitis Organisation and a key author of their guidelines on ulcerative colitis concerned with its aetiology, diagnosis and treatment. Dr Ainley recognises him as a leader in the field of research and knowledge of inflammatory bowel disease.

34. He reported on 24 June 2008. He did not meet C but saw all the relevant medical records and witness statements. He agreed that C had developed ulcerative colitis in 2004, possibly as late as May. However, although he concedes that it is possible that Rofecoxib caused the ulcerative colitis, he concludes that the balance of probabilities is firmly against its having done

so. He accepts that Rofecoxib can exacerbate pre-existing ulcerative colitis, but after a proper search of the literature was unable to find a single case where there was a convincing argument for a causal relationship between exposure to Rofecoxib and the development of ulcerative colitis.

35. The medical experts produced a joint statement on about 26 September 2008, only a few days before the trial began.

36. They agreed that C did not have ulcerative colitis before his exposure to Rofecoxib.

37. They agree that ulcerative colitis was correctly diagnosed in June 2004.

38. They agreed that Rofecoxib, like many drugs, could trigger an episode of ulcerative colitis in a patient with a previous diagnosis.

39. Dr Ainley argues that factors causing a relapse may share characteristics with factors precipitating the disease but accepted that this cannot be put higher than a possibility.

40. Professor Forbes is of the view that there is no recorded evidence in published literature of Rofecoxib or any other NSAID causing the original onset of ulcerative colitis. He accepts that the absence of such evidence does not prove that it cannot happen. In his view it does make it much less than probable.

41. Professor Forbes accepts that it is known that NSAIDs, including Rofecoxib, can cause a colitis. He said that it is not known to cause ulcerative colitis. He had searched the literature without finding anything to support NSAIDs causing the onset of ulcerative colitis. He said that he was looking for a clear, unambiguous cause with reproducibility to establish this. He would want a history, a physical examination, endoscopy and histology all consistently showing ulcerative colitis before he could discuss its relevance to causation. He would also want to see that the association could not have occurred by chance.

42. Professor Forbes also takes the view that the fact that C had been taking Rofecoxib for about 4 to 5 months before suffering symptoms of ulcerative colitis makes it less than probable that there is a causal connection. He accepts that there are known to be many delayed effects from NSAIDs and that it is possible that causing ulcerative colitis is such an effect. However this is not the case with drug related colitis and he regards it as improbable that it has happened in this case.

43. Dr Ainley agreed in oral evidence that 5 months delay is unusual and made the causation by Rofecoxib less likely.

44. Dr Ainley said that various drugs, including NSAIDs are known to induce colitis. Rofecoxib is an NSAID. It can be concluded as probable that Rofecoxib can induce ulcerative colitis.

45. In oral evidence Dr Ainley went further. He said that NSAIDs as a class can cause de novo onset of ulcerative colitis. That suggests that Rofecoxib, which is an NSAID, can cause de novo onset of ulcerative colitis.

46. He said that this was based on an article by a Dundee group headed by J.M.M. Evans in 1997. This was later produced. Its conclusion in summary was: "The use of NSAIDs may be associated with an increased risk of emergency admission to hospital for colitis due to inflammatory bowel disease, particularly among patients with no previous history."

47. Professor Forbes said that this paper merely provided data which allowed a hypothesis to be created. It had never been followed up. It remained a hypothesis and had not changed his view.

48. Dr Ainley agreed that this study was of NSAIDs generally, not limited to Rofecoxib. About 45% of the cases analysed were of ulcerative colitis. Although the article concluded with an appeal for more studies to be carried out in this field, he was not aware of any such follow up studies. He still regarded the article as good persuasive evidence with nothing in the literature to contradict it.

49. Dr Ainley agrees that most drug induced colitis, including ulcerative colitis would probably occur earlier than 4 months after starting on the drug. However, there is evidence in respect of other NSAIDs that it can occur after up to 180 days.

50. They disagree on the question of C's recovery. Dr Ainley considers that C has not had any problems from ulcerative colitis since the initial attack subsided. He believes that this points to Rofecoxib being the cause. He said that C's poor health after discharge from hospital was because he had been knocked sideways by the attack. He had lost 2 stone in weight and he took some time to recover. His reported occasional urgency in going to the toilet no doubt related to the medico-legal process.

51. Professor Forbes does not accept that C has made a recovery. He is still taking Asacol. There are references in the medical records which suggest an ongoing problem. However, even if it is accepted that C has made a complete recovery, he considers that complete and prolonged clinical remission is compatible with the behaviour of spontaneous ulcerative colitis when appropriately treated.

52. It is common ground that ulcerative colitis has to be distinguished from colitis and that it idiopathic; that is, it has no known aetiology (origin.)

53. In the course of the trial the experts examined the records of 82 out of 183 cases reported to D under WAES of adverse experiences of Rofecoxib alleging ulcerative colitis or colitis. These arise from commercial sale as well as testing of the drug. Although they had been disclosed in advance, Dr Ainley had not considered them before. He identified 12 cases indicating de

novo onset of ulcerative colitis with another 9 possible cases. After discussing them with Professor Forbes he believed that 12 cases were of de novo onset.

54. Dr Ainley agreed that the adverse experience reports did not always give a full medical history and will not always show how a diagnosis has been reached. Professor Forbes described them as brief and incomplete and not evidence of a causal connection but flags of something requiring further investigation.

55. He thought case 95238 was the best he could point to in terms of strength of evidence. There was a strong family history of ulcerative colitis. He would have expected pre-existing diagnosis to have been mentioned if it was the case. What it actually reported was: "No symptoms prior to Rofecoxib."

56. He agreed in discussion with professor Forbes that case 106130 could not be relied on.

57. In respect of case 115668 he agreed that this was weakened to a degree by the facts that Rofecoxib had been used for about 150 days before the onset of ulcerative colitis and continued to be used for 3 months afterwards. Professor Forbes commented that this report comes from a Doctor reporting on her 69 year old husband. He thought the diagnosis of ulcerative colitis was correct. He thought it likely that other NSAIDs as well as Rofecoxib may have been involved. There is no basis for this in the report.

58. Case 1091522 involved a 47 year old lady using a hormonal contraceptive which is a risk factor for ulcerative colitis. Dr Ainley saw no reason to doubt that the gastroenterologist involved would have investigated by histology and endoscopy before diagnosing.

59. Case 0206USA02274 involved diagnosis by colonoscopy of ulcerative colitis. Dr Ainley thought it unlikely that there would not also have been a biopsy having regard to the fact that this is a United States of America case. The case involved a very swift onset of symptoms after Rofecoxib was begun and a recovery after it was discontinued.

60. Case 0208FRA is a French case where a 60 year old lady began suffering symptoms of subsequently diagnosed ulcerative colitis 10 days after starting to take Rofecoxib. Rofecoxib was stopped and the patient recovered. Dr Ainley saw no reason to question the diagnosis. He assumed there would have been a biopsy in addition to the reported colonoscopy. He did not regard a second colonoscopy 10 months later, after recovery as throwing doubt on the diagnosis.

61. I find case 0208USA02118 less than convincing because the patient had a very complicated medical history which may have masked colitis and rather more because the onset of diagnosed ulcerative colitis was 9 months after the patient began to take Rofecoxib.

62. Dr Ainley thought that case 0212DEU00060 (a German case) presented fascinating data. This was a 61 year old lady who after starting to take Rofecoxib developed symptoms of acute ulcerative colitis. Rofecoxib was interrupted and she recovered. 20 days after the first symptoms, they recurred. Acute ulcerative colitis was diagnosed. Rofecoxib was discontinued and she recovered. "The reporting physician felt that gastrointestinal bleeding and acute ulcerative colitis were possibly related to Rofecoxib. He also stated that a possible infectious colitis can be taken into consideration as a cause." Professor Forbes said that this was simply a wrong diagnosis. Dr Ainley believes a biopsy would have been carried out in Germany and sees no reason to doubt the diagnosis. He felt that the history of re-starting Rofecoxib and recurrence of ulcerative colitis made the causal relation much more likely.

63. Professor Forbes observed that it was not clear for how long the patient had initially taken Rofecoxib. The circumstances looked to him like a drug related colitis – not ulcerative colitis.

64. Both experts agree that the Australian case 0308AUS00010 is a case where 18 days after starting on Rofecoxib a 43 year old lady developed symptoms correctly diagnosed as ulcerative colitis. Professor Forbes suggests that this is probably merely coincidental. I summarise his argument about this at paras 69 & 70 below.

65. Dr Ainley believed case 0402FRA00032 to be an onset case despite the pre-existing colonic polyp. However, Robecoxib was started in September 2003. Symptoms only began in January 2004 some days after the patient began to take Ketoprofen as well. I do not regard this as a strong case for C's conclusion.

66. Dr Ainley accepted in respect of case 0410DEU00091 that diabetes is a risk factor for ischaemic colitis. Nevertheless he accepted the German doctor's diagnosis on the basis that such a diagnosis would not be made in Germany without a colonoscopy and biopsy.

67. Dr Ainley conceded that cases 00014 and 0508USA were not cases he would wish to rely on having regard to the 21 months elapsing before the onset of ulcerative colitis in one case and 12 months elapsing after Rofecoxib was ended in the latter case.

68. However, he felt very convinced by the remaining 10 cases that Rofecoxib can cause an initial onset of ulcerative colitis.

69. Dr Ainley agreed that the prevalence of ulcerative colitis was between 50 and 100 per 100,000 of the population and that its incidence was about 1 per 10,000 of population per annum. He agreed that NSAIDs are among the most commonly prescribed drugs in the U.K. He agreed that potentially a case of ulcerative colitis could coincide with a patient taking NSAIDs simply by chance. He accepted that it was possible, although less likely, that the taking

of Rofecoxib could simply coincide with the onset of ulcerative colitis by chance.

70. Professor Forbes said that if a disease is a common one and the proposed cause is also common, you would expect some cases to occur by chance.

71. Dr Ainley was not familiar with the figures produced by Linda Hostelley, D's vice president for safety and quality assurance, (whose evidence I eventually admitted under the Civil Evidence Act,) that D's 2004 Annual Report claimed that they estimated that about 19 million people per annum took Rofecoxib in the U.S.A. between 1999 and 2004. He had no reason to dispute it although he felt that it was a high figure representing nearly 10% of the population. Its use in the U.K. was much more limited because it was expensive.

72. Dr Ainley gave evidence that in colitis (generally) started by NSAIDs there is a pattern of the patient recovering – and usually quite quickly – when the NSAID is withdrawn. If the drug is avoided thereafter, the patient should never have another attack. He regarded C as having recovered from ulcerative colitis. He accepted that the medical records showed some continuing inflammatory process in C's body but did not regard the levels as sufficiently high for ulcerative colitis. He thought that the fact that C was still being prescribed Asacol probably meant that somebody, most likely the nurse practitioner felt that C should still have control of ulcerative colitis. He said that he would have stopped the Asacol. He noted that the treating physician, Dr Middleton, had recorded on 18 October 2004 that C was in remission and had reduced the dose of Asacol. At the next appointment on 14 February 2005, Dr Middleton considered C was in remission and generally not too bad with a once daily bowel movement and no bleeding or pain. The follow up appointment was to be in 9 months time. Dr Ainley regarded the lack of any steroid prescription as indicating remission. He also recognised no signs of iron deficiency in C's blood samples for the last 3 years and felt that there was no reason for the continued prescribing of ferrous sulphate.

73. Professor Forbes thought that the continued prescription by Addenbrooke's of Asacol and ferrous sulphate indicated that ulcerative colitis was under control rather than in remission. He agreed that Asacol would be used to maintain remission and that it would be responsible of Addenbrooke's to take a safe course. He accepted that he could not discount the poorly formed motions and occasional urgency being due to the stress of this litigation.

74. Dr Ainley accepted that ulcerative colitis usually develops in the first 30 years of life and is becoming unusual by the age of 70. He makes the point that C is unusual in never having taken NSAIDs before this trial. This is relevant when considering the fact that he got to the age of 70 before developing ulcerative colitis.

75. The experts agreed to within a few percentage points that the broad picture of patients with ulcerative colitis is that about 5% never have a second attack, about 70 – 85 % are maintained mostly in remission on medication and the

remainder are so affected that surgery is required. Dr Ainley felt that C could be in the 5% who never have a second episode.

76. Dr Ainley felt that it was possible that the original stomach upset suffered by C and his wife may have made C more vulnerable to Rofecoxib because it inhibits Cox 2 which is normally induced to promote healing as an inflammatory response. Rofecoxib may impair that healing process so that ulcerative colitis can develop.

77. Professor Forbes said that he was comfortable with Dr Ainley's theory that Rofecoxib may inhibit Cox 2 from its normal healing process.

78. Professor Forbes said that many people use NSAIDs. Probably 5% of the American population had taken Rofecoxib. Probably 20% of the population suffer food poisoning every year. Therefore the concurrence of Rofecoxib and food poisoning must be quite common. If a combination of food poisoning and Rofecoxib could cause ulcerative colitis, he would have expected it to have become apparent before now.

79. Dr Ainley confirmed that patients with ulcerative colitis would not normally be prescribed NSAIDs. Professor Forbes said that the reason for that is that NSAIDs were likely to make the ulcerative colitis worse. There was a high chance of exacerbating an existing condition.

80. There is some important cross examination of Professor Forbes, the meaning of which is hotly disputed between the parties. Professor Forbes said that the ulcerative colitis most likely developed naturally. Assuming that the diarrhoea began on about 12 – 13 April 2004, C continued to take Rofecoxib for a further month. It is possible that Rofecoxib exacerbated the symptoms after their onset. If C had had pre-existing ulcerative colitis on the balance of probabilities Rofecoxib would have exacerbated it. On that basis some of C's symptoms were caused by Rofecoxib. It was put to him that the Rofecoxib probably put C into hospital. Professor Forbes replied: "If the ulcerative colitis began in April, I'd accept the drug could aggravate it and possibly put him in hospital."

81. Professor Forbes readily accepted an invitation to row back from this position in re-examination. He said that by exacerbation he meant that a person with ulcerative colitis in remission may suffer a flare up. I find it perfectly clear that he accepted in cross examination that the symptoms from ulcerative colitis could be so exacerbated as to hospitalise the patient.

82. Professor Forbes was asked about his view in paragraph 6 of the Joint Statement that a single case of proof would over rule his opinion and his acceptance that the Australian case 0308AUS00010 appears to be a correctly diagnosed case of ulcerative colitis. He said that there was a difference between accepting it, as he did, as a reasonably convincing case of de novo ulcerative colitis and accepting it as a proven case of ulcerative colitis caused by Rofecoxib. He was criticised by counsel for not mentioning this case expressly in his report, having regard to the duty of an expert witness. He

said that he was looking for clear and unambiguous proof and insisted that the standard he was applying was not too high.

83. Mr Jonathan Waite Q.C. addressed me on behalf of D.

84. He submitted that the only dispute of fact which needed to be resolved was the onset of the illness. For the reasons set out at paragraphs 14, 15, 16 and 19 above I conclude on balance that the symptom of diarrhoea began on or about 13 April 2004. C's wife is likely to be right about it starting 2 to 3 weeks before the move to Hunstanton. C's evidence about the Sandringham walk shows it is more likely to be 2 weeks than 3. It seems likely that the figure of 2 weeks given to Dr Douglas was an approximation and under reported the matter.

85. Mr Waite pointed out that the formulation of the preliminary question did not raise an issue of exacerbation. The only questions really raised are firstly, is Rofecoxib capable of causing ulcerative colitis and secondly, did it cause it in this case?

86. He submitted that D's expert witness is the better qualified in the relevant field and that C's expert was more concerned with the pancreas. Whereas Professor Forbes had made an extensive search of relevant professional literature, Dr Ainley cited no authority in his report and had not read the WAES adverse experience reports before coming to court. When Dr Ainley did cite the Dundee group article, it turned out to be of only marginal relevance. Of course, Dr Ainley had recognised Professor Forbes as a leader in the relevant field. Mr Ritchie for C defended Dr Ainley as self effacing but determined. He had worked overnight to review about half of the WAES adverse experience cases. He was willing to listen to the other side and give ground appropriately.

87. He submitted that Dr Ainley had produced no real evidence to satisfy the burden upon C of proving that Robecoxib had caused C's ulcerative colitis. The Dundee paper is the high watermark and that provides only a hypothesis unsupported by further research in general or a study of clinical cases in particular.

88. He submitted that having regard to the extent to which Rofecoxib was prescribed and the prevalence and incidence of ulcerative colitis one would have expected a body of case reports of Rofecoxib having caused ulcerative colitis. The fact that the literature is silent suggests that there is no evidence to show that Rofecoxib can cause the de novo onset of ulcerative colitis. It is therefore difficult to say that it happened in this case.

89. He submitted that the WAES adverse experience reports were not adequate to satisfy the tests of reliability set out by Professor Forbes in his oral evidence.

90. He submitted that, as Dr Ainley had agreed in his oral evidence, the fact that Rofecoxib can cause an exacerbation of an existing ulcerative colitis only gives rise to the possibility – rather than proof - that it may cause its onset.

91. Mr Waite submitted that the elapse of more than 4 months between the start of the Rofecoxib trial and the first symptoms of diarrhoea argued strongly against a causal connection. Professor Forbes had given evidence that the usual experience with drugs and adverse reactions affecting the gastrointestinal tract is a relatively rapid one measured in days rather than weeks. Dr Ainley agreed that the 4 to 5 months in this case was unusual and that NSAID induced colitis usually comes on within a few weeks of commencing the medication.

92. Paragraph 8 of the Joint Statement deals with this issue. "There are many examples of drugs causing adverse effects after the patient has been exposed for many months. This is not usual in the case of drug related colitis, but there are known to be many delayed effects from non steroidal drugs and it is certainly possible that this is the case here. Again, Professor Forbes has taken the line of argument based on the balance of probabilities using both the literature referring to non-steroidal drugs and colitis in general and his own (negative/absent) experience of this conjunction. This opinion is not shared by Dr Ainley."

93. Mr Waite submitted that although it is common ground that exacerbation of an existing ulcerative colitis was possible, there is no evidence that Rofecoxib ever caused it de novo and Professor Forbes submission on the time gap could not be disputed.

94. Finally, Mr Waite submitted that Professor Forbes is right about the categorisation of C's present state as being in remission under reasonable control rather than completely recovered.

95. On behalf of C, Mr Ritchie submitted that the question whether Rofecoxib could cause ulcerative colitis should not be approached on the basis proposed by Professor Forbes which really amounted to proof beyond reasonable doubt. The approach of the Court should be on the usual civil basis of the balance of probabilities. I accept that submission. It seems to me that professor Forbes in setting his own criteria for establishing a case of de novo ulcerative colitis set the bar artificially high in the context of civil litigation.

96. Mr Ritchie submitted that it was very unusual to suffer ulcerative colitis at the age of 70. Professor Forbes agreed that the majority of cases of ulcerative colitis occurred before the age of 70. Indeed it was put to Dr Ainley in cross examination that ulcerative colitis usually presents in the first 30 years of life. He agreed.

97. Mr Ritchie adopted Dr Ainley's argument that C's case is one of a small minority in complete remission. If the ulcerative colitis had occurred naturally, one would expect relapses. The fact that it is in remission tends to indicate that the illness was drug induced.

98. Mr Ritchie drew attention to 5 relevant factors.

99. Firstly, as a 70 year old man with no family history of the disease, it was unlikely that C would develop ulcerative colitis in April 2004.

100. Secondly, C developed ulcerative colitis while taking Rofecoxib.

101. Thirdly, C has not suffered any relapse and whether that is because of maintenance by medication or not does not matter.

102. Fourthly, the Patient Information Sheet was amended in 2004 to add colitis as a possible side effect of taking Rofecoxib.

103. Fifthly, the experts agree that NSAIDs can cause de novo other forms of colitis. These involve ulceration and bleeding in the gut. These are the same symptoms as ulcerative colitis. Visual probes are needed to distinguish the diseases by their "architecture." The Court is asked to take a short step from the inflammation, ulceration and bleeding in another category of colitis to the inflammation, ulceration and bleeding in ulcerative colitis. On common sense grounds this is the width of a tissue paper away.

104. Mr Ritchie argued that the Court should be very wary of accepting D's statistics from U.S.A. The figures of Linda Hostelley contained many approximations and we do not know how long American prescriptions last for.

105. Mr Ritchie argued that it is common ground that Cox 2 helps to repair the colon and that Rofecoxib inhibits Cox 2, the repairing agent. That is how it aggravates existing cases of colitis. The inhibition of Cox 2 is probably what is happening in de novo causation of other forms of colitis.

106. He further submitted that Professor Forbes' treatment of the WAES adverse experience reports, refusing to accept all bar one as de novo ulcerative colitis, at best amounted to the application of too high a standard of proof – perhaps appropriate to academic research but not too fact finding in a civil action – and at worst to a lack of impartiality. A fair approach is that on the balance of probabilities 10 of the cases show de novo ulcerative colitis.

107. Finally, Mr Ritchie submitted that if he had failed to prove a de novo case of ulcerative colitis, the continued taking of Rofecoxib after it arose, so exacerbated C's condition that D was in any event responsible for that exacerbation, the worst of the illness suffered by C including the hospitalisation necessitated by the exacerbation.

108. I have found that the symptoms commenced on about 13 April 2004. C took Rofecoxib from 8 December 2003 to about 15 May 2004. He restarted on Dr Douglas' advice on 17 May but seems to have stopped finally by 20 May 2004. He was, therefore, on Rofecoxib for about 5 weeks after the symptoms began.

109. As I understood it, Mr Waite then sought to distinguish between "exacerbation" as used by Professor Forbes meaning to cause a flare up of a pre-existing but quiescent illness and "aggravation" meaning the worsening of the symptoms of an illness. I have already noted a clear rowing back by Professor Forbes in re-examination from what he had agreed in cross examination. I also note that Mr Waite in his Skeleton Opening (para 12(b)) writes: "the experts are agreed that there is evidence . . . to support the contention that many drugs can exacerbate ulcerative colitis, i.e. bring about a deterioration in a patient's pre-existing condition. . ."

110. I was left in no doubt by Professor Forbes' careful answers in cross examination that he accepted the probability of some of C's symptoms being caused by Rofecoxib. (See para 80 above.)

111. Before entering upon the drug trial C was a 70 year old man in generally good health. He was plainly very fit for his age enjoying a lot of walking including fell walking and playing badminton. Six months later he was so ill as to be rushed to hospital by ambulance and remain as an in patient for 3 weeks. It is not surprising that he and his wife are unable to understand how that change in his health cannot be related to the drug trial. I have to approach the case on the basis of whether C has proved on the balance of probabilities that Rofecoxib was a causative factor in the development of the illness.

112. I, of course, accept that C had never been diagnosed with ulcerative colitis before the events in question. I accept that no case of causation of ulcerative colitis de novo by Rofecoxib has ever been proved to the hilt, as required by Professor Forbes. I also accept that it is unusual for a drug induced colitis to occur more than a few days or weeks after the commencement of the drug.

113. Dr Ainley's argument that C's virtually complete recovery or long lasting remission after the withdrawal of the drug lends support to his case is of comparatively little weight. It is difficult to know the extent of C's recovery because it is clear that Addenbrooke's hospital have taken a properly cautious line. The medical records tend to indicate that C is maintained in remission by appropriate medication. It is certainly possible but, not in my judgment proven, that the medication is no longer necessary.

114. However, it seems to me that Professor Forbes sets the bar far too high in determining whether there are other known cases of Rofecoxib causing ulcerative colitis. In my judgment the data in 7 of the WAES adverse experience cases show, on the balance of probabilities, that Rofecoxib has been a cause of ulcerative colitis. Those are cases 95238, 1091522, 0206USA02274, 0208FRA, 0212DEU00060, 0308AUS00010 and 0410DEU0009. I accept Dr Ainley's judgment that it is most unlikely that these diagnoses would have been submitted without proper diagnosis following endoscopy and histology samples.

115. Of course Professor Forbes himself accepts the probable accuracy of the diagnosis in one case – 0308AUS00010. However he points to the probability of this being coincidence having regard to the widespread use of Rofecobix and prevalence of ulcerative colitis. We do not actually have any information about the use of Rofecoxib in Australia. That apart, 7 such cases, rather than just one, greatly diminish the probability of these being chance coincidences of Rofecoxib and ulcerative colitis.

116. I am satisfied that it is not only possible that Rofecoxib may cause ulcerative colitis, but that on the balance of probabilities it has done so in these 7 cases. In the Joint Statement Professor Forbes said that a single case of proof would overrule his opinion (that there is no evidence that a drug can truly cause ulcerative colitis.) Of course, he was referring to proof by his very high standard.

117. It remains the case that reported cases of Rofecoxib causing ulcerative colitis are fairly rare and that there is a time lag of more than 4 months between the taking of Rofecoxib and the onset of symptoms later diagnosed as ulcerative colitis.

118. It seems to me significant that the onset of symptoms in the form of tummy troubles coincided with C's wife having a similar problem. It is likely that both suffered some form of "food poisoning" or, as Dr Ainley puts it, infective enteritis. Dr Ainley's evidence that infective enteritis can precipitate ulceration colitis was not challenged.

119. Rofecoxib is mainly used in the treatment of arthritis. It includes a Cox 2 inhibitor. Cox 2 is naturally induced to promote healing. Robecoxib inhibits Cox 2 so that the healing process is impaired. The food poisoning or infective enteritis suffered by C did not heal up as it normally would (and did in his wife's case) in a few days because Rofecoxib was impairing healing.

120. Accordingly, although Rofecoxib was not the only, or even the initiating cause, it played an important part in the causation of C's ulcerative colitis.

121. On this analysis, provided by Dr Ainley, the significance of being on Rofecoxib for 4 months before ulcerative colitis developed disappears because it is not simply Rofecoxib which caused the ulcerative colitis but its combination with food poisoning.

122. There remains Professor Forbes' argument on coincidence. However, C can also point to the coincidence of himself as a pretty fit man, of 70 years of age, with no previous ulcerative colitis, no family history of ulcerative colitis. It is unlikely that he would have developed ulcerative colitis from a bout of food poisoning in April 2004. The unusual factor was the Rofecoxib.

123. For these reasons I am satisfied on the balance of probability that Rofecoxib ingested during the drug trial was a significant cause of C developing ulcerative colitis from a few days after 13 April 2004.

124. In case I should be held to be wrong in my conclusion, I address Mr Ritchie's alternative argument that if the ulcerative colitis was caused other than by Rofecoxib, the drug operated almost immediately to exacerbate the condition. I have really dealt with this submission at paras 80 and 108 to 110 above. I conclude that Professor Forbes' attempts to row back from this case as put to him by Mr Ritchie in cross examination were at best disingenuous. I am afraid that I did begin to feel that for a moment he forgot he was here to help the Court rather than simply advance D's case.

125. I am quite clear that if it should be decided elsewhere that C has failed to prove causation of ulcerative colitis, he has nonetheless clearly proved that Rofecoxib aggravated the symptoms by impairing the healing process to the point where he had to be treated for 3 weeks in hospital.

126. This would raise the further problem that this conclusion is not within the terms of the issue raised for this hearing. This might be met by an application to amend those terms based on the assertion that all the material is already before the Court or by an application for a further issue trial. Those applications, or any other that the legal genius may suggest, are not presently before me and I happily absolve myself from even attempting to decide them in advance.

H. H. Judge O'Brien,

Cambridge County Court,

27th November 2004.