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February 15, 2004

Mr. Louis C. Woolf  
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Re: Lebron v. Shell Oil Company, et al

Dear Mr. Woolf,

Thank you for allowing me to review the medical records, expert reports and depositions you have provided concerning the above action. As you are aware, I am a board-certified hematologist in private practice at Christus St. Joseph Hospital, in Houston, Texas, where I also serve as Director of the Transitional Internship Program. I am a member of the Board of Directors of the Stehlin Foundation for Cancer Research, at Christus St. Joseph Hospital, and a trustee of the Gulf Coast Regional Blood Center, where I serve as Chairman of the Education and Research Committee. I have approximately 35 years experience in clinical hematology, and I am familiar with the disorders classified as hematological malignancies and, specifically, with what is known concerning the etiology, diagnosis, clinical course and therapy of multiple myeloma. You have a copy of my curriculum vitae.

The above action concerns a former automobile mechanic and gasoline-related sales worker who alleges that he has multiple myeloma and that this illness is chemically-induced consequent to occupational exposures to various hydrocarbons, including benzene. I will briefly review Mr. Lebron's clinical history, and comment on what is known concerning his listed diagnosis of renal failure consequent to light and heavy chain deposition nephropathy and its relation, if any, with multiple myeloma. I will then comment on the allegations of chemical causation.

Mr. Michael Lebron (SS# 319-36-2471, DOB 12-12-46), a 53 year-old man of Puerto Rican descent, was evaluated at Loyola University Cancer Center in May of 2000, with complaints of progressive edema of his lower extremities. Several months earlier, in December 1999, a number of laboratory tests had been accomplished in an attempt to explain his complaints of foamy urine of one year's duration. Results of these studies included a markedly elevated 24 hour urinary total protein excretion of 3.85 grams, in association with normal renal function, suggesting the nephrotic syndrome. Serum and urine protein electrophoretic studies failed to identify a monoclonal protein, and he was not anemic, hypercalcemic, or with evidence of bone lesions or osteoporosis. He had a past history of peptic ulcer disease and of suspected viral pericarditis. According to Dr. Barton's chart notes, Mr. Lebron had been rejected as a blood donor because of hepatitis B, five years earlier. He also had been treated for hypertension. He had a remote past history of cigarette smoking and no family history of hematological disease. His occupation was listed as an automotive technician for Ford Motor Company.

At this evaluation in December 1999, his serum creatinine concentration was 1.6 mg/dl, serum albumin 2.8 gm/dl and hemoglobin concentration 13.4 gm/dl. His 24 hour urinary total protein had further increased to around 13 grams/24 hours. A small monoclonal gammopathy of IgG kappa specificity was identified in the serum. Free light chains were not identified in the urine. To better explain his renal disease, a percutaneous kidney biopsy was carried out at another institution. The pathology report describes an increase in the mesangial matrix of several glomeruli, with fibrocellular crescents and interstitial lymphoplasmacytic infiltrates. With electron microscopy, subendothelial capillary deposits were identified. An IgG kappa globulin was also identified by tissue fluorescent antibody stains. The Congo Red stain for amyloid gave negative results. Essentially, this biopsy showed a membrano-proliferative glomerulitis with IgG kappa immunoglobulin deposition. The descriptive terminology chosen of "light and heavy chain deposition disease" might be confusing to some, and suggests separate deposits of both light chains and heavy chains in the kidney when it is actually the intact gamma globulin molecule that is deposited. Such misleading terminology would be akin to describing an intact body as a pair of arms and legs. Isolated light and heavy chain renal deposition (separate component parts of the gamma globulin molecule) disease can occur, but it is very unusual, and the tests done here do not suggest or confirm this phenomenon (1-2). Pure light chain tissue deposition may be associated with large amounts of free light chains in the urine and may be seen in multiple myeloma.

On May 3, 2000, a bone marrow examination was accomplished. The pathology report describes, "...a slight increase in mature plasma cells...of approximately 5% of the total cellularity". As I have mentioned to you, I would like to review these slides, should they become available. The medical records indicate his attending physicians felt that Mr. Lebron did not meet the generally accepted criterion essential for the diagnosis of multiple myeloma. Nevertheless, in an attempt to reverse his proteinuria and renal disease, he received chemotherapy with the VAD (vincristine, Adriamycin, dexamethasone) program, presumably hoping that this treatment would reverse immunoglobulin deposition in the kidney. Unfortunately, his renal disease progressed and, ultimately, he began renal dialysis in December of 2001.

Of importance is that in April of 2001, and prior to initiation of dialysis, he required hospital admission for an altered mental status and was found to have very elevated blood ammonia levels. He was treated for hepatic encephalopathy and recovered after a several week admission. According to Dr. Barton's deposition, Mr. Lebron's condition is currently stable. An additional pertinent report shows a viral load of 14,200 copies/ml of hepatitis B measured in his blood on May 31, 2001. A liver biopsy performed on 8-22-01, was interpreted as showing grade 2, Stage 2 chronic hepatitis. Serial studies of his serum paraprotein by immunofixation techniques showed an IgG kappa monoclonal peak of 0.4 gm/dl, on 6-13-01. On 4-4-02, the peak was measured at 0.3 gm/dl and on 4-2-03, 0.2 gm/dl.

Can we make a specific diagnosis with this material, and does the patient have multiple myeloma, as alleged? We know that Mr. Lebron has chronic active hepatitis B as confirmed by serology, liver biopsy and viral load studies, and that this condition is significant enough to have caused elevated blood ammonia levels and encephalopathy. I was quite surprised by Dr. Durie's comments that hepatitis B does not cause renal failure. Perhaps it was in the context of how the question was asked. In fact, there is extensive literature that documents that hepatitis B may cause glomerulonephritis, the nephrotic syndrome and renal failure in both adults and children, occasionally associated with immunoglobulin deposition in the kidney – particularly of IgA globulins, but also of IgG proteins. In some instances, the renal disease and proteinuria may be reversed by successful hepatic transplantation and/or treatment with interferon (3-9). In describing the consequences of the membranous nephropathy of hepatitis B infection, one author states, **"Spontaneous remission of glomerulonephritis is uncommon in adults. One third of patients develop progressive renal failure..."** (8). Chronic inflammatory diseases, such as viral hepatitis, are frequently associated with an increase in serum gamma globulin levels as well as a mild increase in mature-appearing plasma cells in the bone marrow, which could easily reach 5%, as described in Mr. Lebron.

Various specific hepatitis B antigens may be demonstrated in the renal capillary basement membranes of patients with hepatitis B-induced glomerulonephritis, along with immunoglobulin deposits (5, 7-8). Fluorescent stains for these specific antigens were not performed on Mr. Lebron's kidney biopsy, and it is uncertain if the pathologists interpreting the biopsy were even aware of the fact that he had chronic hepatitis B infection.

The renal biopsy performed in this case does demonstrate monoclonal IgG kappa deposition in the kidney. Whether this deposition is an inciting factor or simply a consequence of the basic disease of glomerulonephritis is uncertain. Immunoglobulin deposition is common in many forms of non-myelomatous renal disease and, specifically, monoclonal immunoglobulin deposition has been well-described as a consequence of hepatitis C (9-10). With sensitive electrophoretic gel techniques, oligoclonal globulin bands are also common in hepatitis B, and when such bands are of high concentration, they may be seen as monoclonal by routine electrophoretic techniques (11-14). Monoclonal gammopathy, including that of the IgG kappa type, and in association with marrow plasmacytosis, has been well-described as a consequence of hepatitis B (11-14). As the liver disease improves, such elevated immunoglobulin levels may recede. Long-term follow-up is also available on a number of patients with monoclonal immunoglobulin renal deposition disease, including IgG kappa globulin deposition, without

obvious underlying cause, and multiple myeloma did not subsequently occur in a total of 20 such patients described in two different series (11-12).

I would agree with Dr. Barton that the published and usually accepted criteria for the diagnosis of multiple myeloma are not met in this case. For example, Mr. Lebron meets none of the three major and none of the four minor diagnostic criteria, according to the Salmon-Durie classification as outlined in modern hematological texts, nor does he meet the most recent World Health Organization (WHO) criteria (appended). All we really have here is a minimal bone marrow plasmacytosis, which could easily be attributed to the chronic hepatic disease, and very small monoclonal protein concentrations in the serum and in the kidney, neither of which are specific for multiple myeloma and which also could be a consequence of the chronic hepatitis B infection. Mr. Lebron does not have bone lesions or osteoporosis and did not exhibit the common clinical findings of multiple myeloma such as anemia, hypercalcemia, or neuropathy. Moreover, after several years of continued follow-up, he apparently still has no evidence for myeloma, which, by its nature, is typically a progressive disease.

I suspect that chronic hepatitis B, alone, is likely the cause of the entire illness in Mr. Lebron, although without special stains of the kidney biopsy, this could not be confirmed. No diagnostic criteria for multiple myeloma are met here, but even assuming this illness was the underlying diagnosis, is there evidence to support his allegation of a work-related etiology, possibly through exposure to chemicals such as benzene? Multiple myeloma is a generally easily recognized and specific hematologic disorder that affects about 15,000 persons per year in the United States or, in observations made during 1978-1990, an incidence of 4.1 cases/100,000 individuals (17). It has its peak incidence around age 64-66, and is typically sporadic in appearance. Unusual, but well described, is the appearance of multiple myeloma in a familial pattern (18-19). In these circumstances, aside from multiple myeloma, some other family members will have an isolated monoclonal gammopathy, and the appearance of multiple myeloma shows "anticipation" or appearance at an earlier age, in successive generations. Aside from this occasional hereditary predisposition, as stated in a recent review of multiple myeloma, **"Its epidemiologic pattern remains obscure and its cause is unknown"** (20). While many patients respond well to initial therapy, including autologous bone marrow (stem cell) transplantation, the illness is still considered to be incurable. Median survival after diagnosis remains about 3-4 years, although some patients may have an indolent course and live longer than 10 years. Several newer agents approved for treatment may extend the mean survival significantly.

Over the years, attempts have been made to link multiple myeloma with various chemical exposures or excessive stimulation of the immune system. In particular, petrochemical, gasoline and solvent workers have been studied because of their potential exposure to benzene, a rare cause of acute myeloid leukemia (AML), under certain conditions. The longitudinal study of the Pliofilm factory workers, who were exposed to high levels of pure benzene, remains the benchmark study cited by OSHA, EPA and other governmental agencies for the risk of hematological malignancies caused by excessive benzene exposure (21-24). In this intensively studied cohort, only AML was found in increased incidence and, specifically, the incidence of multiple myeloma was not increased (23). Similarly, multiple myeloma was not identified as appearing in increased incidence in the large, "Chinese" study of more than 74,000 factory workers, primarily painters, exposed to disputed, but probably massive, amounts of benzene and

other chemicals, although an excess number of cases of AML and myelodysplasia was observed (25-27). Large studies of petrochemical and gasoline workers with the potential for benzene and other hydrocarbon exposures, as well as rubber/butadiene workers and painters exposed to multiple solvents, also have shown no increase in the incidence of myeloma (28-37). Many of these epidemiological studies have been carried out on specific cohorts with long term serial follow-up of exposed workers. Reviews of meta-analyses and other studies fail to support a chemical-induced etiology for multiple myeloma (21, 38).

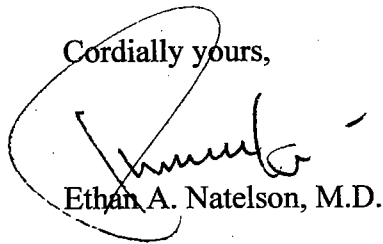
The lack of any evidence of an increased incidence of multiple myeloma after exposure to potentially genotoxic chemicals, such as benzene and butadiene, should not be surprising. We have an infinite variety of extremely powerful genotoxic and mutagenic drugs that are widely used in the treatments of various malignancies and, in some instances, as immunosuppressive agents. These chemicals have caused several thousand well-documented cases of so-called secondary or therapy-induced AML and myelodysplasia through many different pathways of genetic damage (39-41). Yet, there is no such companion syndrome as secondary or therapy-induced multiple myeloma. Even among patients with Hodgkin's disease, having been exposed to both chemotherapy and radiation, and then surviving for many years thereafter, the incidence of multiple myeloma is not increased (42). Finally, cigarette smoke, with its content of its many potential carcinogens, has not been associated with an increased risk of multiple myeloma, although the incidence of acute myeloid leukemia/myelodysplasia may be increased (43).

In recent years, attention has been focused on the ability of viral infection to induce human cancer. For example, the human papilloma virus accounts for virtually all cases of cervical cancer, in women. The Epstein-Barr virus is a well-known cause of both Hodgkin's and non-Hodgkin's lymphoma, and hepatitis C may also cause non-Hodgkin's lymphoma (39-43). Certain strains of Herpes virus are linked to the etiology of Kaposi's sarcoma in HIV-infected patients. There also has been speculation that strains of Herpes virus may also cause multiple myeloma, although this etiology has not yet been fully confirmed (44). A viral etiology might account for the interesting observation that school teachers appear to have an increased incidence of multiple myeloma, perhaps through their wide exposure to young students potentially carrying a variety of proliferating viral agents (45).

In summary, and in my opinion, there is no definitive clinical and/or laboratory evidence that Mr. Lebron has multiple myeloma. All aspects of his illness are quite consistent with chronic hepatitis B infection. However, even assuming that he did have myeloma, to claim that this illness is consequent to alleged exposures to industrial chemicals during his work in the automotive industry, seems totally unreasonable based upon the body of knowledge that we have about this specific disease, as well as detailed long-term observations on vast numbers of workers exposed to a wide variety of hydrocarbons. Addressed in terms of "specific" causation, there is no test that would allow one to prove that any particular patient with multiple myeloma contracted the disease from any particular chemical. In terms of "general" causation, there are no consistent epidemiological studies that have shown multiple myeloma be a consequence of exposure to any particular chemical, at any particular threshold of exposure.

I hope this information is of benefit to you, and please let me know if you require any additional information.

Cordially yours,



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#### REFERENCES:

1. Mai, HL, et al Immunoglobulin heavy chain can be amyloidogenic: Morphologic characterization including immunoelectron microscopy. Amer J Surg Pathol 27:541-545, 2003.
2. Copeland, JN, et al Metachronous development of nonamyloidogenic lambda light chain deposition disease and IgG heavy chain amyloidosis in the same patient. Amer J Surg Pathol 27:1477-1482, 2003.
3. Ozdamar, SO, et al Hepatitis-B virus associated nephropathies: a clinicopathological study in 14 children. Pediatr Nephrol 18:23-28, 2003.
4. Quan, A, et al Resolution of hepatitis B virus-related membranoproliferative glomerulonephritis after orthotic liver transplantation. Pediatr Nephrol 9:599-602, 1995.
5. Conjeevaram HS, et al Long-term outcome of hepatitis B virus-related glomerulonephritis after therapy with interferon alfa. Gastroenterology 109:540-546, 1995.
6. di Belgiojoso, GB et al Virus-related glomerular diseases: histological and clinical aspects. J Nephrol 15:469-479, 2002.
7. Pyrsopoulos, NT, Extrahepatic manifestations of chronic viral hepatitis. Curr Gastroenterol Rep 3:71-78, 2001.
8. Lhotta, K, Beyond hepatorenal syndrome: glomerulonephritis in patients with liver disease. Semin Nephrol 22:302-308, 2002.

9. Lin, J, et al Renal monoclonal immunoglobulin deposition disease: The disease spectrum. *J Am Soc Nephrol* 12:1482-1492, 2001.
10. Rosenstock, JL, et al Fibrillary and immunotactoid glomerulonephritis: Distinct entities with different clinical and pathologic features. *Kidney Internat* 63:1450-1461, 2003.
11. Tsianos, EV, et al Oligoclonal immunoglobulin bands in serum in association with chronic viral hepatitis. *Amer J Gast* 85:1005-1008, 1990.
12. Perez Losada, J, et al Oligoclonal gammopathy and infection by hepatitis B. *An Med Interna* 15:399-398, 1998.
13. Heer, M, et al Monoclonal gammopathy in chronic active hepatitis. *Liver* 4:255-263, 1984.
14. Aprosina, ZG, et al Monoclonal immunoglobulinopathy in chronic active hepatitis and liver cirrhosis. *Ter Arich* 62:105-111, 1990
15. Alpers, CE, et al Single light chain subclass (kappa chain) immunoglobulin deposition in glomerulonephritis. *Human Path* 16:294-304, 1985.
16. Nasr, SH, et al Proliferative glomerulonephritis with monoclonal IgG deposits: A distinct entity mimicking immune-complex glomerulonephritis. *Kidney Int* 65:85-96, 2004.
17. Kyle, RA, et al Review of 1027 patients with newly diagnosed multiple myeloma. *Mayo Clin Proc* 78:21-33, 2003.
18. Lynch, HT, et al Familial multiple myeloma: a family study and review of the literature. *J Natl Can Inst* 93:1479-1483, 2001.
19. Grosbois, B, et al Familial multiple myeloma: report of fifteen families. *Brit J Haematol* 105:768-770, 1999.
20. Bataille, R, et al Multiple Myeloma *New Eng J Med* 336:1657-1664, 1997.
21. Bergsagel, DE, et al Benzene and Multiple Myeloma: Appraisal of the Scientific Evidence. *Blood* 94:1174-1182, 1999.
22. Williams, PRD, et al Reconstruction of benzene exposure for the Ploofilm cohort (1936-1976) using Monte Carlo techniques. *J Toxicol Environ Health* 66:677-781, 2003.
23. Bayliss, DL, et al Carcinogenic Effects of Benzene: An Update. *Nat Cent Environ Access*, Washington Office EPA/600/P-97/001G, pg 1-57, 1998.
24. Paxton, MG, et al Leukemia Risk Associated with Benzene Exposure in the Ploofilm Cohort: I. Mortality Update. *Risk Analysis* 14:147-154, 1994.

25. Hayes, RB, et al Benzene and the dose response incidence of hematologic neoplasms. *J Natl Can Instit* 89:1065-1071, 1999.
26. Wong, O, Investigation of benzene exposure, benzene poisoning and malignancies in China. *Reg Toxicol Pharm* 35:126-135, 2002.
27. Budinsky, R, et al An evaluation of modeled benzene exposure and dose estimates published in the Chinese-National Cancer Institute Collaborative Epidemiologic Studies. *Reg Tox Pharmacol* 30:244-258, 1999.
28. Wong, O, Risk of acute myeloid leukemia and multiple myeloma in workers exposed to benzene. *Occup Environ Med* 52:380-384, 1995.
29. Wong, O, and Rabbe, GK Multiple myeloma and benzene exposure in a multinational cohort of more than 250,000 petroleum workers. *Reg Toxicol Pharm* 26:188-199, 1997.
30. Lynge, E, et al Risk of cancer and exposure to gasoline vapors. *Amer J Epidemiol* 145:554-568, 2000.
31. Satin, KP, et al A 50 year mortality follow-up of a large cohort of oil refinery workers in Texas. *J Occup Environ Med* 38:492-506, 1996.
32. Divine, BJ, et al Update of the Texaco mortality study 1947-93: Part II., Analyses of specific cause of death for white men employed in refining, research, and petrochemicals. *Occup Environ Med* 56:174-180, 1999.
33. Sathiakumar, N, et al Mortality from cancer and other causes of death among synthetic rubber workers. *Occup environ Med* 55:230-235, 1998.
34. Divine, BJ, et al A cohort mortality study among workers at a 1,3 butadiene facility. *Chemico-Biological Interactions* 135-136:532-553, 2001.
35. Tsai, SP, et al A mortality, morbidity, and hematology study of petrochemical employees potentially exposed to 1,3-butadiene monomer. *Chemico-Biological Interactions* 135-136:555-567, 2001.
36. Glass, EC, et al Leukemia risk associated with low level benzene exposure. *Epidemiol* 14:569-577, 2003.
37. Brown, LM, et al Exposures in the painting trades and paint manufacturing industry and risk of cancer among men and women in Sweden. *J Occup Env Med* 44:258-264, 2002.
38. Sonoda, T, et al Meta-analysis of multiple myeloma and benzene exposure. *J Epidemiol* 11:249-254, 2001.

39. Smith, MA, et al The secondary leukemias: Challenges and research directions. *J Natl Cancr Instit* 88:407-418, 1996.
40. Mauritzson, N, et al Pooled analyses of chemical and cytogenetic features in treatment-related and de novo adult acute myeloid leukemia and myelodysplastic syndromes based on a consecutive series of 761 patients analyzed 1976-1993 and on 5098 unselected cases reported in the literature. 1974-2001. *Leukemia* 16:2366-2378, 2002.
41. Smith, SM, et al Clinical-cytogenetic associations in 306 patients with therapy-related myelodysplasia and myeloid leukemia: The University of Chicago series. *Blood* 102:43-52, 2003.
42. Dores, GM, et al Second malignant neoplasms among long term survivors of Hodgkin's disease: A population based evaluation over 25 years. *J Clin Oncol* 29:3484-3494, 2002.
43. Adami, J, et al Smoking and the risk of leukemia, lymphoma and multiple myeloma (Sweden). *Cancer Causes Control* 9:49-56, 1998.
44. Ambinder, R, Infection and lymphoma. *New Eng J Med* 349:1309-1311, 2003.
45. Mele, A, et al Hepatitis C virus and B-cell non-Hodgkin lymphomas: an Italian multicenter case-control study. *Blood* 102:996-999, 2003.
46. Luppi, M, et al The new lymphotropic herpesviruses (HHV-6, HHV-7, HHV-8) and hepatitis C virus (HCV) in human lymphoproliferative diseases. An overview. *Haematol* 81:265-281, 1996.
47. Goedert, JJ, et al Spectrum of AIDS-associated malignant disorders. *Lancet* 351:1833-1839, 1998.
48. Hsu, H, et al Detection of Kaposi-sarcoma associated Herpesvirus in bone marrow samples from patients with multiple myeloma. *Cancer* 91:1409-1413, 2001.
49. Figgs, LW, et al Risk of multiple myeloma by occupation and industry among men and women. A 24-state death certificate study. *J Occup Med* 36:1210-1221, 1994.