UNITED STATES DISTRICT COURT
DISTRICT OF MINNESOTA

IN RE: NATIONAL HOCKEY LEAGUE PLAYERS' CONCUSSION INJURY LITIGATION	)	MDL No. 14-2551 (SRN/BRT)
This Document Relates To: ALL ACTIONS	)	**REDACTED**

SUPPLEMENTAL DECLARATION OF ROBERT C. CANTU, MD

I. INTRODUCTION

I have reviewed the reports signed by Drs. Castellani (Dkt. 733), Hazrati (Dkt. 738), Olanow (Dkt. 741), Schneider (Dkt. 746), Iverson (Dkt. 732-5), Finkel (Dkt. 735), Yaffe (Dkt. 748), McCrory (Dkt. 732-07), Guskiewicz (Dkt. 732-04), Randolph (Dkt. 732-11) and the Declaration of John Beisner (Dkt. 732-2). I understand the NHL has submitted those reports in opposition to Plaintiffs' Motion for Class Certification. I have prepared this supplement to my initial declaration and in response to those reports and declarations.

II. DISCUSSION

A. "Association" Versus "Causation"

1. The Critical Differences Between Association And Causation

The NHL seeks to avoid the long-known causal association between brain trauma, especially repetitive brain trauma (RBT), and the increased risk of neurodegenerative diseases (NDD), including CTE. The NHL, through the reports it has submitted, ignores

the increased risk of neurodegenerative diseases arising from brain trauma, and instead attempts to reframe the issue as a question of association versus definitively proven scientific causation.[1] This is not the issue, of course. But, even if it was, the NHL has misconstrued the distinction between association and causation as it pertains to the link, a link acknowledged by the National Football League in Congressional Testimony and internally by the NHL.[2] Furthermore World Rugby's Position Statement on CTE since 2013 has recognized "the proposed link between repetitive head injuries and dementia. World Rugby acknowledges that studies on boxers report an association between high levels of exposure to head injury and long term neurological problems. Further we acknowledge the autopsy based studies in contact sports, such as American Football, report an association between repetitive head injuries and neuro-degenerative disease."[3] The difference between a mere observed association, and the strong causal association

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[1] Internal NHL documents show the NHL is aware of the increased risk. *See* NHL2054171-81 at 2054177 "[CTE]...has been associated with repetitive TBI in collision sports and warfighters, however, association is not causation."); [redacted]

[2] *See* NHL0026415-16 (Dr. Echemendia: "I informed [N.Y. Times reporter Jeff Klein]...that a link has been made between head trauma and CTE."); and Testimony of Jeff Miller, Senior Vice President, National Football League, before the Subcommittee on Comm., Manuf. and Trade of the Cttee. on Energy and Commerce, U.S. House of Rep., March 14, 2016, www.c-span.org/video/?406450-1/hearing-concussions at 1:24:25-1:25:15.

[3] "Position Statement" of World Rugby adopted 2013 and reaffirmed November 2017.

observed linking head trauma to NDD such as CTE is significant. Scientific causation, in the medical community, generally requires the establishment of a baseline background risk of an outcome, a prospective study of a population, and a subsequent comparison of the risk of that outcome in the targeted population to the risk of the control group. Scientific causation can only be reached after all confounders, bias, and random chance have been eliminated from the study. Due to the cost and decades required to complete them such scientific causation studies are infrequently done. When such scientific causation studies are done, they are frequently undertaken to confirm what has become an accepted fact. The acceptance of causation frequently occurs based on the strength of association and confirmed dose response effect. Indeed, most FDA-mandated warnings on medications or best practices in medicine are not based on statistically proven cause and effect but rather avoidance of substances or interventions based on side-effects or consequences produced by a presumed causal-relationship.[4]

Scientific association, on the other hand, refers to study of a population that has found that certain outcomes are associated with certain variables. To bridge the gap between association and causation, epidemiologists consider the following Bradford-Hill criteria:[5]

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[4] Glass TA, Goodman SN, Hernan MA, Samet JM. Causal Inference in Public Health. Annu. Rev. Public Health 2013;34:61-75.

[5] Hill AB, The Environment and Disease: Association or Causation? President's Address, Section of Occupational Medicine Meeting Jan. 14, 1965, in Proceedings of Royal Soc'y of Med. 1965;58 (5): 295-300.

1. strength of the association;
2. consistency of findings;
3. specificity of the association;
4. temporal sequence of association;
5. biological gradient (a dose-response relationship);
6. biological plausibility;
7. coherence; and
8. experimental evidence.

Some of the NHL reports attempt to define these criteria.[6] However, the NHL misconstrues how the Bradford-Hill criteria apply to the connection between head trauma and – for example – CTE, which I address *infra*.

To transition from association to causation definitively, a prospective study is required. In the case of retired NHL players, the NHL's experts appear unanimous in saying a prospective study of NHL players would be necessary to determine if the head trauma they sustain in their careers increases their risk of NDD. This study would require cooperation from the NHL and NHLPA to embark on a study of their players, spanning at least multiple decades, to determine the incidence rates of NDD, control for all confounders and variables, and compare those results to a control-matched population of those who do not have any history of head trauma.[7] If fully funded and started today, this

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[6] *See, e.g.,* Cassidy Decl. (Dkt. 732-2).

[7] The NHL has studiously avoided doing or funding any such study. [redacted]

would not be completed before 2030, at the earliest. Such research would increase our knowledge of the risks associated with NHL hockey, but would not change the repeatedly observed fact that the risks of NDD associated with repetitive head trauma sustained by NHL players places them at a greater risk of suffering from neurodegenerative diseases than someone who does not participate in NHL hockey or other contact sports.

2. The Scientific Literature Demonstrates An Overwhelming Causal Association – Nearly 100%

With respect to CTE, scientific understanding will likely follow a similar trajectory to other neurodegenerative diseases, which underwent intense scrutiny, debate and revision before formal diagnostic, pathological and clinical criteria were validated and agreed upon.[8] All but one published study on the topic of CTE have determined that head trauma is a necessary occurrence, but alone does not guarantee that CTE will occur. The National Institute of Health consensus panel that defined the pathologic criteria for the diagnosis of CTE stated "this pathology has only been found in individuals exposed

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[redacted]; NHL1971101; NHL2132286-88 (Dr. Echemendia: "I know discussing this [the issue of long term consequences of head injuries and the relationship to dementia, CTE, depression] is akin to touching the third rail...1"); NHL2304283-84 (Dr. Echemendia: "Bill [Daly] questioned whether we really want to look at this question ["Are these neurocognitive and psychological consequences of playing in the NHL?"] at all."); NHL2469718-20; NHLPA_0001308-10 (Dr. Echemendia and I. Penny: "Daly was crudely dismissive of the idea [of study of the long-term health effects for concussed hockey players]."); NHL2110271-74 (J. Grand: "Leave the dementia issues to the NFL!")

[8] Hutchinson AD, Mathias JL. Neuropsychological Deficits in Frontotemporal Dementia and Alzheimer's disease: a Meta-Analytic Review. J Neurol Neurosurg Psychiatry 2007;78:917-928.

to brain trauma, typically multiple episodes."[9] In other words, receiving repetitive head trauma does not mean that an athlete will absolutely have a later-life CTE diagnosis, but receiving ***no*** head trauma will almost certainly preclude CTE.[10] There is a lone reported instance of a CTE diagnosis in a deceased individual whose wife reported no known head trauma.[11] But, this study is of dubious, if any, scientific value because the deceased's wife was the sole historian, meaning that knowledge of head trauma in youth and prior to marriage was lacking. Because the deceased's history was incomplete this study fails to rebut the scientific community's understanding that CTE requires repetitive head trauma. Likewise, I know of no literature that has ever reported an instance of "punch-drunkenness" or dementia pugilistica in any patient without a history of head trauma, reinforcing the conclusion that head trauma is a necessary predicate for this condition. The published case studies overwhelmingly demonstrate a causal association of nearly 100% between head trauma and neurodegenerative diseases such as CTE.

With this understanding, the Bradford-Hill criteria support the conclusion that the causal association between head trauma and CTE and other NDD is extremely strong. In

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[9] McKee AC, Cairns NJ, Dickson DW, Folkerth RD, Keene CD, Litvan I, Perl DP, Stein TD, Stewart W, Vonsattel JP, Tripodis Y, Alvarez VE, Bieniek KF, Crary J, Dams-O'Connor K, Gordon W, TBI/CTE group. The First NINDS/NIBIB Consensus Meeting to Define Neuropathological Criteria for the Diagnosis of Chronic Traumatic Encephalopathy. Acta Neuropathologica 2016; 131:75-86.

[10] The NHL is aware of this fact. *E.g.,* NHL07877093-101 ("What we know is that repetitive brain trauma is necessary for CTE to develop, but it is not sufficient."); [redacted].

[11] Gao AF, Ramsay D, Twose R, Rogaeva E, Tator C, Hazrati LN. Chronic Traumatic Encephalopathy-like Neuropathological Findings without a History of Trauma. International Journal of Pathology and Clinical Research 2017; 3:50.

addition to the strength of the association, the consistency of findings can be observed across various contact sports and other activities associated with head trauma, such as domestic abuse victims. It has also been reported in autism with repetitive head banging, and grand mal epilepsy with multiple head trauma.[12] Where CTE is expected (violent activities like contact sports), it is typically found, and where it is not (noncontact sports), CTE is not found.[13]

A recent study by Tagge does prove causation between RBT and CTE in a rodent animal model.[14] It is the repetitive head hits not concussion that is shown to cause CTE. While there is not a correlation between concussion and CTE in this rodent model there is a positive correlation with cumulative head impact exposure and the development of the neuropathology of CTE.

Temporally, CTE diagnoses are usually made several decades after sustaining repetitive head trauma, with occasional outliers where CTE has been diagnosed

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[12] McKee AC, Cantu RC, Nowinski CJ, AB, Headley-Whyte ET, Gavett BE, Budson AE, Santini VE, Lee HS, Kubilus CA, Stern RA. Chronic Traumatic Encephalopathy in Athletes: Progressive Tauopathy After Repetitive Head Injury. Journal of Neuropathology and Experimental Neurology 2009; 68 (7):709-735.

Athletes: Progressive Tauopathy After Repetitive Head Injury. Journal of Neuropathology and Experimental Neurology 2009;68(7):709-735.

[13] Glass TA, Goodman SN, HernanMA, Samet JM. Causal Inference in Public Health. Annu. Rev. Public Health 2013; 34:61-75.

[14] Tagge CA, et al. Concussion, Microvascular Injury, and Early Tauopathy in Young Athletes After Impact Head Injury and An Impact Concussion Mouse Model. Brain 2017; awx350, https://doi.org/10.1093/brain/awx350.

posthumously in younger athletes such as Junior A hockey players.[15] Children have not been diagnosed with CTE.

As to the existence of a dose-response relationship, both the literature and the work of Boston University have shown that increased exposure to head trauma leads to a greater scoring of CTE severity.[14, 16, 17, 18] Increased head impact exposure also has been shown to lead to increased tau pathologies in the brain.[19] Furthermore, increased head impact exposure has been shown to lead to increased later-life neurodegenerative diseases other than CTE.[20] Also consistent with dose-response relationship is the just

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[15] McKee AC, Kiernan P, NicksR, Alvarez V, Abdolmohammadi B, Alosco M, Mez J, Stein T, Huber B, Nowinski C, Cormier K, Caroline Kubilus C, Douglas Katz D, Stern R, Cantu R, Kowall N, Goldstein L. Clinicopathological Findings in 8 Young Ice Hockey Players. Journal of Neuropathology and Experimental Neurology 2017; 76:523.

[16] McKee AC, Stern RA, Nowinski CJ, Stein TD, Alvarez VE, Daneshvar DH, Lee HS, Wojtowicz SM, Hall G, Baugh CM, Riley DO, Kubilus CA, Cormier KA, Jacobs MA, Martin BR, Abraham CR, Ikeau T, Reichard RR, Wolozin BL, Budson AE, Goldstein LE, Kowall NW, Cantu RC. The Spectrum of Disease in Chronic Traumatic Encephalopathy. Brain 2013; 136:43-64.

[17] Cherry JD, Tripodis Y, Alvarez VE, Huber B, Kiernan PT, Daneshvar DH, Mez J, Montenigro PH, Solomon TM, Alosco ML, Stern RA, McKee AC, Stein TD. Microglial Neuroinflammation Contributes to Tau Accumulation in Chronic Traumatic Encephalopathy. Acta Neuropathologica Communications 2016; 4:112.

[18] Stein TD, Alvarez VE, McKee AC. Concussion in Chronic Traumatic Encephalopathy. Curr Pain Headache Rep 2015;19(10):522.

[19] Alosco, ML., et al. Repetitive Head Impact Exposure and Later-Life Plasma Total Tau in Former National Football League Players. Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring 2017; 7:33-40.

[20] Montenigro PH., et al. Cumulative Head Impact Exposure Predicts Later-Life Depression, Apathy, Executive Dysfunction, and Cognitive Impairment in Former High School and College Football Players. Journal of Neurotrauma 2017;34(2) 328-340.

published JAMA article of 202 football players where all cases of high school players with CTE had mild pathology while most college, semipro, and professional athletes had severe CTE pathology. This clearly demonstrates those with CTE pathology with the least exposure had much less severe pathology compared to those with greater exposure to repetitive head trauma.[21]

The biological plausibility of this connection is well-established and described in my Declaration,[22] albeit more research is needed to better understand the pathway or steps leading to the neuropathological findings that have been reported at length.[23] It is also important to understand that all of the criteria or what Hill calls "viewpoints" are not absolute nor does inference of a causal relationship require that all criteria be met.[24]

Lastly, the experimental evidence requirement asks if removal of the head impact exposure alters the frequency of the reported outcome – in this case, CTE. Put simply, barring the single reported instance of CTE diagnosis in a patient with no reported history

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[21] Mez J, Daneshvar DH, MD, Tiernan PT, Abdolmohammadi B, Alvarez VE, Huber BR, MD, Alosco ML, Solomon TM, Nowinski CJ, McHale L, Cormier KA, Kubilus CA, Martin BM, Murphy L, Baugh CM, Montenigro PH, Chaisson CA, Tripodis Y, Kowall NW, Weuve J, McClean MD, Cantu RC, Goldstein LE, Katz DI, Stern RA, SteinTD, McKee AC,. Clinicopathological Evaluation of Chronic Traumatic Encephalopathy in Players of American Football, JAMA 2017; 318(4):1-12.

[22] Cantu Declaration §§ IV.A.4-5, IV.E.3.

[23] *See* [redacted]; 2008 Zurich Consensus Statement ("Epidemiological studies have suggested an association between repeated sports concussions during a career and late life cognitive impairment.").

[24] Glass TA, Goodman SN, HernanMA, Samet JM. Causal Inference in Public Health. Annu. Rev. Public Health 2013;34:61-75.

of head trauma – unreliable and poorly documented – every single one of the hundreds of CTE diagnoses was to a patient with a history of brain trauma, almost always repetitive.[25]

Aggregated, these factors compel a single and overwhelming conclusion: the causal association between head trauma and neurodegenerative CTE is extremely strong, even if it does not yet reach the absolute conclusiveness of scientific causation.[26]

B. The Effects Of Head Trauma On White Matter And Brain Reserve

My Declaration, along with the Declaration of Dr. Hoshizaki, discuss the means by which repetitive head trauma can cause asymptomatic injuries or changes that increase the risk, severity, or speed the onset of NDD.[27] The validity of these findings is not diminished by their relative recency. In addition to the changes observed in boxers and football players,[28] hockey players,[29] and varsity soccer players,[30] newly reported research has reinforced these findings in varsity women's soccer players[31] and an animal model involving mice has concluded that "Chronic White Matter Inflammation Is Induced by

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[25] Bieniek KF, et al., Chronic Traumatic Encephalopathy Pathology in a Neurodegenerative Disorders Brain Bank, 130 ACTA NEUROPATHOLOGICA 2015;130:877-889.

[26] Manley GT, et al., A Systematic Review of Potential Long-Term Effects of Sport-Related Concussion. Br. J. Sports Med 2017;0:1-10.

[27] Cantu Declaration § IV.A.5; Hoshizaki Declaration § IV.B.

[28] Cantu Declaration ¶ 47.

[29] Cantu Declaration ¶ 55.

[30] Cantu Declaration ¶ 56.

[31] Ralston J, et al. Non-Linear Correlation Between Cumulative Sub-Concussive Head Impact Trauma and Severity of Localized Brain White Matter Changes in College Athletes. Br. J. Sports Med 2017; 51:e.

RTBI" and "white matter pathology after RTBI is chronic, similar to reports from human TBI brains that show that white matter inflammation is a long-lasting consequence of TBI. . . ."[32] This same white matter inflammatory response to RTBI was observed by Tagge and Cherry in their publications as well.[14, 17]

Other researchers involved in study of head trauma sustained in various ages of rats have observed that head trauma suffered in adulthood was associated with anxiety-like behaviors later in life, and that "Clinical data support that a history of TBI combined with brain changes associated with normal aging can advance cognitive decline in older adults,"[33] as discussed in my Declaration.[34] Given that numerous other researchers have discussed and recognized the effect that head trauma has on white matter and brain reserve,[35] the NHL's characterization of my testimony is hyperbolic and erroneous. It has long been known and accepted, and is beyond reasonable dispute that suffering a

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[32] Winston CN, et al. Dendritic Spine Loss and Chronic White Matter Inflammation in a Mouse Model of Highly Repetitive Head Trauma. The American Journal of Pathology 2016; 186(3):552-567.

[33] Rowe RK., et al. Aging with Traumatic Brain Injury: Effects of Age at Injury on Behavioral Outcome Following Diffuse Brain Injury in Rats. Developmental Neuroscience 2016;38(3):195-205.

[34] Cantu Declaration ¶ 53-54.

[35] *See also* NHL1669037-39 (6/4/10 email; Echemendia criticizes Baycrest study showing that "retired professional hockey players have greater rates of early onset dementia when compared to the general public."); NHL2079759-65 (Dr. Amen: "It seems obvious now that contact sports like football and hockey potentially lead to long-term brain damage for players."); NHLPA_0001308-10 (Dr. Perl: "But if 20% have what should otherwise be a very rare condition, and that could be the case here, you can't rely on the 80% to suggest there is no problem.")

concussion increases the likelihood of subsequent concussion,[36] so it is inherently necessary that a concussion would cause a lasting and permanent change to cause such a change. DTI MRIs have shown these very changes to correspond to repetitive head trauma,[37] noting decreases in fractional anisotropy to indicate a reduction in white matter density.[38] Researchers have noted at length the relationship between brain volume – akin to brain reserve – and neuropathologies,[39] and have also noted that repetitive head trauma is associated with decreases to brain reserve and total brain volume.[40] Though the NHL characterizes the preceding statements as analytical leaps or revolutionary hypotheses, a

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[36] Gerberich S, Priest J, Boen J, et al. Concussion Incidences and Severity in Secondary School Varsity Football Players. Am. J. Public Health 1983; 73:1370-1375.

Albright JP, McAuley E, Martin RK, Crowley ET, Foster DT. Head and Neck Injuries in College Football: An Eight-Year Analysis. Am. J. Sports Med 1985;13:147-152.

Cantu, RC. Recurrent Athletic Head Injury: Risks and When to Retire. Clin. Sports Med 2003; 593-603.

[37] Cantu Declaration § IV.A.5; Hoshizaki Declaration § IV.B.

[38] Cantu Declaration ¶ 49.

[39] Smith C, Review: The Long-Term Consequences of Microglial Activation Following Acute Traumatic Brain Injury. 39 NEUROPATHOL. APPL. NEUROBIOL 2013; 39:35-44.

Tremblay S, et al., Sports Concussions and Aging: A Neuroimaging Investigation. Cerebral Cortex 2013;23:1159-1166.

Zhou Y, et al., Mild Traumatic Brain Injury: Longitudinal Regional Brain Volume Changes. RADIOLOGY 2013;267(3):880-890.

Bigler E, Traumatic Brain Injury, Neuroimaging, and Neurodegeneration, FRONTIERS IN HUMAN NEUROSCIENCE 395 2013;395(7):1-15.

[40] Jarrett M, et al. A Prospective Pilot Investigation of Brain Volume, White Matter Hyperintensities, and Hemorrhagic Lesions after Mild Traumatic Brain Injury. Frontiers in Neurology 2016;11(7):1-8.

review of the literature demonstrates that these relationships are well-supported and scientifically reliable.

C. Head Trauma From Different Sports Can Certainly Be Compared To NHL Hockey

Fundamentally, the human brain does not recognize what the source of injury is when it is traumatized, regardless of the trauma source. In the context of a contact sport such as NHL hockey, the same physiological responses are expected from the same types of head trauma, regardless of sport of origin or whether that injury occurred outside of sport. This is why CTE has been found in victims of domestic violence,[41] military veterans, autistic head-bangers, and epileptics, along with those who played in contact sports,[42] including ice hockey at the amateur[43] and the NHL level.[44] Overall the published BU experience with ice hockey found CTE in 50% (4 of 8) of amateur ice hockey players and in professionals, CTE was present in 80%: one young player at age 20 had no CTE but 3 of 4 (75%) of NHL players had stage 2 CTE and 1 had stage 3 CTE with Lewey Bodies.

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[41] Roberts GW, et al., Dementia in a Punch-Drunk Wife. Lancet 1990; 335:918–919.

[42] McKee AC., et al. Chronic Traumatic Encephalopathy in Athletes: Progressive Tauopathy after Repetitive Head Injury. Journal of Neuropathology & Experimental Neurology 2009;68.(7) 709-735.

[43] McKee A, et al. Clinicopathologic Findings in 8 Young Ice Hockey Players. Neuropathol Exp Neurol 2017; 76 (6):523.

[44] McKee AC, Stern RA, Nowinski CJ, Stein TD, Alvarez VE, Daneshvar DH, Lee H-S, Wojtowicz SM, Hall G, Baugh CM, Riley DO, Kubilus CA, Cormier KA, Jacobs MA, Martin BR, Abraham CR, Ikezu T, Reichard RR, Wolozin BL, Budson AE, Goldstein LE, Kowall NW, Cantu RC ,The spectrum of disease in chronic traumatic Encephalopathy. Brain, 2013;136 43–64.

Important risk factors for the occurrence of CTE and other NDD associated with head trauma is the length of exposure to head impacts, magnitude of head impacts, and frequency of head impacts, and not just the sport of their origin.[45] It is beyond reasonable dispute that professional boxers (and likely MMA fighters) are struck in the head more than any other contact sport athlete,[46] with football, hockey and lacrosse also in the high risk sport group in terms of head impact exposure.[47] While different contact sports will prove to have different rates of NDD from each other, ***all*** contact sports have increased head impact exposure compared to non-contact sport athletes and those without a history of head trauma. The disparity between the hockey player and football player is far less than the disparity between the hockey player and a control without repetitive head trauma. Therefore, it is clear, and has been for many decades, that NHL hockey players face an increased risk of long-term neurodegenerative diseases such as CTE because of the head trauma they experience in the NHL.

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[45] Montenigro PH., et al. Cumulative Head Impact Exposure Predicts Later-Life Depression, Apathy, Executive Dysfunction, and Cognitive Impairment in Former High School and College Football Players. Journal of Neurotrauma 2017;34(2) 328-340.

[46] Stein TD, Alvarez VE, and McKee AC. Chronic Traumatic Encephalopathy: A Spectrum of Neuropathological Changes Following Repetitive Brain Trauma in Athletes and Military Personnel. Alzheimer's research & therapy 2014 Jan 15;6(1):4.

[47] Hof P R, et al. Neuropathological Observations in a Case of Autism Presenting with Self-Injury Behavior. Acta Neuropathologica 1991; 82(4): 321-326. Once again, the NHL recognizes this fact. *See, e.g.*, NHL1639343 (Dr. Echemendia discussing NCAA Data, 1988-2004, showing "Ice hockey is the sport with the highest risk of concussion among college athletes for both men and women…higher than football for men and soccer for women (by far)….").

My deposition testimony on this matter has been mischaracterized by the NHL. I was asked, as a clinician, which of two hypothetical hockey players – one with a short career and history of concussions, and one with a long career without any diagnosed concussions – would be at increased risk for NDD. I explained that it would not be possible to answer that question at this time with certainty but both would be at increased risk.[48] A very recent publication from our BU group published months after that deposition would lead me now to suggest the hockey player with a long exposure and no recognized concussions would have a higher risk of CTE compared to a hockey player with a short career and a history of concussions.[14] While I explained that it is unclear whether hockey poses a risk equal to football based on total head impacts sustained, I wish to clarify that it is really not disputable that *both* have a significantly increased risk compared to those who do not participate in contact sports, regardless of whether they are at marginally more or marginally less danger than football players. Likewise, when I correctly acknowledged that different sports and different sporting positions carry different head impact exposure profiles, I did not state that the differences are so great as to invalidate research in one sport as it can be applied to another. The NHL repeatedly points to the two Agreement Statements and the subsequent Consensus Statements on concussions in sports. All of those documents involve inter-disciplinary sport data. Further, Dr. Hoshizaki addressed this very topic in his Declaration, noting that the NHL's

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[48] Cantu Dep. 250:8-18.

own research supports a finding that the head impacts sustained by an average NHL player do not differ so significantly based on position.[49]

Comparing head impact exposure profiles across sports and positions is *not* analogous to comparing different risks of different pharmaceuticals in similar categories of drugs.[50] A more apt analogy between football, hockey, and boxing head impact exposures would be, perhaps, a comparison of the side effects of exposure to varying doses of a toxic compound, and comparing risk profiles among those different doses against a control who was not exposed to the toxic compound

III. CONCLUSION

In the case of well-studied trauma-associated human disease, it is not feasible to conduct experimental studies to provoke disease in human subjects and no direct determination of causality can be ethically conducted. As such, the determination that needs to be made is whether the preponderance of the evidence allows one to reasonably conclude that the disease is associated with traumatic exposure, a constant of almost all reported cases of CTE.

Indeed, the NIH panel also stated that: "[CTE] pathology has only been found in individuals exposed to brain trauma, typically multiple episodes." Although further research is needed to identify the critical variables essential to the development of CTE after RTBI including the role of genetics, inflammatory response, age, gender, and

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[49] Hoshizaki Declaration Table 9.

[50] Motion to Exclude Testimony of Robert C. Cantu, M.A., M.D., FACS, FAANS, FICS, FACSM, Dkt. 769 at *29-30.

substance abuse, the overwhelming preponderance of evidence especially the 99% occurrence with head trauma, almost always repetitive, and high dose response relationship, supports the conclusion that CTE is directly associated with RTBI.

The best analogy between the relationship between repetitive head trauma and NDD including CTE is the smoking saga. As increasing epidemiologic evidence mounted between the relationship of cigarette smoking and lung cancer, the tobacco industry carried out a strategy to question the credibility of the epidemiologic data, especially of the most salient studies.[51] The creation and dissemination of doubt remain current strategies widely employed by those whose interests are threatened by a causal finding.[52]

I declare under penalty of perjury under the laws of the State of Massachusetts that the foregoing is true and correct. I reserve the right to amend, modify or supplement my declarations as I deem appropriate.

EXECUTED this 6th day of February, 2018, at Concord, Massachusetts.

Robert C. Cantu

Robert C. Cantu, M.D.

[51] Phillips CV, Goodman KJ. The Missed Lessons of Sir Austin Bradford Hill. Epidemiol. Perspect. Innov 2004;1(3):1-5.

[52] Macintyre S, Ellaway A, Cummins S. Place Effects on Health: How Can We Conceptualise, Operationalise and Measure Them? Soc. Sci. Med. 2002;55:125-139.