

Exhibit 3

HEALTH

On C.T.E. and Athletes, Science Remains in Its Infancy

By **BENEDICT CAREY** MARCH 27, 2016

BEDFORD, Mass. — In a small room banked by refrigerators of preserved brains, a pathologist held a specimen up to the light in frank admiration. Then it was time to cut — once in half and then a thick slice from the back, the tissue dense and gray-pink, teeming with folds and swirls.

It was the brain of a professional running back.

“There,” said Dr. Ann McKee, the chief of neuropathology at the V.A. Boston Healthcare System and a professor of neurology and pathology at Boston University’s medical school, pointing to a key area that had an abnormal separation. “That’s one thing we look for right away.”

Over the past several years, Dr. McKee’s lab, housed in a pair of two-story brick buildings in suburban Boston, has repeatedly made headlines by revealing that deceased athletes, including at least 90 former N.F.L. players, were found to have had a degenerative brain disease called chronic traumatic encephalopathy, or C.T.E., that is believed to cause debilitating memory and mood problems. This month, after years of denying or playing down a connection, a top N.F.L. official acknowledged at a hearing in Washington that playing football and having C.T.E. were “certainly” linked.

His statement effectively ended a very public dispute over whether head blows sustained while playing football are associated with the disorder. But it will not resolve a quieter debate among scientists about how much risk each football player has of developing it, or answer questions about why some players seem far more vulnerable to it than others.

Some researchers worry that the rising drumbeat of C.T.E. diagnoses is far outpacing scientific progress in pinpointing the symptoms, risks and prevalence of the disease. The American Academy of Clinical Neuropsychology, an organization of brain injury specialists, is preparing a public statement to point out that much of the science of C.T.E. is still unsettled and to contend that the evidence to date should not be interpreted to mean that parents must keep their children off sports teams, officials of the group say.

“I’ve had parents come into my practice, their child had a single concussion and they think he or she has permanent brain damage,” said Karen Postal, the organization’s president and an instructor at Harvard. “There’s no basis for that.”

Dr. Postal has been jointly designated by the N.F.L. Players Association, which represents the players, and the league as a neutral expert available to assess players as part of the injury grievance process. Dr. Postal said she had not received any research support from the N.F.L. or the players. The organization she heads includes some members who have worked for N.F.L. teams; most have not, she said.

The Boston lab, which has amassed the largest C.T.E. brain bank in the world, contends that anyone playing a head-jostling sport like football, hockey, rugby or soccer runs some level of risk, and that it is cumulative exposure to head hits, not only concussions, that is most critical. But others in the field contend that far more study is needed.

“The problem is that these findings are being put out there too fast, and stated too strongly, by one group, before we understand who gets C.T.E., how it evolves over time, what’s the risk — any of that,” said Dr. Lili-Naz Hazrati, a brain pathologist at the University of Toronto who said she had received no financial support from either the N.F.L. or the Players Association.

Members of the Boston lab say they have raised the alarm for a good reason — the risk is real — but agree that the C.T.E. story is far from complete. “This research is in its infancy,” said Robert Stern, a professor of neurology and neurosurgery at the Boston University School of Medicine, who works with Dr. McKee. “There are many outstanding questions, but we’re now working to answer them and making some

progress.” The National Institutes of Health has committed some \$20 million to research, and the N.F.L. more than \$70 million.

The group has made its diagnoses of C.T.E. with authority, often stating them in terms of “stages” similar to a cancer diagnosis. Dr. McKee has determined four pathological stages, which she has linked to psychological problems, like depression or explosive anger. She said the stages themselves are clearly distinguishable on post-mortem slides of brain tissues, but she acknowledged that their proposed link to specific symptoms is “totally preliminary; it probably won’t hold up. We don’t know yet how the pathology stages predict behavior.”

Part of the challenge in answering these questions is that doctors can only diagnose C.T.E. after death, by dissecting a brain. That process allows them to identify a subtle pattern of a brain protein called tau, clumped in critical areas.

It was only last year that a panel of experts, convened by the federally funded National Institute of Neurological Disorders and Stroke, agreed that this tau pattern was definitively distinct from patterns of tau that signal other conditions like Alzheimer’s disease or age-related decline.

“That was a first step, nothing more,” said Dr. Walter Koroshetz, the institute’s director. “We had to establish minimal criteria,” so that all researchers were using the same standards. The agency is now funding research into detecting C.T.E. in living people and clarifying the link between its stages and symptoms.

The medical literature generally describes C.T.E. as closely related to punch-drunk syndrome, or “*dementia pugilistica*” — the stiffness, tremors and early dementia first found in some professional boxers a half-century ago. But when Dr. Bennet Omalu, a pathologist in Pittsburgh, reported the telltale pathology in a deceased football player in 2005 — which became the basis for the 2015 movie “*Concussion*” — the research took a different turn. Team contact sports produce different kinds of blows to the head than boxing, and research into those athletes accelerated.

Dr. McKee and Dr. Stern had studied Alzheimer’s disease for decades. After Dr. Omalu’s report, Dr. Stern was giving a lecture about dementia when he met Chris

Nowinski, a former wrestler and football player who spoke to him about C.T.E. “He said, ‘Look, this is a big problem, are you interested in looking into it?’ ” Dr. Stern said.

Dr. Stern and Dr. McKee said they immediately saw an opportunity to make a contribution in the relatively unexplored area. Dr. McKee had been running brain banks for years, including one for the landmark Framingham Heart Study, and Dr. Stern had been studying brain trauma as a risk factor for later dementia.

By 2014, Mr. Nowinski had helped their lab collect more than 100 brains from athletes, and the team found the tau signature in dozens of them. Perhaps their most explosive finding was a report released last fall, which found that 76 of the 79 pro football players’ brains they examined showed evidence of C.T.E.

But the Boston group’s collection of brains is not representative of the pro-football population, as the researchers there acknowledge. The brains were given to the center by families of athletes who were showing severe symptoms of the injury, and not from former players who were not. “We can’t say from this sample whether the rate of C.T.E. in pro players is 1 percent or what; we have no idea,” Dr. McKee said.

“But,” she added, “I don’t think it’s extremely rare. I would have to have some golden touch to see this many, if it were.”

In the best study to determine risk so far, published in December, a research team at a Mayo Clinic bank in Jacksonville found C.T.E. in 21 of 66 brains of people who had played contact sports. It found no evidence of the disorder in 198 people with no record of playing such sports. But the authors said they had no way to know whether those 21 former athletes had symptoms linked to C.T.E.; some had other neurological disorders as well when they died.

“These are very early days, and we badly need larger studies, that include both athletes and nonathletes,” said Dr. Dennis Dickson, the study’s senior author.

Another uncertainty is individual susceptibility to risk. The Boston group has found C.T.E. in people who played only high school football and in Tyler Sash, the 27-year-old former New York Giant who was found dead of an apparent drug overdose in

September. “These are young people; what are they doing in my lab?” Dr. McKee said. “This tells me that some people are at high risk.”

Four of the brains from pro players in her lab had no evidence of the disorder. Half the 22 athletes in the University of Toronto’s bank did not have C.T.E., including the former hockey “enforcer” Todd Ewen, the researchers reported last month.

“These are extremely important cases,” Dr. Hazrati, the University of Toronto pathologist, said. “Some people are clearly resistant to developing this, for reasons we don’t understand.”

Others may be living with the telltale signature brain scarring of C.T.E. without having any related symptoms, Dr. Hazrati and others said. This also happens with the plaques and tangles of Alzheimer’s disease: some people’s brains are found to be riddled with them, even though they showed no evidence of dementia while alive.

The answers to these questions are likely to be slow in coming, most scientists said.

Researchers are now testing methods of diagnosing C.T.E. in living people, including a brain scan intended to identify the tau signature. In a just-concluded study funded by the National Institutes of Health, Dr. Stern and a research team compared about 100 living former N.F.L. players with 30 healthy men of the same age. The team is still analyzing the data.

Dr. Stern and another team have also begun a second study funded by the National Institutes of Health to follow 120 former N.F.L. players, 60 former college players, and 60 healthy men of the same age who had not played football. “What we’d like to know, in addition to predicting risk, is whether we can pick it up early, whether we can intervene, to stop it from getting worse — or, is it reversible?” Dr. Stern said.

Until then, athletes and parents will have to weigh the real but poorly understood risk of C.T.E. against the upsides of contact sports. Dr. Postal, the Harvard-affiliated neuropsychologist, has two boys who play football and a 7-year-old daughter in a flag league. “If she wants to play tackle, I’ll be delighted,” Dr. Postal said.

The Boston group's Dr. Stern has a son who played football in high school but decided not to play in college. "In retrospect, I am very glad that he did not play in college," Dr. Stern said, "and, if he were in high school now, he would not be playing football."