## SAFETY OF GDNF

36. The only remaining issue is safety. Indeed, for those required to read this document this is the only section to concentrate on, since Amgen has stated, officially and publicly, that the only issue preventing reinstatement is safety (also see Perlmutter ¶ 75).

37. While on vacation in England, on or about September 1, 2004, I received a telephone call from Mr. Dan Lee at Amgen. He told me that the study was to be stopped because of damage seen in the cerebellum in three of the monkeys. Not for a moment did I consider that Amgen may have made a mistake, and I called my coordinator to have the patients follow-up in the week of my return, so that I could break the bad news. I was fully expecting to turn the pumps off.

38. Upon my return to New York, on or about September 8th 2004, I reviewed the pathology slides that had been emailed to us. My first reaction was astonishment. There was indeed some loss of Purkinje cells, but no evidence of inflammation, arguing against hypoxic-ischemic change or direct toxicity.

39. Then I noticed that the three affected monkeys were all in the high-dose recovery group. The animal experiment was as follows: 15 animals received high doses of GDNF. All fifteen animals had their pumps abruptly switched off at six months. Ten were sacrificed immediately and their brains examined for signs of toxicity. None were found. The five remaining monkeys had their pumps switched off but were kept alive for an additional three months (the "recovery phase") before being sacrificed. Lesions were seen in the cerebellum in 3/5 of these monkeys.

40. If Amgen's hypothesis were correct, i.e., that the lesions were due to the direct toxicity of GDNF, then all monkeys would be equally at risk, since they had all been exposed for

six months. The math is simple. Assuming Amgen's hypothesis of direct GDNF toxicity is correct, the probability that lesions would only be seen in the five recovery animals can be calculated exactly. It is 2.2%. Therefore Amgen's hypothesis is rejected with 97.8% confidence, i.e. beyond reasonable scientific doubt.

41. I therefore hypothesized that this was a withdrawal phenomenon.

42. It is a tenet in neuroscience that one does not abruptly withdraw a drug that is active in the brain, especially one, like GDNF, that is active at a receptor.

43. I immediately telephoned Dr. Perlmutter to express my alarm. What Amgen was asking us to do was abruptly withdraw GDNF from our patients.

44. Dr. Perlmutter returned my call on September 9th, and was refreshingly candid. He told me that Amgen had never considered this possibility. He would call a meeting the next day and get back to me.

45. I contacted some of the other investigators and was dismayed to discover that four groups had already shut down their pumps. To his credit, Dr. Lang had called Dr. Masterman to push for a broader discussion, but his calls had not been returned. As Dr. Lang put it "The silence from Donna is deafening." His group had finally shut down the pumps in all patients.

46. The following week, Dr. Harper telephoned me and told me that, after long discussion, Amgen had decided not to reverse their decision. When I asked why, given my conversation the previous week with Dr. Perlmutter, he could not provide a reason. Instead he told me how much sleep he was losing.

47. Shortly thereafter I found a paper, recently published, by Dr.Heidenreich of the University of Colorado. Dr. Heidenreich is an international authority on neurotrophic factors and on the mechanisms of cell death. Her paper was on the abrupt withdrawal of high concentrations

of neurotrophic factors from cultured cerebellar tissue. She found precisely the same pathology that had been seen in the monkeys, i.e. loss of Purkinje cells and the molecular layer of tissue, along with relative preservation of the granular layer of tissue, and all without inflammation. The mechanism of cell death was apoptosis.

48. Further information began to come in. Neurotrophins such as BDNF and GDNF can reduce the excitability of cell membranes. This is part of their neuroprotective repertoire. Sudden withdrawal leads to hyperexcitability, which leads to excitotoxicity, which leads to apoptosis within hours.

49. Information of this kind was repeatedly brought to the attention of Amgen and the other investigators, to no avail.

50. Along with the investigators at three other sites, together representing 2/3 of the patients, I presented my case to the local Ethics Committee at NYU. Contrary to the out-of-context assertions made by Amgen regarding the NYU position, the Ethics Committee was unanimously appalled that Amgen should have made such an abrupt decision without consulting either its own Safety Board or any of the trial investigators. The Ethics Committee permitted me to fill the pumps with buffered saline and to keep them open in "sleep mode," until such time as the entire issue had been resolved to their satisfaction. This way, GDNF would be slowly tapered off within 3 weeks.

51. In October 2004, Dr. Heidenreich testified at the Fox Summit meeting in New York that, in her opinion, the cerebellar lesions represented a withdrawal phenomenon.

52. At the same meeting, a pathologist from Amgen announced a new finding. The brains of the 10 monkeys sacrificed at 6 months, which had not been withdrawn, had been re-examined. One of them had cerebellar lesions similar to those seen in the monkeys sacrificed in

the withdrawal phase. These lesions had initially been missed. If this were correct, then the calculus of probability could no longer reject Amgen's hypothesis.

53. We understand that this monkey is what Amgen refers to as Primate #28.

54. Evidence has since come to light that all the facts about Primate #28 were not revealed. With additional information about this monkey, it is now possible to reject Amgen's hypothesis, i.e. that GDNF is toxic, with 97.4% confidence.

55. Therefore, beyond reasonable scientific doubt, these lesions represent a phenomenon resulting from abrupt withdrawal of GDNF.

56. What has happened to the patients in the centers which switched off their pumps? They have been subjected to abrupt withdrawal of GDNF.

57. While we recognize and fully understand that this is uncomfortable for both Amgen and for the investigators involved, we must face uncomfortable scientific truths.

58. Regarding the antibody issue, "neutralizing antibodies" are almost invariably seen when proteins are injected into the body. This is true of Amgen's leading drug, Epogen. This is true of the interferons used to treat multiple sclerosis, where up to 50% of patients develop them. Despite the pejorative appellation, neutralizing antibodies simply reduce the effectiveness of a drug and very rarely cause life-threatening complications. They are to be expected.

59. It can now be said that about 10% of patients treated with GDNF will develop neutralizing antibodies. Two out of fifteen patients in Bristol and Kentucky have them, and have presumably had them for years (since they take only about 3 months to develop), yet have suffered no ill effects.

60. Importantly, in a telephone conversation with me on February 8th 2005, Dr. Perlmutter told me that he had "never been bothered" by the antibodies. Given his background as

an immunologist, I found this reassuring. However it appears to contradict points 37, 38, 39 and 40 of his testimony.

61. When reminded of this statement on February 11th 2005, during a teleconference which included inter alia, Dr. Gash, Dr. Penn and Mr.Gill, Dr. Perlmutter said "Well what I meant was I was much less concerned about the antibodies. I was really concerned about the cerebellar toxicity." When asked why he was still concerned about this, given the evidence that the lesions most likely represented a withdrawal phenomenon, he did not, in my opinion, provide a reasonable scientific answer.

## CONCLUSION

62. I forcefully reject Amgen's suggestion that I made promises to my patients that they would receive GDNF no matter what the results of the study. This makes no sense whatsoever and would be entirely out of character. For example, one of my patients asked me if he would continue to receive GDNF after the study was completed, and I told him that if the study was successful, Amgen would of course keep him on the drug. He asked me to confirm this with Amgen, and I telephoned the director of the project, Michael Traub, who confirmed this.

63. The patients certainly had every reason to believe that if the drug were safe and effective, Amgen would continue to supply it.

64. Intraputamenal infusion of GDNF is almost certainly effective and at this time appears safe beyond reasonable scientific doubt.

65. Nevertheless, in the most unlikely event that Amgen were correct, and GDNF is capable of causing lesions in the cerebellum, the following must be noted.

66. First, there have been approximately 40 human years of exposure to GDNF in Bristol and Kentucky. None of the 15 patients has developed problems suggestive of cerebellar toxicity, and none has demonstrated cerebellar lesions on MRI scanning.

67. Second, none of the three monkeys with lesions in the recovery phase demonstrated observable signs of cerebellar damage. These would have been very obvious, and would have included imbalance to the point that they would have been unable to walk or climb.

68. When cerebellar lesions, even very large lesions, such as a hemorrhage, occur in humans, after a week or two of deficit, almost complete recovery is the rule. This is taken to imply that there is a great deal of redundancy, or indeed plasticity, in the cerebellum, unlike most other areas of the brain.

69. Therefore, even in the most unlikely event that Amgen were correct in its assertion that GDNF may be toxic to the cerebellum, it appears unlikely that there would be observable changes, in a significant number of human beings, suggestive of cerebellar toxicity.

70. This must also be placed in the context of the grievous nature of Parkinson's Disease.

71. Representatives of the investigators (specifically, Dr. Gash and Dr. Penn) met with scientists from the Food and Drug Administration (FDA), in Washington D.C., on January 10th 2005. Also present at the meeting were representatives from Amgen. The FDA made a thorough review of the existing data. They noted that there was signal in both the phase I and phase II studies suggesting that GDNF is efficacious, and they were well aware that efficacy is difficult to prove in small phase II studies. They concluded that it was reasonable for Amgen to refill the pumps with GDNF, and gave Amgen the green light to do so, provided the patients were closely monitored.

72. On February 11th 2005, Amgen officially refused.

73. This, despite the backing of the Food and Drug Administration.

74. This, despite a unanimous decision by a distinguished panel of experts forming the Executive Committee of the Parkinson's Disease Foundation, (whose scientific director, Dr. Stanley Fahn, is arguably the foremost clinical expert on Parkinson's Disease alive today), to recommend reinstatement of GDNF.

75. This, despite a similar resolution by the Washington-based Parkinson Action Network.

76. This, despite a public declaration by Dr. Lieberman, head of the Miami-based National Parkinson Foundation, in favor of reinstatement.

77. This, despite exhortations from the vast majority of patients, many of whom had already had their lives returned to them.

78. I certify under penalty of perjury under the laws of the United States of America that the foregoing statements are true and based upon my personal knowledge. I am aware that if any of the foregoing statements are false, I may be subject to punishment.

Dated: Monday, May 23, 2005

Michael Hutchinson, M.D.