I. Personal Section

Ever since I was young, I recall my parents taking me to museums on our family trips around the world. I began to think about the world around me, whether it was the air I breathed, the cars I saw on the road, or the water shooting out of our sprinklers. I began to inquire as to how the Earth came to be, and what made our planet unique. I suppose these thoughts at age 7 can be considered my first real observations and inferences. This curiosity followed me through the years as I began to embark on real research in various fields.

In high school, I endeavored to participate in the Brain Bee competitions – the equivalent of the Scripps National Spelling Bee or National Geography Bee, except on neuroscience trivia. Here, I became exposed to the fascinating aspects of the nervous system, especially its striking adaptive capabilities called plasticity. Having read about extraordinary cases in which patients afflicted with neurological disorders managed to survive with minimum personality change or psychological impact, I wondered how far the brain's resiliency can extend, and more importantly, if it could be harnessed to treat neurological disorders in the future. I reached out to Dr. Nick Spitzer at the University of California, San Diego, who was investigating the plasticity of the brain's chemical messengers called neurotransmitters. As the first high school student in his lab, I began to study the plasticity of a *gaseous* transmitter, nitric oxide, induced by alterations in electrical activity. I faced many challenges as I mastered intricate brain microdissections, sliced fine sections of embryonic brains, and operated complex machinery. Research absorbed my time and energy - there were even times when I dreamed about the embryonic tadpoles that I interacted with in the lab! But every moment was worth it –

spending three years and nearly every holiday in between in the lab made it my second home.

Although my research project employs more biological, biochemical and biophysical concepts than purely mathematical ones, I can speak to the importance of applied mathematics and the importance of statistical analysis. Without statistics, an experiment can be rendered useless. Statistics govern validity and reliability. It almost doesn’t matter what the observations are if the data in question is based solely upon one or two samples. How can you prove that you will notice the same effects in most samples? Only by using a larger sample size – which is exactly what I did. Granted, the brains of embryonic tadpoles were thinner than a strand of hair, so perfecting techniques itself took months and months, and obtaining a large sample size as definitely hard for me to achieve. But I persevered. There was nothing sweeter than looking at the delicate neurons under the confocal microscope, fluorescing brightly and majestically as if to reward me for all of my struggles to reach that point.

If there’s anything that I can pass on from my experiences, first and foremost, I’d have to say that a student should never embark on research for the sole purpose of entering or winning competitions. Do it for the pleasure of seeking answers, of venturing into unknown terrain, or of making a difference through a discovery. Do it because of your curiosity. Do it because *you* want to do it. Savor it. The experiences will make you a much stronger person, and undoubtedly more knowledgeable as well. You’ll surely find that the experimental data is the reward, and that praise from your mentor or Principal Investigator is worth more than any accolades that naturally follow as a result of your passion and drive for your research in science and/or math.

II. Research Section

Nitric oxide (NO) plays an essential role in several physiological functions including sleep, feeding, memory, vision, olfactory regulation and sensorimotor integration. In the central nervous system alone, nitric oxide synthase (NOS), the enzyme that generates NO, is involved in the regulation of blood flow, long term potentiation (formation of memories due to strengthening of synapses), mediation of neurotransmitter release, formation of cGMP, and formation of synapses. Therefore any abnormalities in these functions could contribute to an array of cognitive and neurodegenerative pathologies. Additionally, the fascinating dual role of nitric oxide as both a neuroprotective and a neurotoxic agent under different circumstances implies the need for maintaining homeostasis of the neurotransmitter expression. Any imbalance could result in dire consequences, which means that treatments should coincide with regulating the levels of nitric oxide. The World Health Organization, in 2007, reported that up to 1 billion people globally suffered from neurological disorders. Clearly something has to be done.

In my study, conducted at the University of California, San Diego, I sought to understand how electrical activity can be used to induce the plasticity of a gaseous neurotransmitter like nitric oxide. Plasticity refers to the brain's adaptive capabilities. Neurotransmitter plasticity is a recent phenomenon describing the flexibility and resiliency of the brain's chemical messengers. Electrical activity refers to the flow of sodium and potassium ions in the membranes of neurons. Examining the hindbrain (involved in regulating key sensorimotor functions) of the embryonic Xenopus laevis tadpole through brain dissections, cryostat sectioning, immunohistochemistry, confocal microscopy, and behavioral tests, I established for the first time that nitric oxide synthase, a marker for NO expression, can be respecified via electrical activity in a localized manner within the raphe, reticulospinal and mid-hindbrain regions. Furthermore, I found neurotransmitter phenotype plasticity in the form of coexpression with serotonin and GABA. My research establishes protocols for studying localized NO respecification and suggests that alterations in electrical activity induce remarkable NO plasticity by recruiting reserve pools of neurons. In a third phase of my experiment, I investigated the physiological effects of activity-induced nitric oxide regulation by monitoring the total distances traveled and maximum velocity achieved by tadpoles, before and after nitric oxide inhibition. The last phase aimed to elucidate the effects of localized activity blockade, through surgical ablation of the cement gland, on the expression of nitric oxide in the reticulospinal nucleus. In the span of the last three years, in each segment of my novel research, I've mastered intricate and complicated in vivo laboratory skills and techniques, worked with the most unpredictable of apparatuses, and developed protocols that can be applied for future studies on related topics. Overall, this comprehensive study suggests that such a novel approach to correcting neurotransmitter imbalances would aid the development of non- invasive, localized therapies hitherto unimaginable for neurological disorders.

As mentioned in the previous section, statistical analysis proved to be quite a valuable tool. Two-sample t-tests became my best friend as I calculated means, standard errors, and p-values to assess the significance of my results. Data analysis (using specific software) I performed for the physiological studies was long and sometimes tedious, but statistical analysis made it worthwhile. I was able to apply what I had learned in my

Advanced Placement Statistics class to my research, making Statistics one of the most valuable classes I've ever taken in high school, and allowing me to proudly write the words "statistically significant" next to my results in each phase.

I'd like to acknowledge my wonderful mentors at UCSD, Dr. Spitzer and Dr. Dulcis, who continue to inspire me to make a difference through research. My high school teacher Ms. Slijk was an immense source of encouragement throughout the past few years, and my parents supported me and made time in their busy schedules to aid my daily commute to the lab.