The Second Annual Evans Family Lecture Series in Pulmonary Medicine:

Jonathan S. Stamler, M.D.

The Principles of NO Biology

Nitroglycerin use is a Catch-22: it relieves the effects of devastating diseases such as angina and pulmonary hypertension, yet the longer a patient takes the compound, the less effective it becomes. Jonathan S. Stamler, M.D., Professor of Medicine and Biochemistry at Duke University and Associate Researcher at the Howard Hughes Medical Institute, shared the results of his pioneering research in nitric oxide (NO) compounds at the second annual Evans Family Lecture Series in Pulmonary Medicine at Stanford University Medical Center.

Stamler received extensive training in both pulmonology and cardiology as an intern, resident, and fellow at the Brigham and Women's Hospital and Harvard Medical School. Prior to joining the Duke University faculty, he served as an Assistant Professor at Harvard Medical School. He has published more than 175 original articles, reviews, and book chapters and holds approximately 50 issued patents to date.

Stamler's exploration of NO biology represents a collaborative effort involving many of the world's experts in cardiology, pulmonology, cardiac surgery, and other disciplines. Stamler began his lecture by emphasizing this point, noting his consideration of all major nitroglycerin compound (GTN) findings from the late 1800s until the last decade. These findings by Guthrie, Needleman, Ignarro, and others lead to the establishment of a framework for the mechanism of nitrosovasodilators, or the agents that relax constricted blood vessels.

The framework involves three compounds - amyl nitrite, sodium nitroprusside, and GTN - that react with thiols, or types of sulfur atoms, to form a class of compound called S-nitrosothiol (SNO). Scientists once widely believed SNO was responsible for the release of nitric oxide into the smooth muscle cells surrounding constricted blood vessels, causing the blood vessels to relax and widen. Blood was then able to flow more easily through the expanded vessels.

In their research, Stamler and his colleagues demonstrated problems inherent in this framework, namely that the reaction of GTN with a thiol does not produce SNO. They found the enzyme mitochondrial aldehyde dehydrogenase (mtALDH) uses a four-step process to break down GTN into SNO compounds, which then exit their staging area inside the blood cell and adhere to the smooth muscle cells of blood vessels.

Stamler and his colleagues also discovered that repeated exposure to GTN impairs mtALDH enzymes, rendering the enzymes incapable of making GTN into SNO compounds. With a lack of SNO, blood vessels remain constricted and continue to impede blood flow. This important work resulted in a revision of the formerly accepted framework governing the mechanism of nitrosovasodilators.

As Stamler pointed out, the results of many long-term clinical trials provide support for his research findings. Some clinical trials have indicated GTN use can increase the patient's risk of eventual health problems or even death. Stamler believes his data provide a starting point for the development of new classes of nitric oxide-based therapy.

After presenting his work on the role of GTN and SNO compounds in the relaxation of blood vessels, Stamler described the primary function of SNO in the blood: "The new insight is the respiratory cycle is controlled at all levels - brain, lung, and tissue - by S-nitrosothiols." Stamler cited his team's research on rats, dogs, and human volunteers revealing SNO compounds were found mainly in oxygenated, arterial blood and much less so in deoxygenated, venous blood. "When oxygen comes up, NO comes up," Stamler maintained. These results have caused scientists to revise their definition of the respiratory cycle to include three gases - oxygen, carbon dioxide, and nitric oxide.

Stamler remains interested in the possibility that an imbalance between hemoglobin and NO may account for various heart, lung, and blood diseases such as asthma, cystic fibrosis, and thalassemia. Using pulmonary hypertension as an example, he characterized those deficiencies. "We measured SNO content in these patients and found a profound deficiency, which correlates with defects in red blood cells," he said.

Stamler continues to search for molecules that can replete SNO hemoglobin in vitro and hopefully one day in vivo. With this search, Stamler remarked, "we've come full cycle...creating a whole new horizon of therapeutic possibilities in diseases of the heart, lung, and blood."