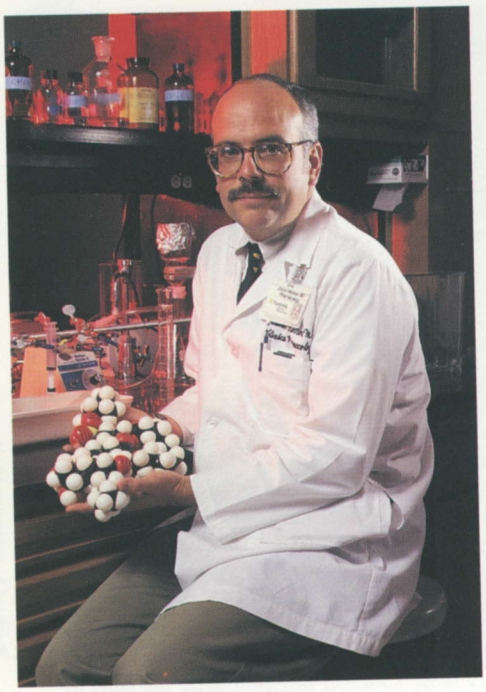
Hughes fellow makes radical discovery



John C. Howser

Jason Morrow, an HHMI postdoctoral fellow at Vanderbilt University, holds a molecular model of an isoprostane containing lipid, a combination that could accelerate atherosclerosis or rheumatoid arthritis.

Jason Morrow almost gave up on the experiments that led him to discover a unique set of compounds that may help explain why smokers are more likely to develop atherosclerosis and why other disorders — including certain cancers, strokes and rheumatoid arthritis — can occur.

Morrow, a physician, was carrying out research at Vanderbilt University under an HHMI fellowship. He and his colleagues thought they had pinpointed the pathway the body uses to produce the hormone-like compounds termed prostaglandins. They hoped to prove their theory by blocking the pathway and causing the prostaglandin to disappear. But their experiments did not work; mass spectrometric analyses kept picking up signals that prostaglandins were still there.

The signals, it turned out, were being triggered not by prostaglandins but by isoprostanes, compounds that can mimic prostaglandins. Morrow, who had just started in the lab in Nashville, became frustrated with the isoprostanes and thought about turning his attention elsewhere. His mentor at Vanderbilt, L. Jackson Roberts II, however, encouraged him to continue to explore the irksome compounds. Morrow did just that — and made discoveries about isoprotanes that shed new light on several diseases. His results were recently published in *The New England Journal of Medicine* and *Science*.

Isoprostanes, Morrow found, are the products of the charged encounters between fats in the blood and highly reactive oxygen compounds known as oxygen free radicals. These free radicals turn the fats rancid. Some scientists postulate that the rancid fats trigger an attack from the immune system when they are deposited on artery walls. This causes plaque to build up, the hallmark of atherosclerosis.

Morrow wondered whether this process might help explain why smokers are more likely to get atherosclerosis. Cigarette smoke, he knew, is replete with oxygen free radicals. Perhaps these compounds in smoke were turning blood fats rancid, leading to the artery-clogging disease.

Morrow measured the levels of isoprostanes in the blood samples of a small group of heavy smokers. Sure enough, the smokers had significantly more isoprostanes in their blood than the nonsmokers. If they stopped smoking for two weeks, moreover, the levels of the compounds dropped markedly. The findings, reported by Morrow, Roberts and seven co-authors in the May 4 issue of *The New England Journal of Medicine*, provided intriguing evidence about one of smoking's deadliest effects.

Morrow has also found that isoprostanes may be involved in certain cancers. When free radicals alter blood fats, he says, they foster the production not only of isoprostanes but also of compounds that damage DNA. This DNA damage can lead to cancer.

Morrow and Lawrence J. Marnett, also of Vanderbilt University, fed rats a compound that induces free radicals. They found that blood levels of isoprostanes in the animals correlated with the amount of DNA damage found in the rats' livers. The results, published in the September 9, 1994 issue of *Science*, may help explain the link between high-fat diets and certain cancers that some epidemiological studies have reported.

Isoprostanes are not only generated in the presence of cigarette smoke and other pollutants, but are also generated by the body while digesting food, fighting infections and at other times. Morrow expects them to be used by researchers in other studies because they are such sensitive markers of the damage that oxygen free radicals appear to cause in disorders that range from cardiovascular diseases to septic shock and autoimmune diseases such as rheumatoid arthritis. "When we first got into this research, the field was emerging," Morrow said, "and now we're riding the crest of a wave."

Morrow says his HHMI fellowship made it possible for him to test the research waters in the first place. He received his M.D. from Washington University in St. Louis in 1983 and then trained in internal medicine and infectious diseases at Washington University and Vanderbilt. He had been interested in research since college and wanted to see how he liked it before entering medical practice. "I thought I'd give research a try for a year or two and if it didn't work out, I'd go into practice," Morrow recalls. "I didn't want, ten years down the road, to be in practice and feel that I'd missed something."

Morrow began giving research a try and applied to an HHMI fellowship program that enables physicians to spend three years carrying out research in leading biomedical laboratories. The fellowship program, one of three offered by the Institute's grants program, gave him the financial stability to focus on isoprostanes and discover their surprising relationship to diseases. It also led to his receiving a research grant from the National Institutes of Health and a faculty appointment at Vanderbilt. ■