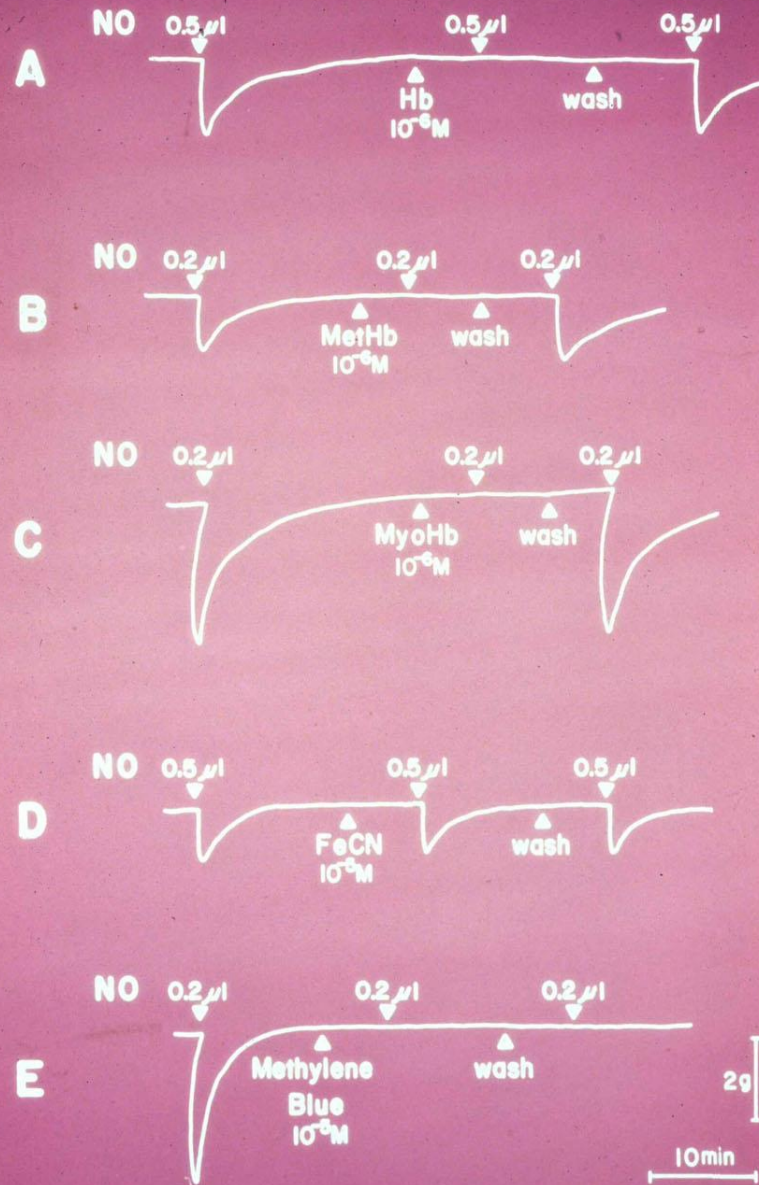
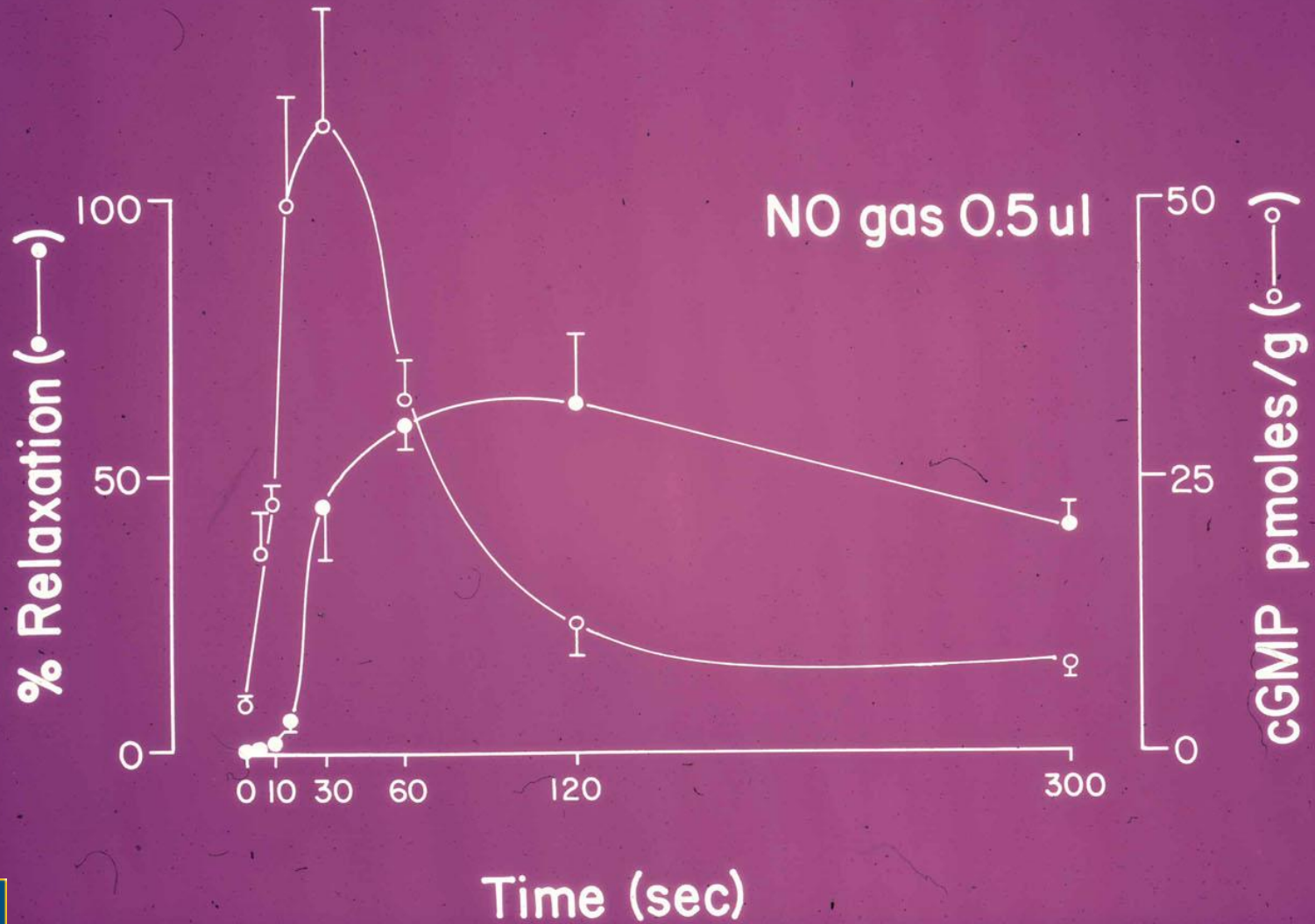


# It all started in the 1970's

- ✓ **NO activates cytosolic guanylate cyclase**
- ✓ **Nitroglycerin and nitroprusside stimulate cyclic GMP production**
- ✓ **Nitroglycerin and nitroprusside are NO donors in presence of cells**
- ✓ **QUESTION: is NO a vasorelaxant?**









# Observation Made by Serendipity

- *Nitroprusside was found to inhibit platelet aggregation*

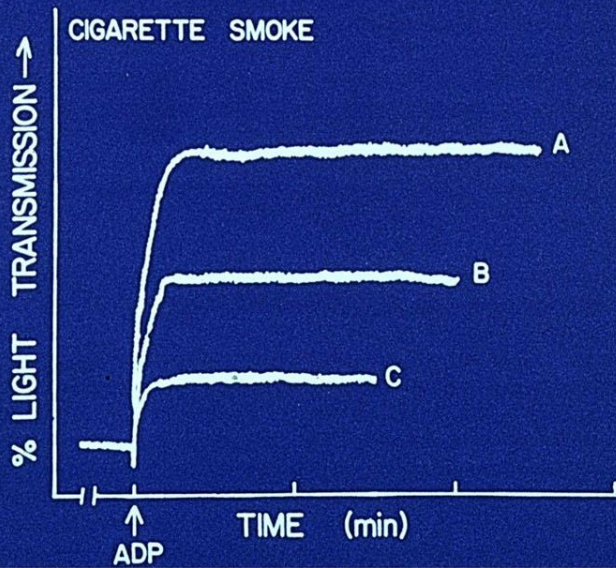
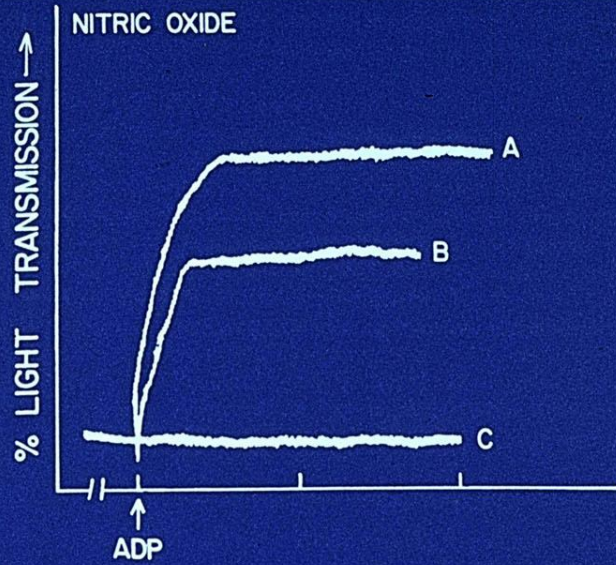




# QUESTION

- *Is the anti-platelet effect of nitroprusside also mediated by NO and cyclic GMP?*





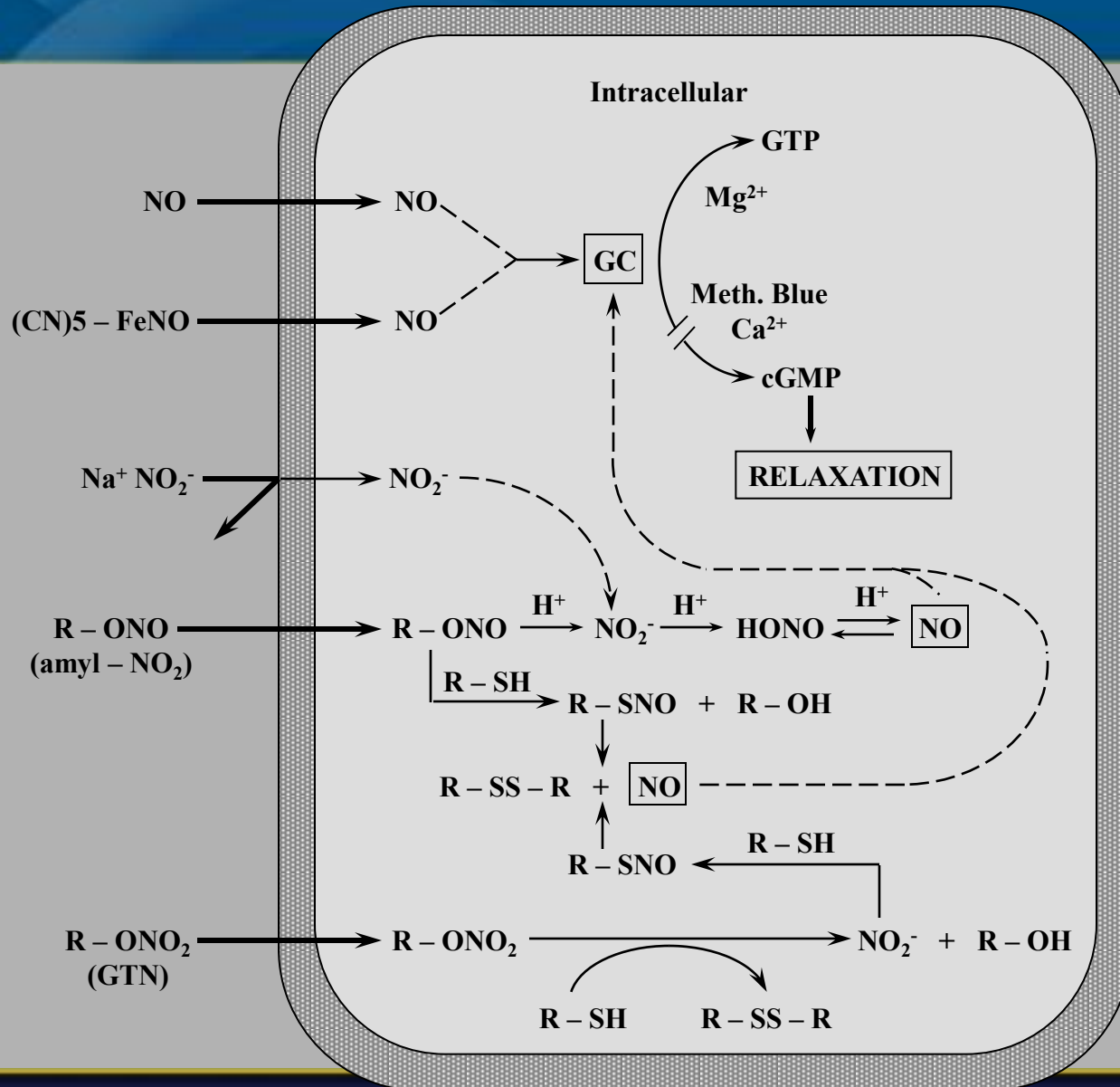
# What is the mechanism of action of the so-called Direct-Acting Vascular Spasmolytic Drugs?

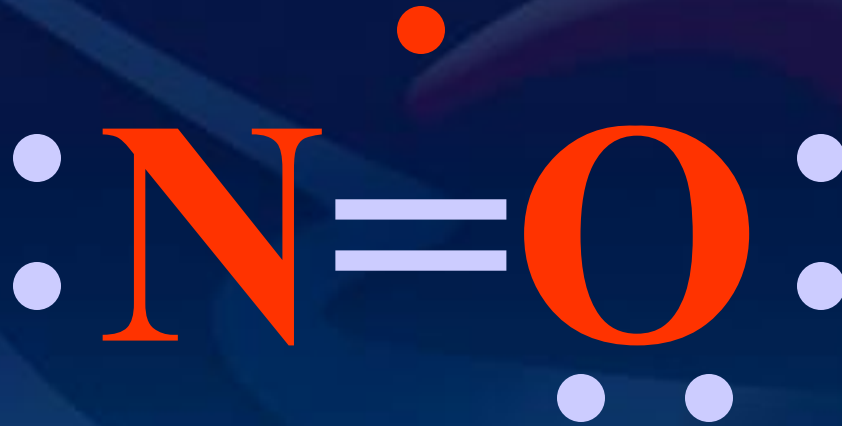
- *Nitroglycerin*
- *Nitroprusside*
- *Isoamyl Nitrite*





## Vascular Smooth Muscle Cell





**The unpaired electron gives Nitric Oxide  
its chemical properties as a  
Biological Mediator**

# Guanylate Cyclase





# Cytosolic Guanylate Cyclase is a Hemoprotein Containing One Mole of Heme per Mole of Holoenzyme Dimer

- *Enzyme-bound HEME is an absolute requirement for enzyme activation by NO*

**KNOWN:** Nitroglycerin and NO are very potent vasodilators

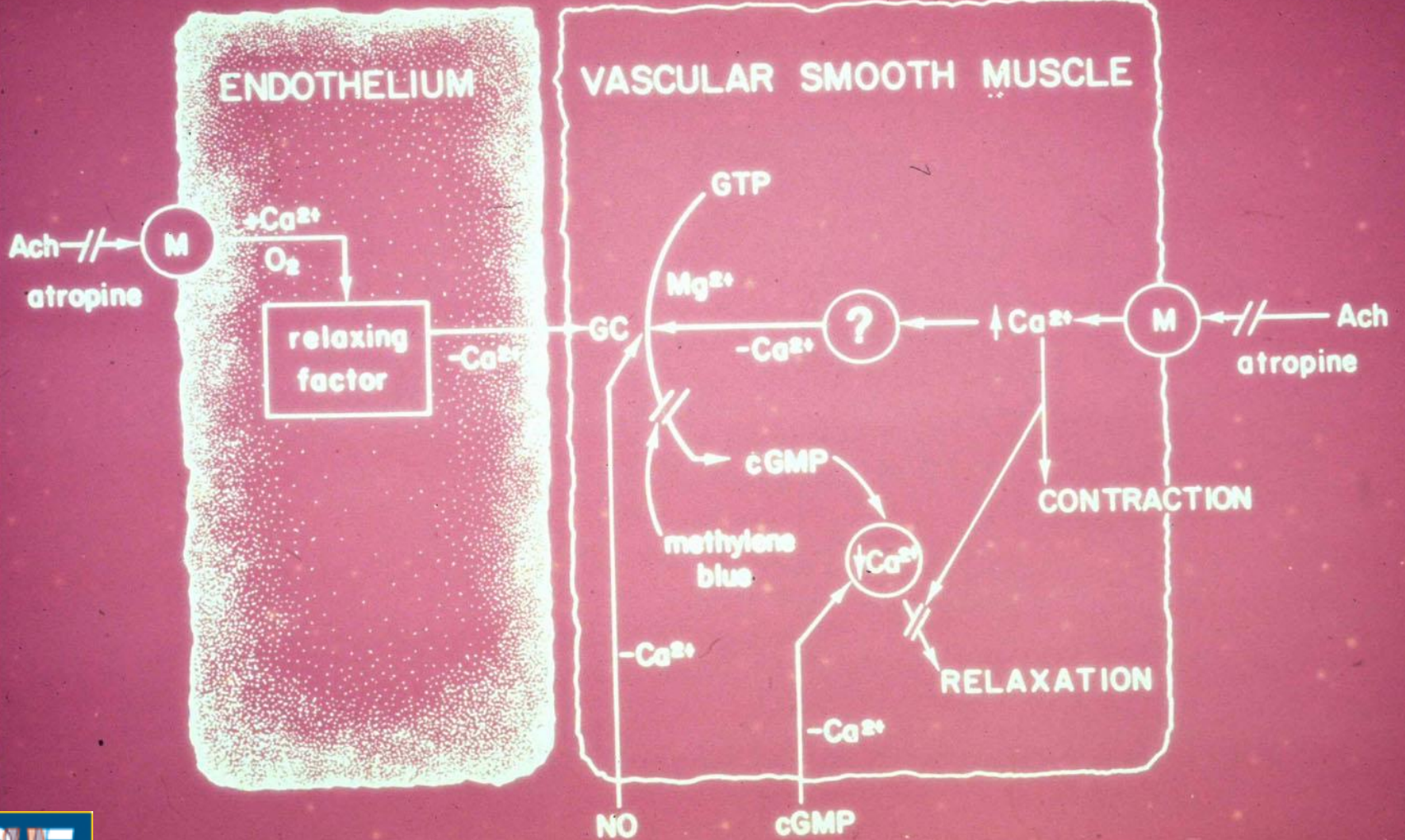
**QUESTIONS:**

- ✓ *Why do we have receptors for nitroglycerin and NO?*
- ✓ *Is there an endogenous nitro-vasodilator like NO?*

# QUESTION

- *Does Endothelium-Dependent Vasorelaxation Involve the Actions of Cyclic GMP?*





Do you know what  
EDRF is?

• *NO*

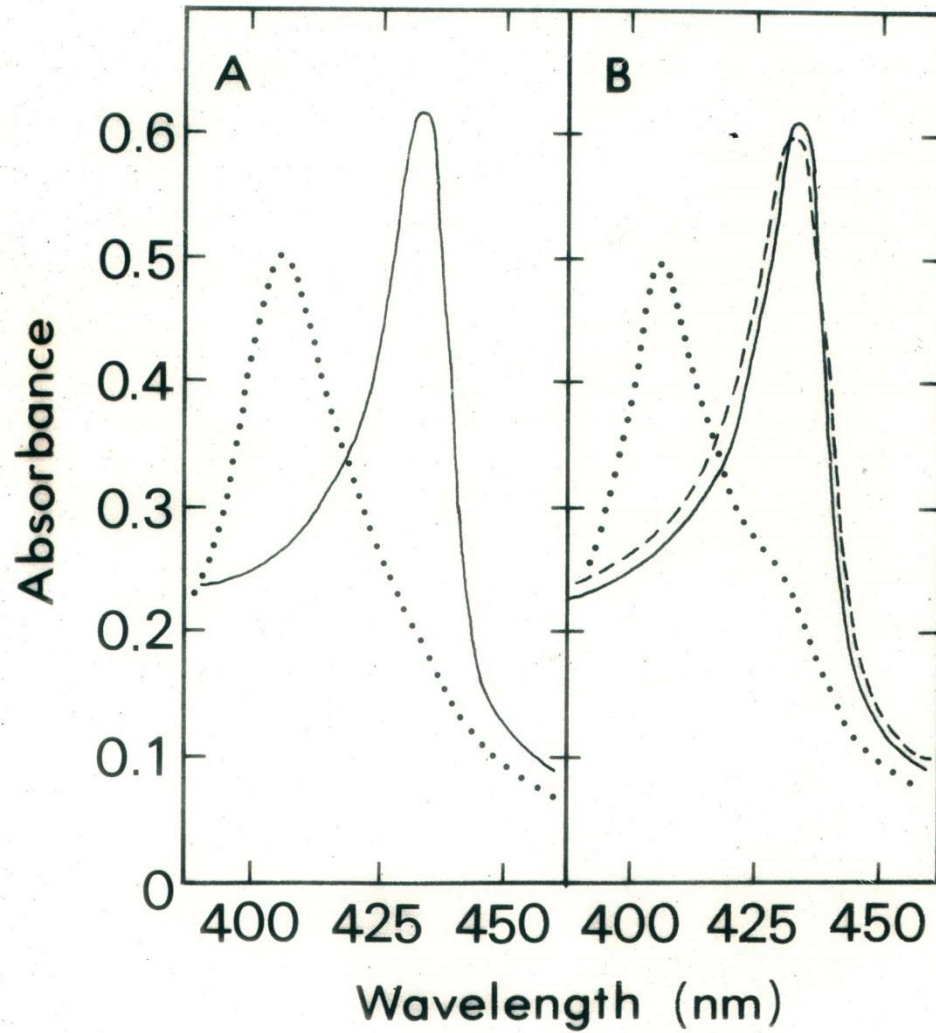
**EDRF is  
Nitric Oxide**

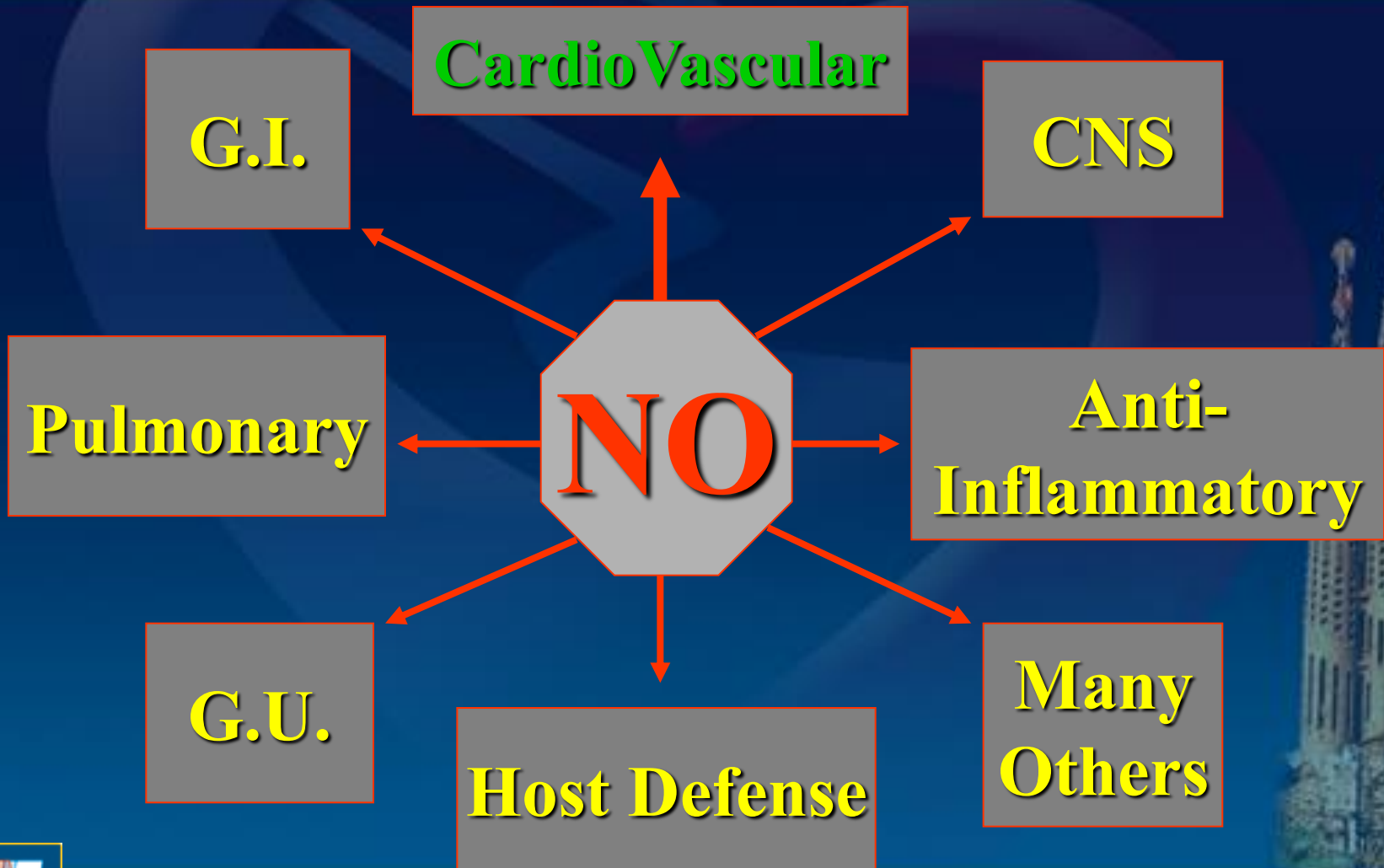


**Activation of purified soluble guanylate cyclase by EDRF from Intrapulmonary artery and vein. Stimulation by acetylcholine and bradykinin**

- ✓ *Ignarro, L.J., Harbison, R.G., Wood, K.S. Kadowitz, P.J.*
- ✓ *J. Pharmacol. Exp. Ther. 230: 602-610, 1986*



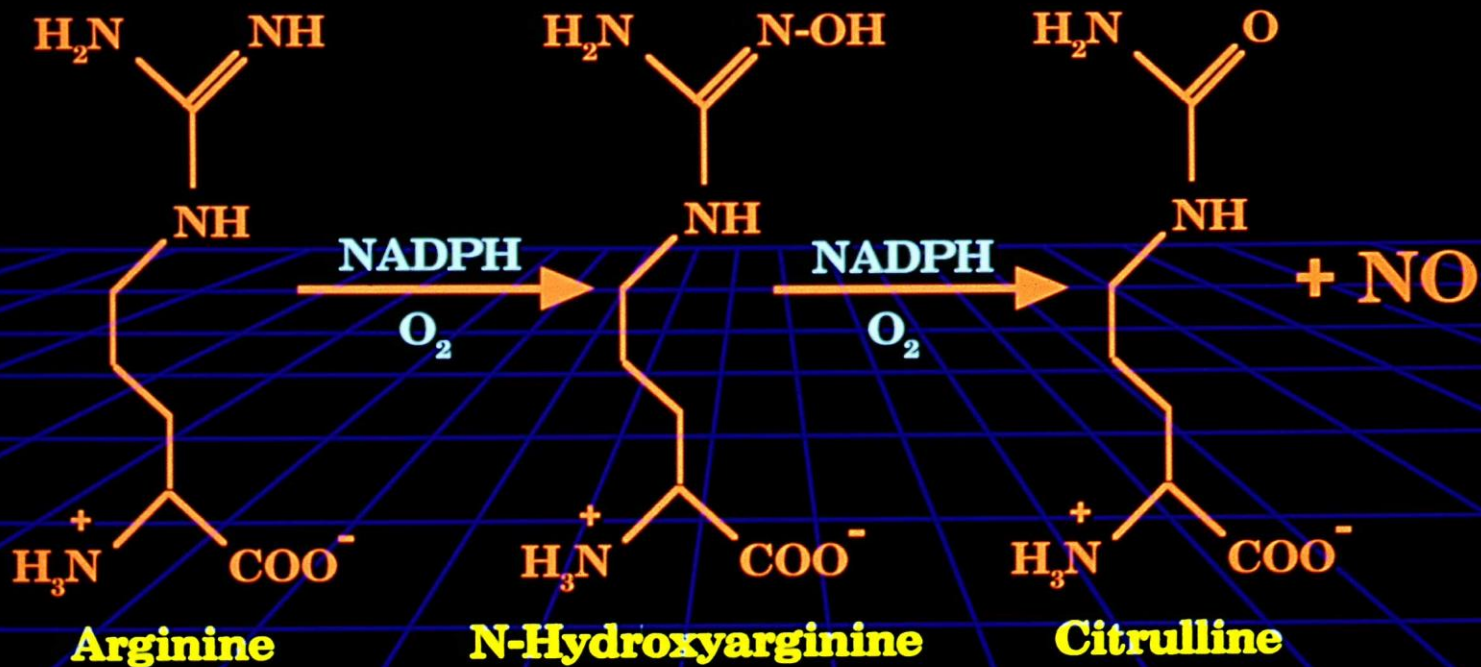




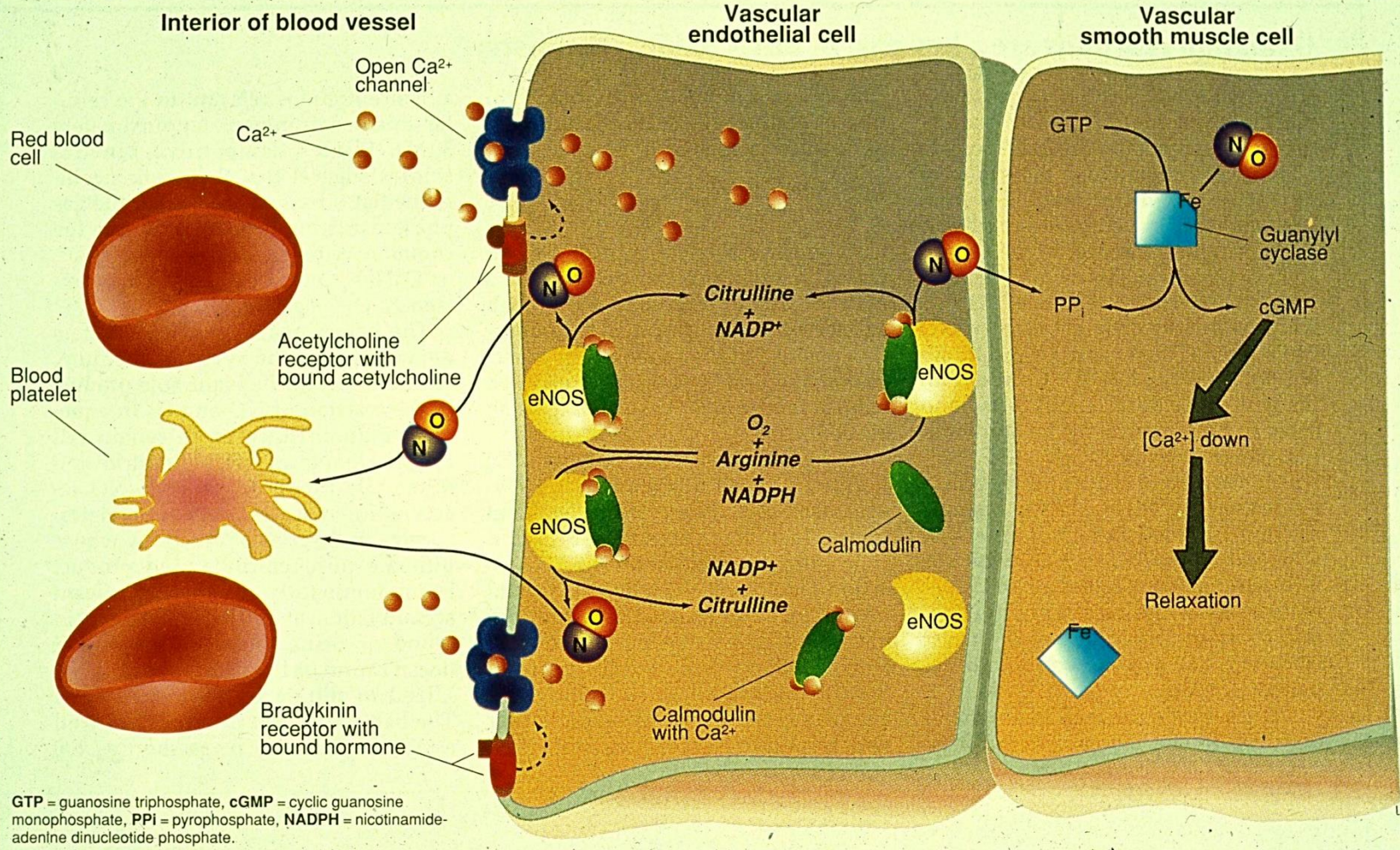
# NO Synthase Isoforms

- ✓ *Endothelial (eNOS) – constitutive*
- ✓ *Neuronal (nNOS) – constitutive*
- ✓ *Inflammatory (iNOS) – inducible*

# NO Synthase Reaction











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# What is the Role of Neuronal NO Synthase?

# Physiologic Neurotransmitter Actions of NO

- *Mediator of erectile function*
- ✓ *Modulator of G.I. And G.U. functions*
- ✓ *Modulator of airway function*
- ✓ *Peripheral sensory transmission*
- ✓ *Central mediator of learning, memory, nociception and olfaction*



# QUESTION

- *Is NO responsible for neuronally-induced relaxation of corpus cavernosum smooth muscle and, therefore,*
- *penile erection?*



# The New England Journal of Medicine

Established in 1812 as The NEW ENGLAND JOURNAL OF MEDICINE AND SURGERY

Abstracts in the  
advertising  
sections

VOLUME 326

JANUARY 9, 1992

NUMBER 2

## Original Articles

- The Frequency of Familial Dilated Cardiomyopathy in a Series of Patients with Idiopathic Dilated Cardiomyopathy** ..... 77  
V.V. MICHELS AND OTHERS
- Comparison of Amphotericin B with Flucanazole in the Treatment of Acute AIDS-Associated Cryptococcal Meningitis** ..... 83  
M.S. SAAG AND OTHERS
- Nitric Oxide as a Mediator of Relaxation of the Corpus Cavernosum in Response to Nonadrenergic, Noncholinergic Neurotransmission** ..... 90  
J. RAJFER, W.J. ARONSON, P.A. BUSH, F.J. DOREY, AND L.J. IGNAIRO
- Iron Overload in Africa — Interaction between a Gene and Dietary Iron Content** ..... 95  
V. GORDEK AND OTHERS
- Results of a Randomized Trial of Partner Notification in Cases of HIV Infection in North Carolina** ..... 101  
S.E. LANDIS AND OTHERS

## Review Article

- Drug Therapy: Manipulating the Immune System with Immune Globulin** ..... 107  
J.M. DWYER

## Case Records of the Massachusetts General Hospital

- Chorea and Progressive Dementia in an 88-Year-Old Woman** ..... 117  
D.S. SAX AND J.-P. VOSSATTE

## Editorial

- Causes of Iron Overload** ..... 126  
B.R. BACON

## Sounding Board

- AIDS, Activism, and the Politics of Health** .. 128  
R.M. WAGNER

## Correspondence

- Drug Promotion and Scientific Exchange** ..... 133
- Screening for Colorectal Cancer** ..... 134
- Absence of Birth Defects in Offspring of Women Treated with Dactinomycin** ..... 137
- Hazard of Lead in Infant Formula** ..... 137
- Sensitivity of Erythrocyte Protoporphyrin as a Screening Test for Lead Poisoning** ..... 137
- Balloon Aortic Valvuloplasty** ..... 138
- Prophylactic Immune Globulin in Chronic Lymphocytic Leukemia** ..... 139
- Malpractice and Negligence** ..... 140

- Book Reviews** ..... 140

- Notices** ..... 143

## Correction

- Phenobarbital for Febrile Seizures — Effects on Intelligence and on Seizure Recurrence** ..... 144



"All the News  
That's Fit to Print"

# The New York Times

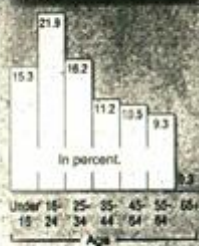
VOL. CXXI . . . No. 48,840

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THURSDAY, JANUARY 9, 1992

## Who's Uninsured

BY AGE



BY RACE

Black 20.2%  
White 11.7%

\*Hispanic people can be of any race.

Monthly averages for the last quarter of 1990.

Source: Census Bureau

The New York Times

## CHEMICAL A FACTOR IN MALE IMPOTENCE

Experts Say Finding May Aid  
in Some New Treatments

By SANDRA BLAKESLEE  
Special to The New York Times

LOS ANGELES, Jan. 8 — Researchers say they have found the physiological explanation for the vast majority of cases of male impotence, a failure to produce a simple chemical that controls a wide variety of biological functions.

The chemical, nitric oxide, initiates a series of events that cause the penis to become engorged with blood and remain erect, said Dr. Jacob Rajfer, a

## PRESIDENT'S PLANS FOR MEDICAL CARE OUTLINED TO A.M.A.

EMPHASIS ON INCENTIVES

Administration Seeks to Control  
Costs by Fostering Health  
Maintenance Groups

By ROBERT PEAR  
Special to The New York Times

WASHINGTON, Jan. 8 — President Bush's election-year prescription for the nation's health-care system is likely to include new incentives for people to enroll in prepaid group health plans, tax credits for the purchase of medical insurance and restrictions on medical malpractice lawsuits, the White House chief of staff, Samuel K. Skinner, told doctors this week.

Mr. Skinner outlined the Administration's ideas at a White House meeting with top executives of the American Medical Association on Tuesday afternoon, as he sampled the doctors' reaction to major proposals being drafted by the Administration for submission to Congress later this month.

Administration officials and medical association executives gave details of the meeting in interviews today.

Trying to Control Cost

A Federal budget official present at the meeting told the doctors they might dislike some of Mr. Bush's proposals. That referred to measures that would prod people, especially Medicare and Medicaid beneficiaries, to join health maintenance organizations and health-care networks, said a medical association official who was at the meeting.

Proponents of such managed care say it controls cost, reduces paperwork and maintains the quality of care, but doctors often complain that it reduces their autonomy and their income.

The health-care networks pay less than doctors usually charge for an office visit, service or procedure. For example, a family doctor might receive \$25 for an office visit that now

## Bush Collapses at State Dinner With the Japanese



President Bush being supported by security officers and Prime Minister Kiichi Miyazawa, crouching at center, after he collapsed at a state dinner in Tokyo yesterday. At right was Barbara Bush.



## President Has Intestinal Flu, Spokesman Says — He Intends to Continue Most of Schedule

By MICHAEL WINES  
Special to The New York Times

TOKYO, Thursday, Jan. 9 — President Bush fell suddenly ill and collapsed at a state dinner being given for him Wednesday night at the home of the Japanese Prime Minister. This morning, his spokesman said the President was "up and about" and making phone calls.

The spokesman, Marlin Fitzwater, said on Wednesday night, after the attack, that Mr. Bush had the kind of gastroenteritis commonly known as intestinal flu, but insisted nonetheless that he was not seriously ill.

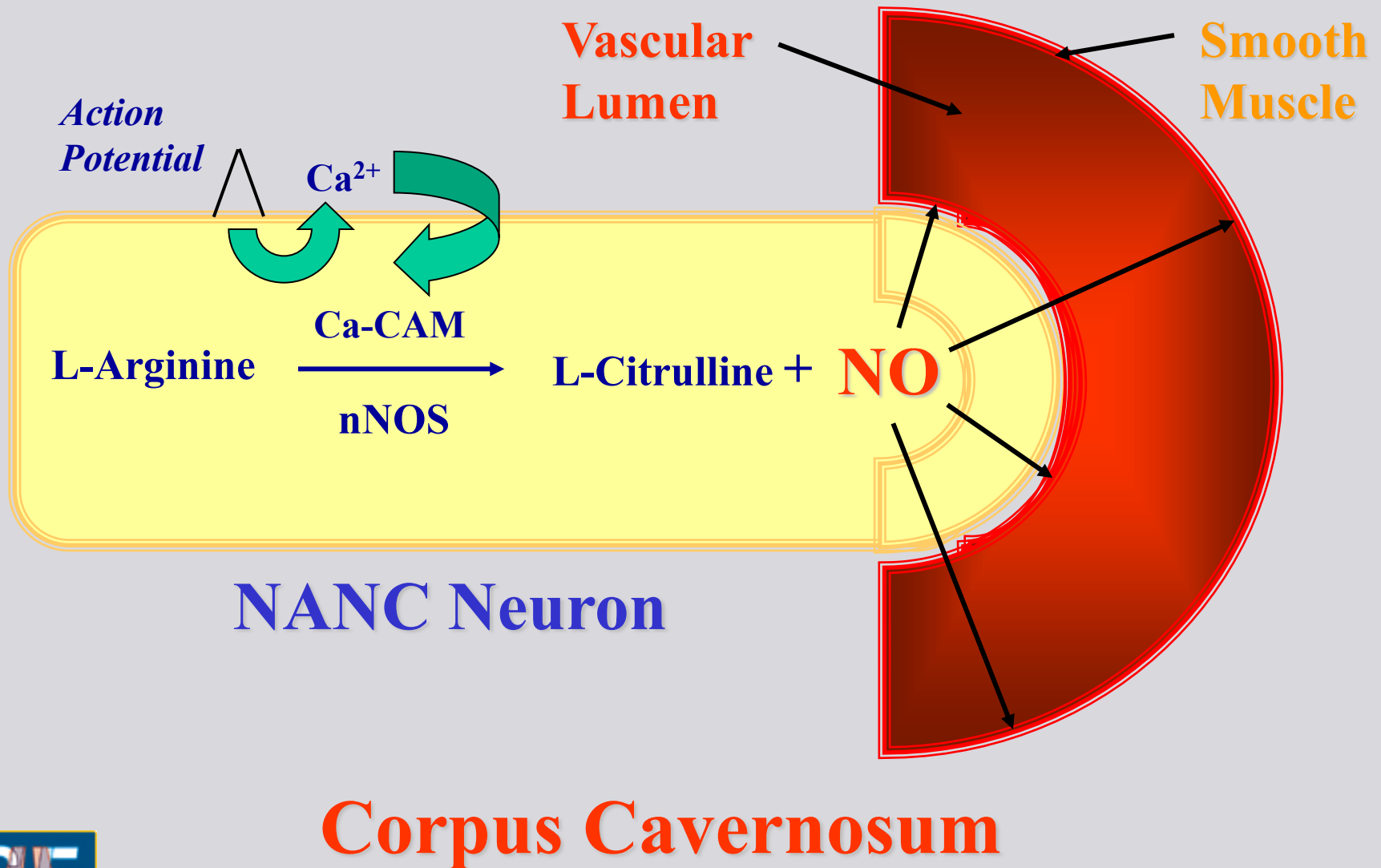
The President's host, Prime Minister Kiichi Miyazawa, cradled his head for some minutes until Mr. Bush was strong enough to get up on his own.

One person who attended the dinner and saw the incident at close range said the President "turned white as a sheet," ruffled his head to the left, and was clearly fainting before being helped to the floor. "It all happened very, very fast," said the guest, who refused to be identified by name.

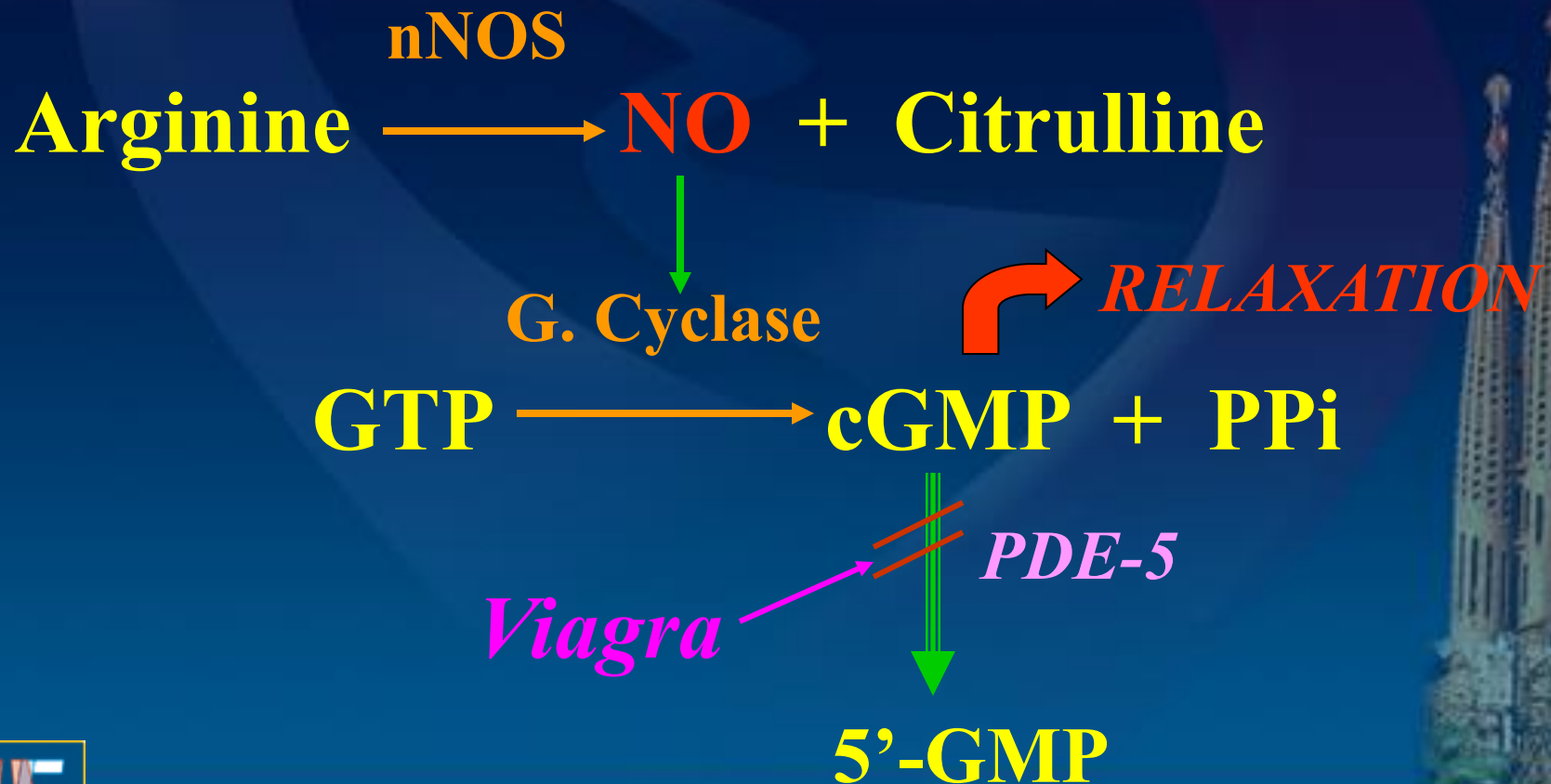
Quayle Is Notified

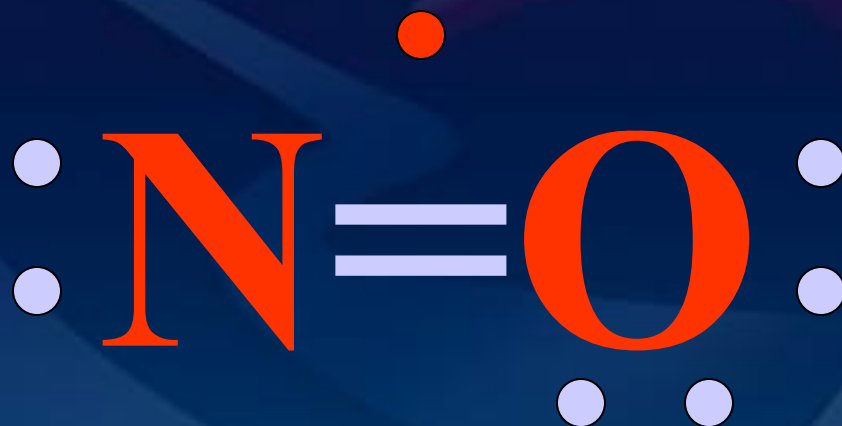






# NO-cGMP Signal Transduction Pathway





**Molecule of the Year**

**Science 1992**



October 12, 1998

















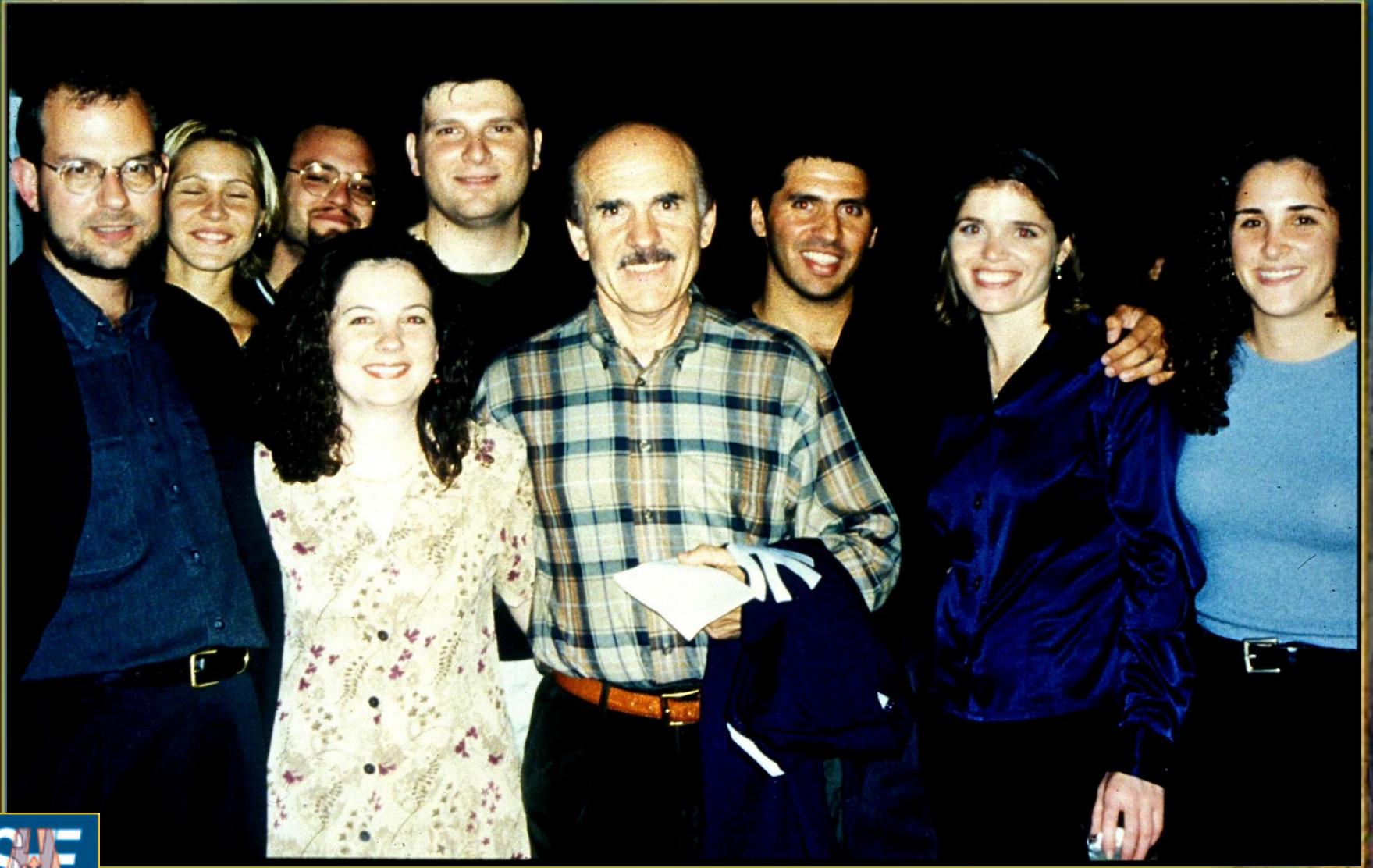








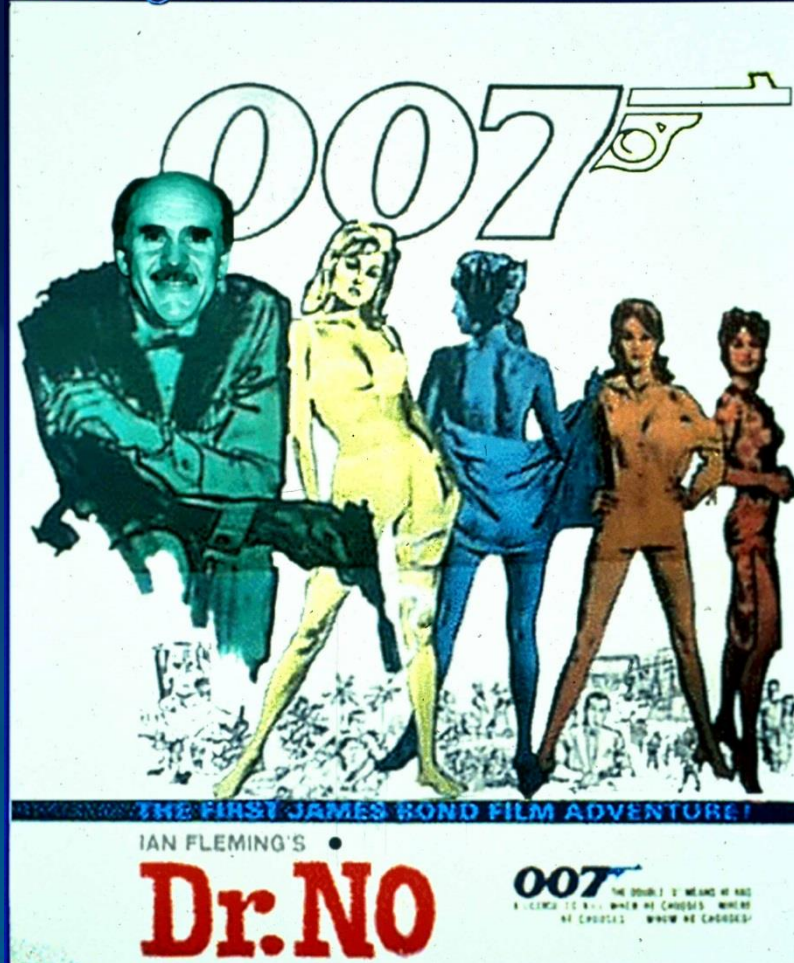








Lou Ignarro as











**Drs. Sharon and Lou Ignarro with President Clinton**





**Dr. Sharon Williams Ignarro with President Clinton**











Lucky Lou at the Karolinska Institute



With the portrait of Alfred Nobel at the Karolinska Institute





The Stockholm Concert Hall, venue for the Nobel Ceremony









**The three Nobel Laureates in Medicine-1998**

"A humble handshake!"



Dr. Louis Ignarro accepts the Nobel Prize  
from King Carl Gustav of Sweden





"I like it!!!"







The Swedish Royal Family entering  
the banquet hall







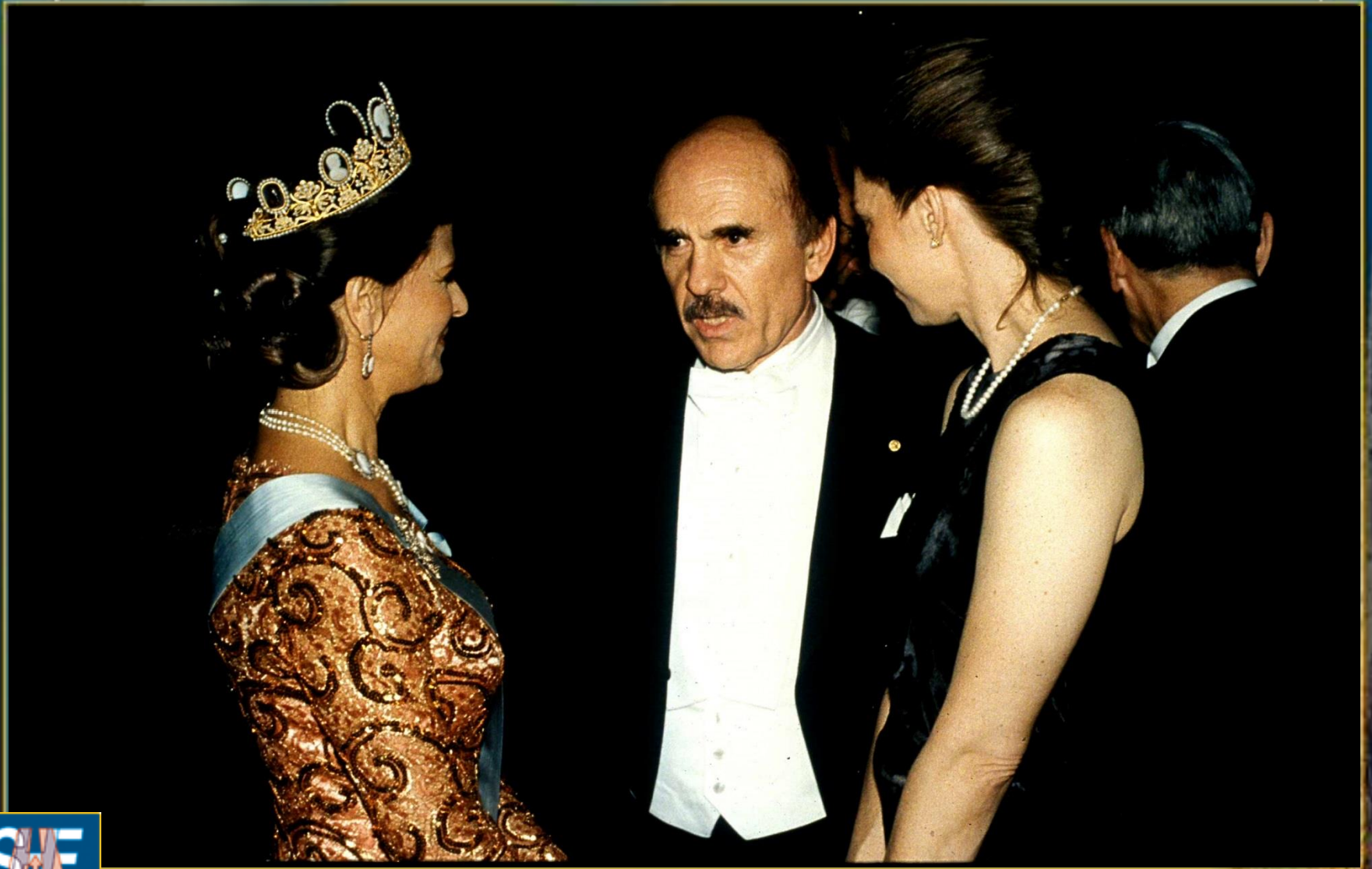


**Dr. Ignarro at the Nobel Banquet**















**At the dance following the Nobel Prize Ceremony  
and Banquet, Stockholm, December 10<sup>th</sup>, 1998**





**Dr. Ignarro adding his signature to the list of all previous Nobel Laureates at the Nobel Foundation**