

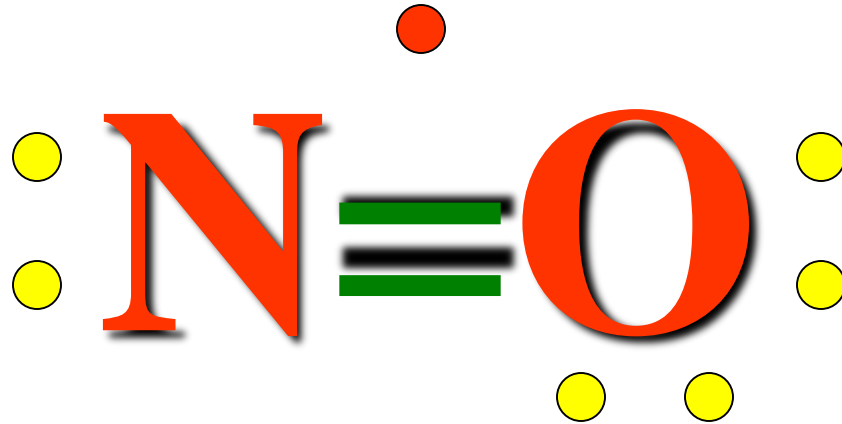
The Road to Stockholm

A Nobel Mission

History and Discovery of a Unique Gaseous Signaling Molecule

Nitric Oxide

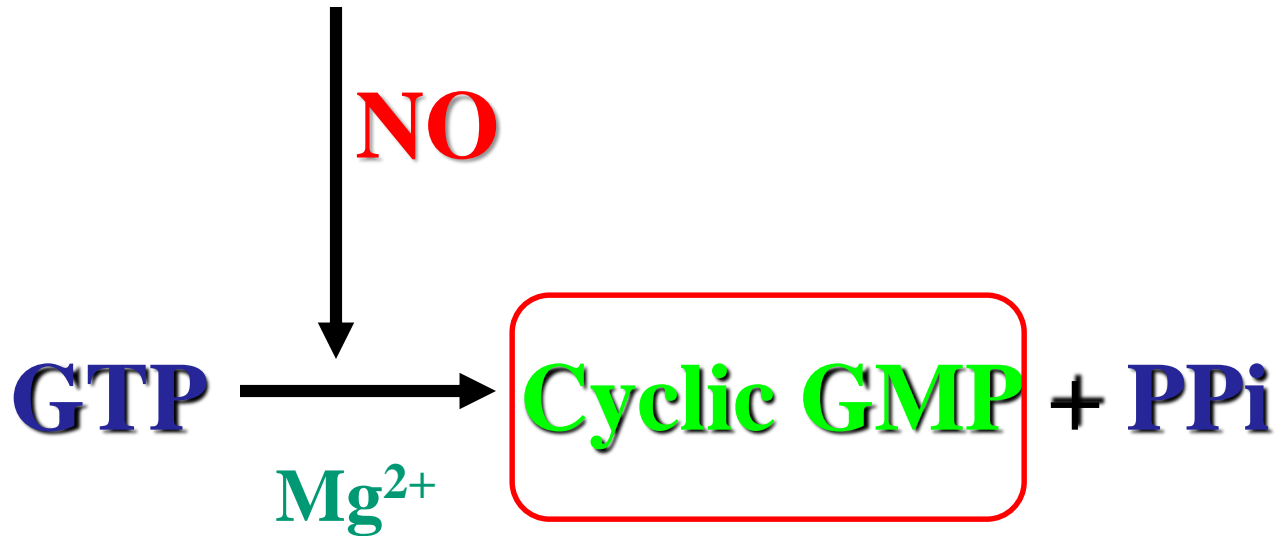
NO



Nitric Oxide is the most widespread signaling molecule in the body

Nitric Oxide is the most widespread “anti-aging” molecule in the body

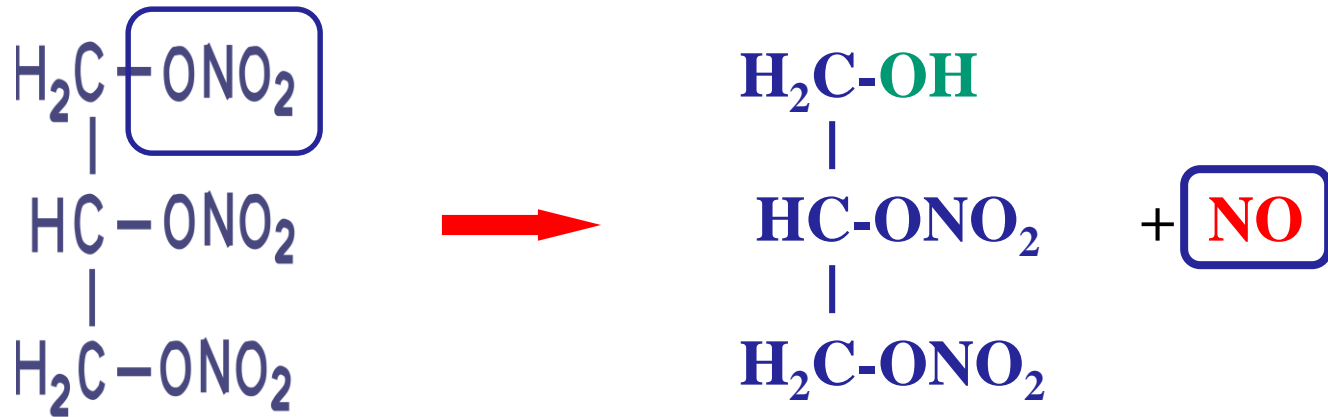
Guanylate Cyclase



Nitroglycerin

- ✓ *Known vasodilator since the 1870's.*
- ✓ *Discovered in Alfred Nobel's dynamite factories in Stockholm.*
- ✓ *Mechanism of action unknown.*
- ✓ *Called a direct acting spasmolytic agent.*
- ❖ *Could it work by a NO/cyclic GMP mechanism?*

Nitroglycerin



Question: Is NO the Active Vasorelaxant Species of Nitroglycerin?

Answer: YES- Authentic NO Gas is a Potent Vasorelaxant.

Pharmacology of Nitric Oxide

- ✓ *Vascular smooth muscle relaxant or vasodilator.*
- ✓ *Lowers the elevated blood pressure in hypertension.*
- ✓ *Improves blood flow.*
- ✓ *Inhibits blood clotting by interfering with platelet aggregation.*

About Nitric Oxide

- ✓ *NO was well known to be a gas present in the earth's atmosphere.*
- ✓ *NO undergoes air oxidation to the noxious nitrogen dioxide (NO₂).*
- ✓ *Not known or even suspected to be present endogenously in mammals.*
- ✓ *No one was thinking about NO as a naturally occurring signaling molecule.*

One Thing Was Missing

- ✓ *The pharmacology was very interesting.*
- ✓ *But what is the physiological relevance of the NO/cyclic GMP system?*
- ❖ *For example, does NO exist endogenously in cells?*

Chemical Properties of Nitric Oxide

- ✓ *Small lipid soluble molecule*
- ✓ *Readily diffuses through cell membranes*
- ✓ *Cannot be stored in organelles*
- ✓ *Reactive free radical with short half-life*
- ✓ *Looks for other paramagnetic species*
- ✓ *Reacts with oxygen radicals*
- ✓ *Also reacts with iron and sulfur species*

**The Mechanism of Vasodilation
by Acetylcholine Remained a
Complete Mystery for Nearly
100 Years Until the Discovery of
EDRF**

Blood

Endothelium

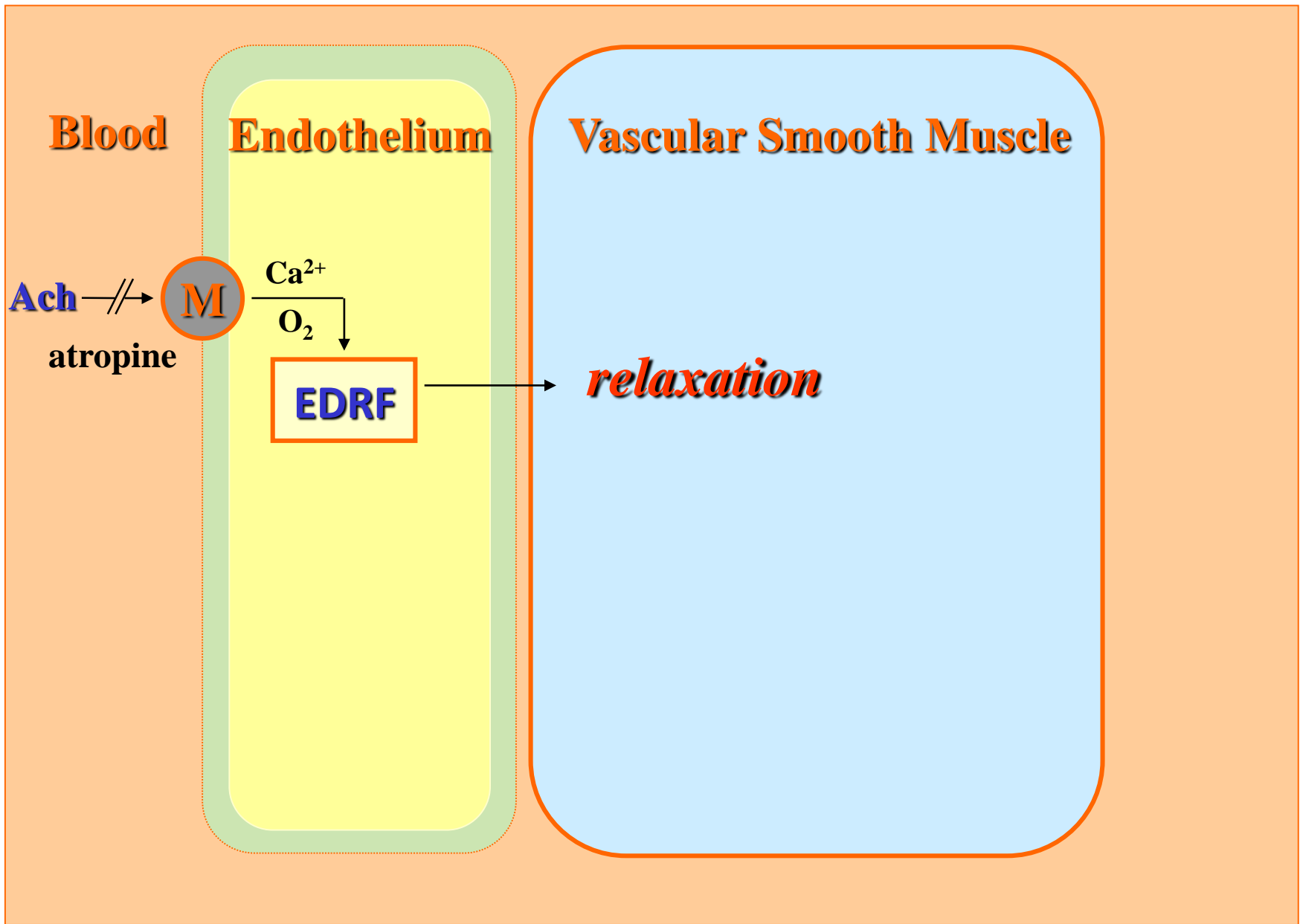
Vascular Smooth Muscle

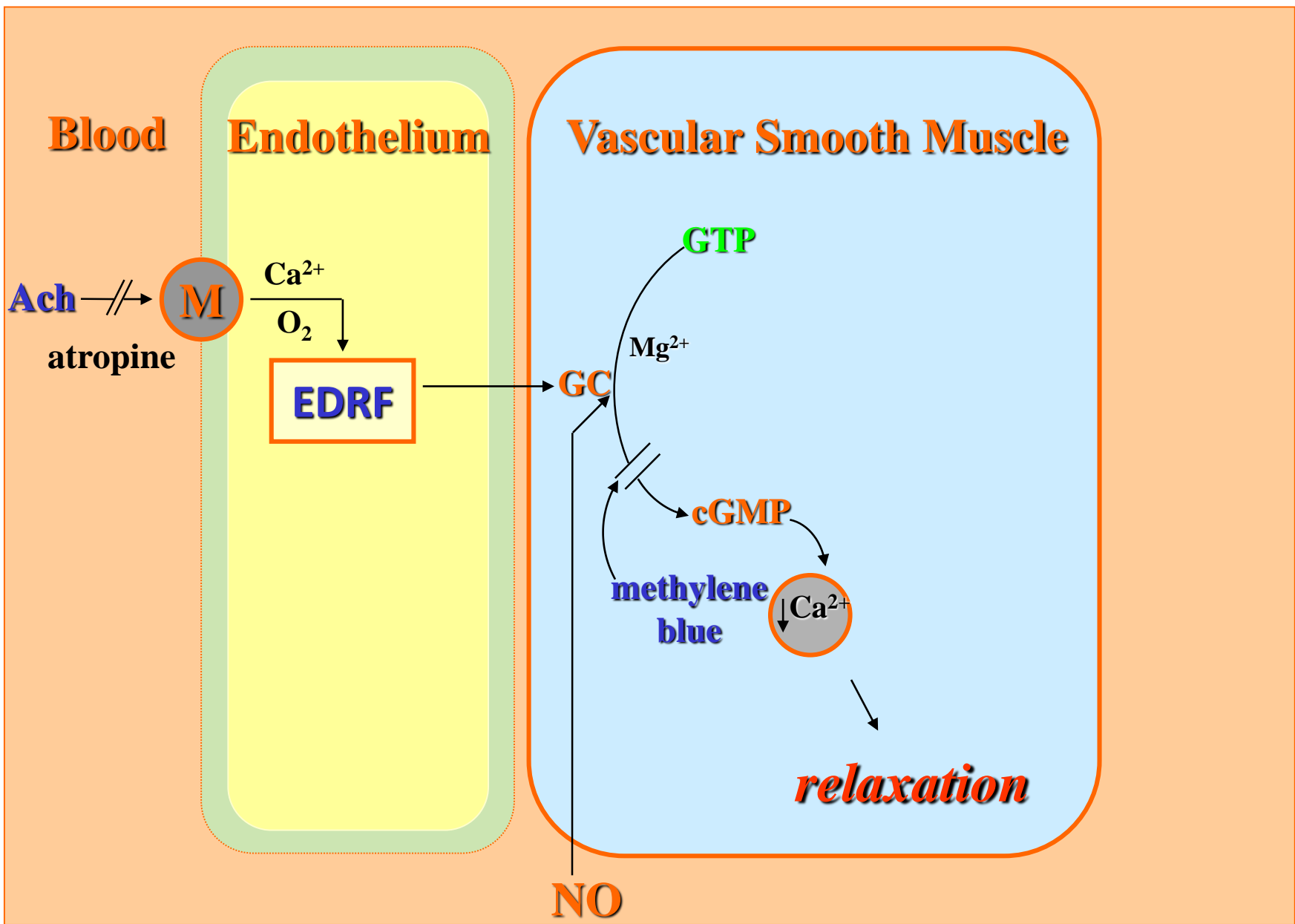
Ach \nrightarrow **M**
atropine

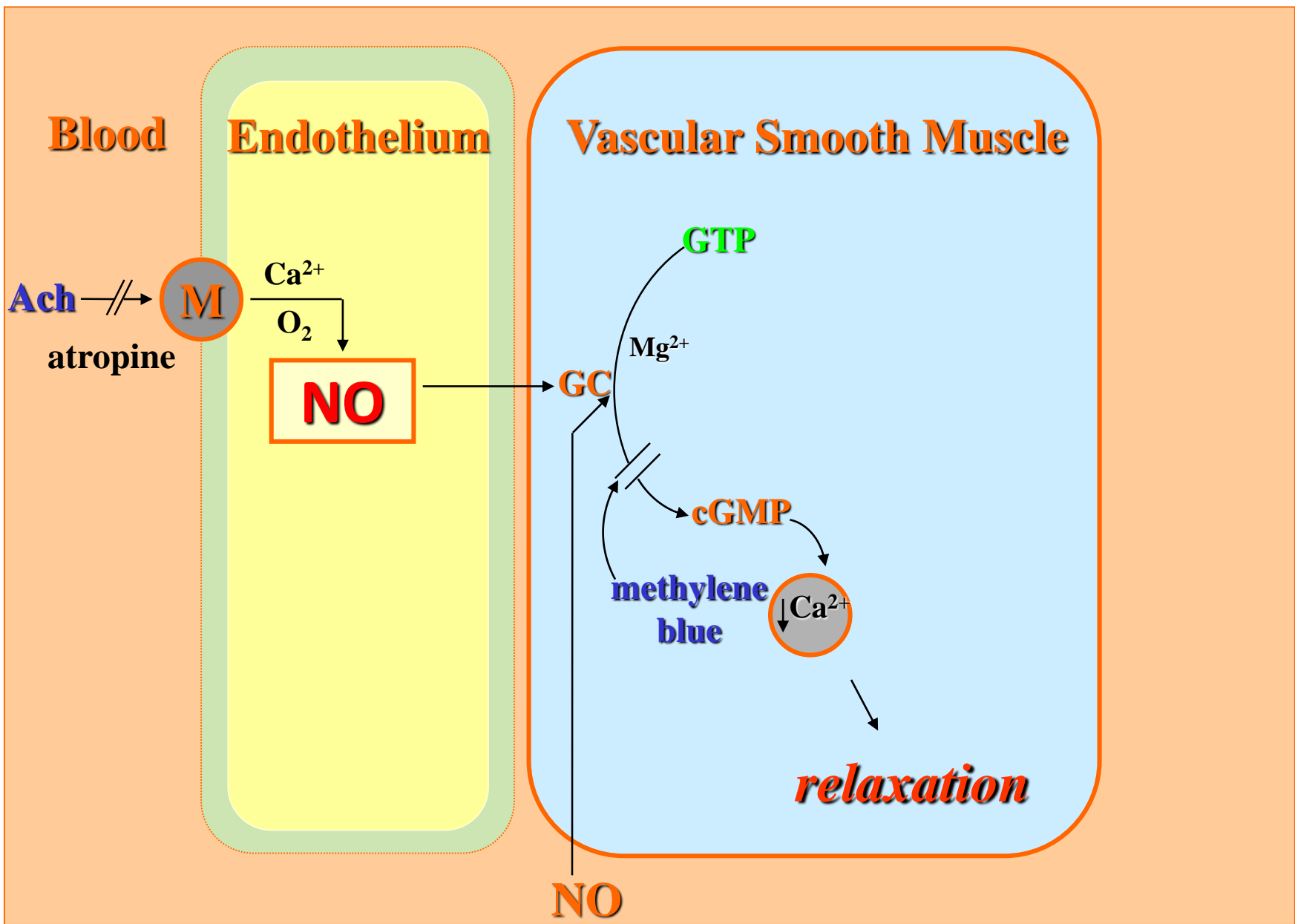
Ca^{2+}
 O_2

EDRF

relaxation

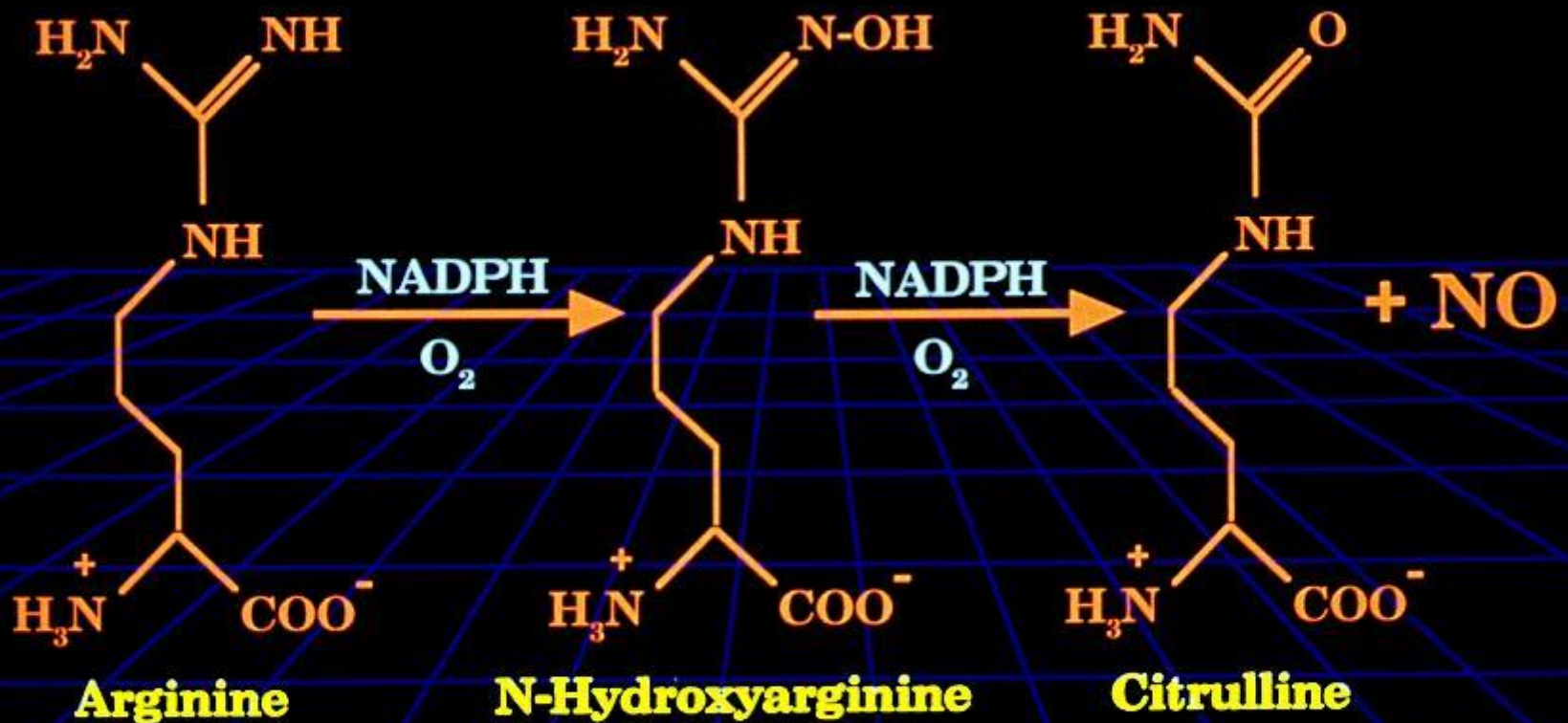






How is Nitric Oxide Produced by Mammalian Cells?

NO Synthase Reaction



**Discovery of Nitric Oxide as the
Principal Neurotransmitter
Mediating Erectile Function**



The New England Journal of Medicine

Abstracts in the
advertising
sections

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

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"All the News
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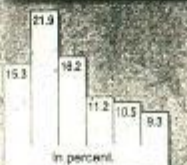
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THURSDAY, JANUARY 9, 1992

Who's Uninsured

BY AGE



in percent

BY RACE



*Hispanic people can be of any race.

Monthly averages for the last quarter of 1991.

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 Kojouhar, 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. They referred to measures that would limit 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, surgery or procedure. For example, a family doctor might receive \$35 for an office visit that uses

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 WINEN

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, Martin 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 his boss would continue most of his

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," rolled his head to the left, and was clearly fainting before being helped to the floor. "It all happened very, very fast," and the guest, who refused to be identified by name,

Quayle Is Named



What Happened Six Years Later?

(1998)

Sildenafil or Viagra

MECHANISM- INCREASES THE
ACTIONS OF CYCLIC GMP AND NO

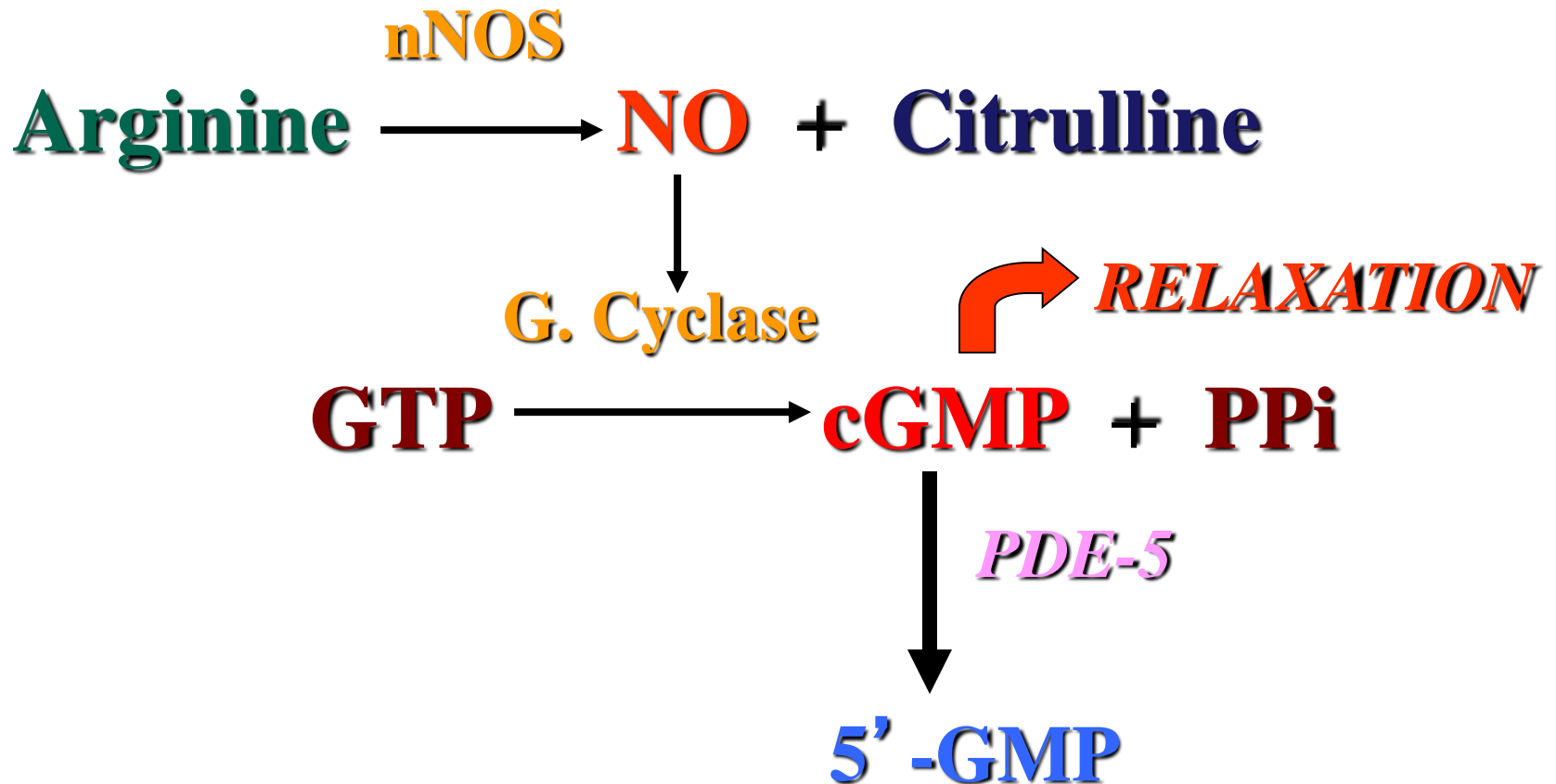
March 1998

Marketing of Viagra

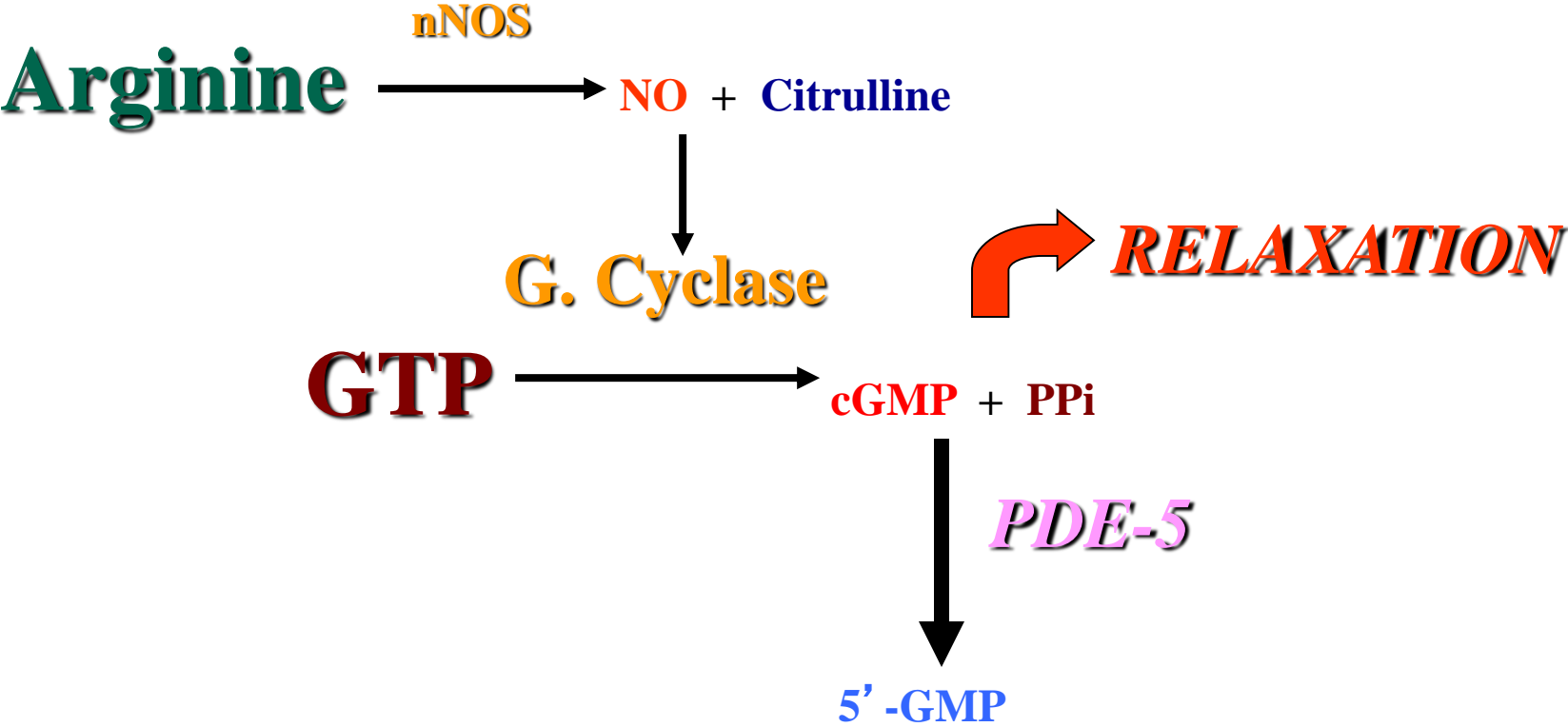
October 1998

Nobel Prize Announcement

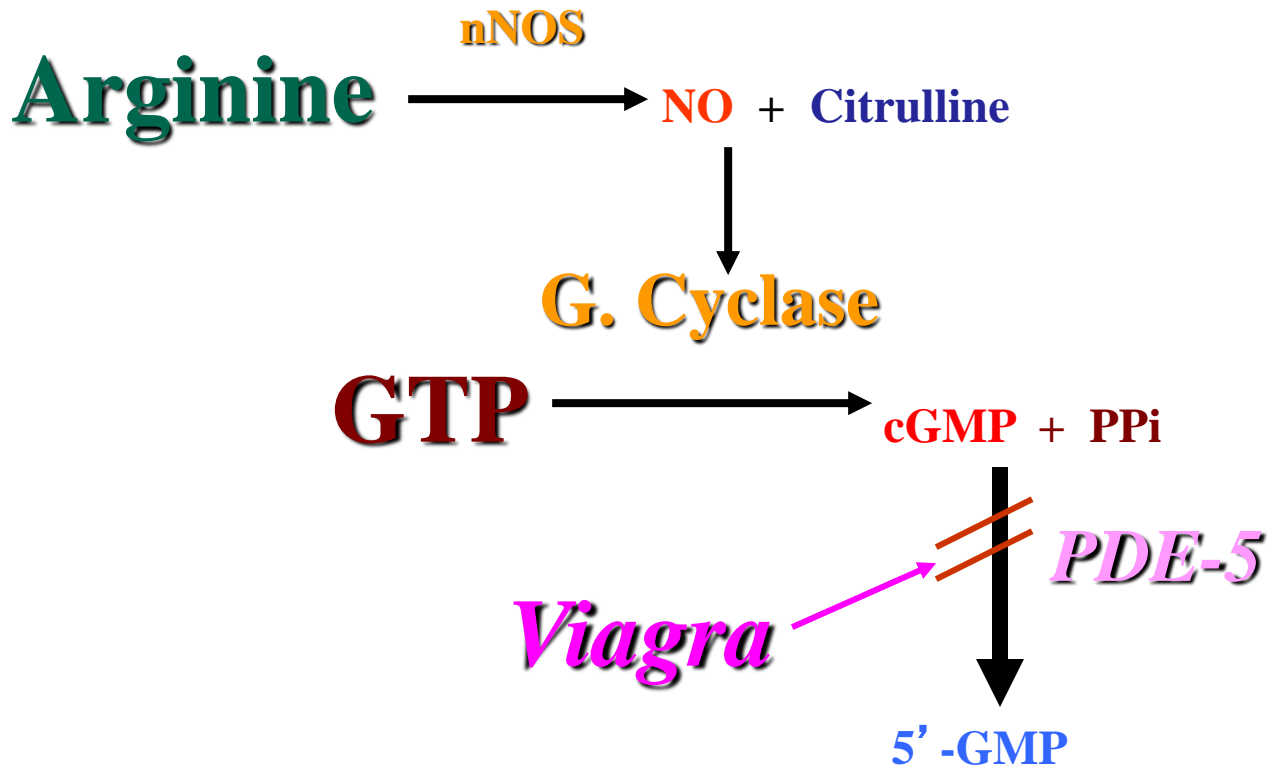
NO-cGMP Signal Transduction Pathway



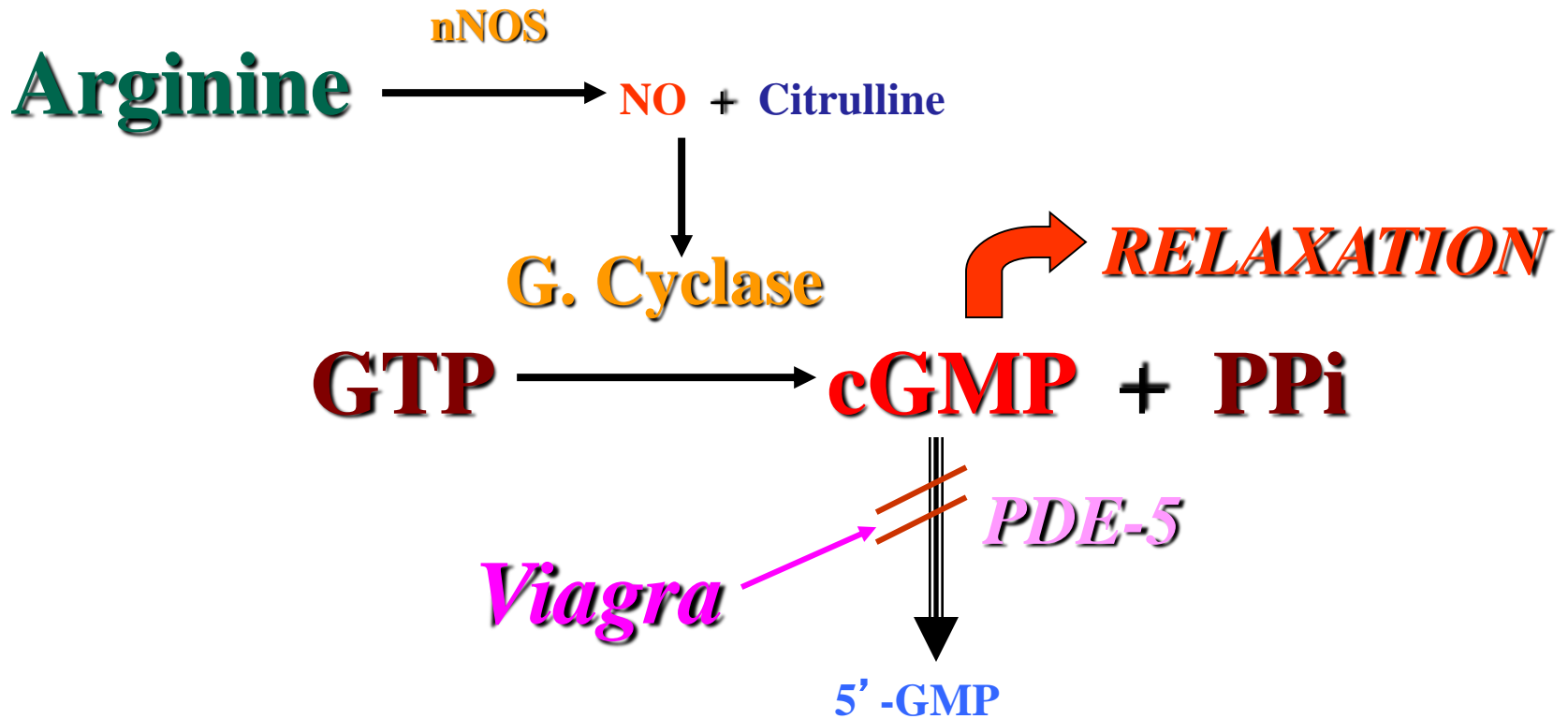
NO-cGMP Signal Transduction Pathway

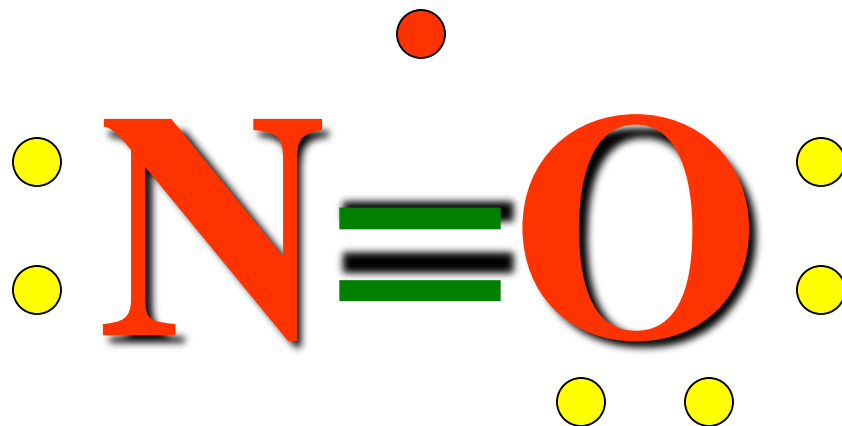


NO-cGMP Signal Transduction Pathway



NO-cGMP Signal Transduction Pathway



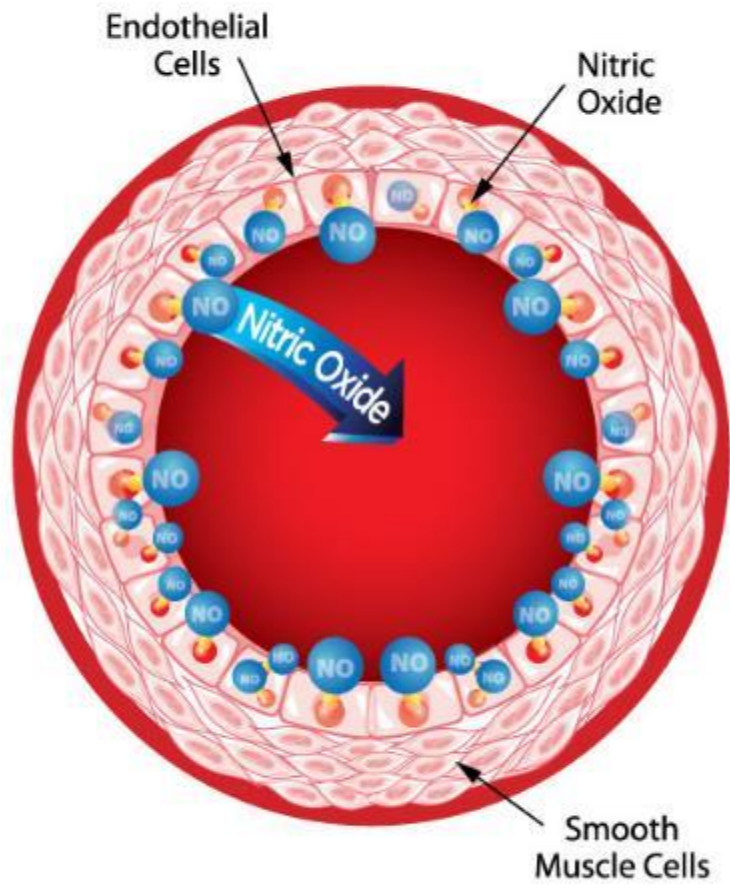


Molecule of the Year
Science 1992

Impact of Nitric Oxide Research on Medicine and Therapeutics

Cardiovascular Disease is the Number One Cause of Morbidity and Untimely Death







THE NOBEL PRIZE IN PHYSIOLOGY OR MEDICINE 1998



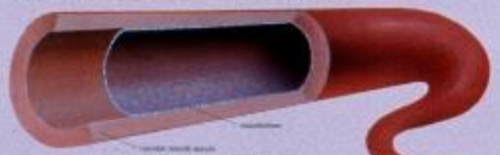
The Nobel Assembly at the Karolinska Institute in Stockholm, Sweden, has awarded the Nobel Prize in Physiology or Medicine for 1998 jointly to **Robert F Furchgott**, **Louis J Ignarro** and **Ferd Murad**, for their discoveries concerning "nitric oxide as a signalling molecule in the cardiovascular system."

A new principle

Nitric oxide, NO, is a short-lived, endogenously produced gas that acts as a signalling molecule in the body. It diffuses

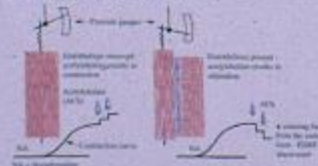
freely across cell membranes, is produced by one cell, which generates paracrine and regulates the function of other cells in an

entirely new principle for signalling in the human organism.



Furchgott's sandwich

Robert F Furchgott observed that acetylcholine induced relaxation of blood vessels was dependent on the endothelium. He "sandwich" experiment was the first for the first endothelium-dependent process. He used two different pieces of the artery: one had the endothelium layer intact, the other it had been removed.



Murad's enzyme activation

Ferd Murad found that nitric oxide (NO) is produced by endothelial cells. The enzyme responsible for this was discovered and named endothelial nitric oxide synthase (eNOS). This enzyme produces and releases NO into the bloodstream. NO is a potent vasodilator and is also involved in many other physiological processes.



Ignarro's spectral analysis

Louis Ignarro realized that EPR is a useful tool for studying nitric oxide. He also identified eNOS as a molecule by using spectral analysis of nitric oxide. When he first discovered eNOS, he was surprised to find that it was a membrane protein. This was the first time a membrane protein was shown to be involved in the production of NO. A new principle for signalling between tissues was discovered.

Endothelial nitric oxide synthase (eNOS) is a membrane protein that is found in endothelial cells. It is responsible for the production of NO. The discovery of eNOS was a major breakthrough in the study of NO signaling.

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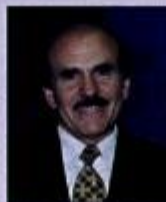
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Robert F Furchgott, born in 1916, Department of Pharmacology, SUNY Health Science Center, New York.



Louis J Ignarro, born in 1941, Department of Molecular and Medical Pharmacology, UCLA School of Medicine, Los Angeles.

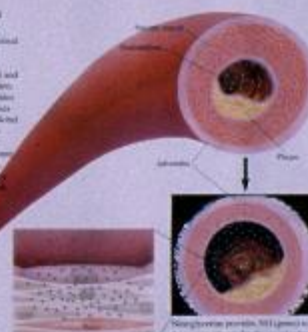


Ferd Murad, born in 1936, Department of Surgery and Biophysics, Pharmacology and Physiology, University of Texas Medical School, Houston.



Nitroglycerin, a 100 year old explosive and heart medicine

In nitroglycerin, glycerol nitrate binds to the arteries. This decreases oxygen supply to the heart muscle causing chest pain (angina pectoris) and sometimes even myocardial infarction. Treatment with nitroglycerin provides NO, dilates the vessels, and decreases blood flow. Thanks to this, the heart muscle receives more oxygen and the heart muscle is protected from damage and cell death.



NO has many clinical applications

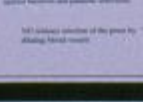
Today, as a gas, NO is also an important signaling molecule in the cardiovascular system and has become a useful tool in the prevention of medicine.



NO is essential for signaling between nerve cells in the brain.



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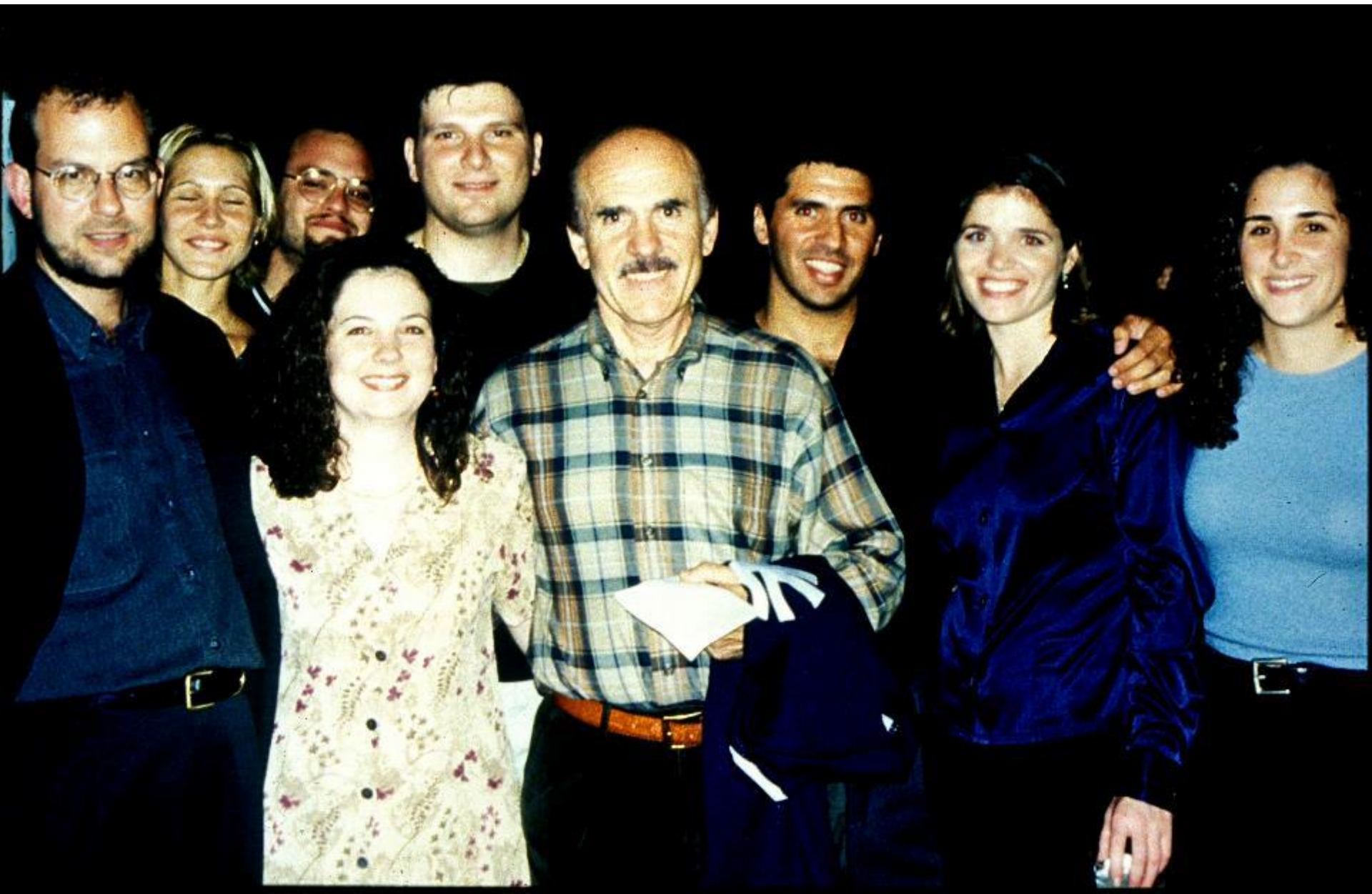
**The Answer to
Cardiovascular Health is
NITRIC OXIDE through
Healthy Diet, Exercise and
Key Food Supplements**

Diet and Aerobic Exercise

- ✓ *Healthy diet elevates NO production and action.*
- ✓ *Fatty and salty diet decreases NO.*
- ✓ *Aerobic exercise stimulates NO formation.*
- ✓ *Sedentary lifestyle decreases NO.*

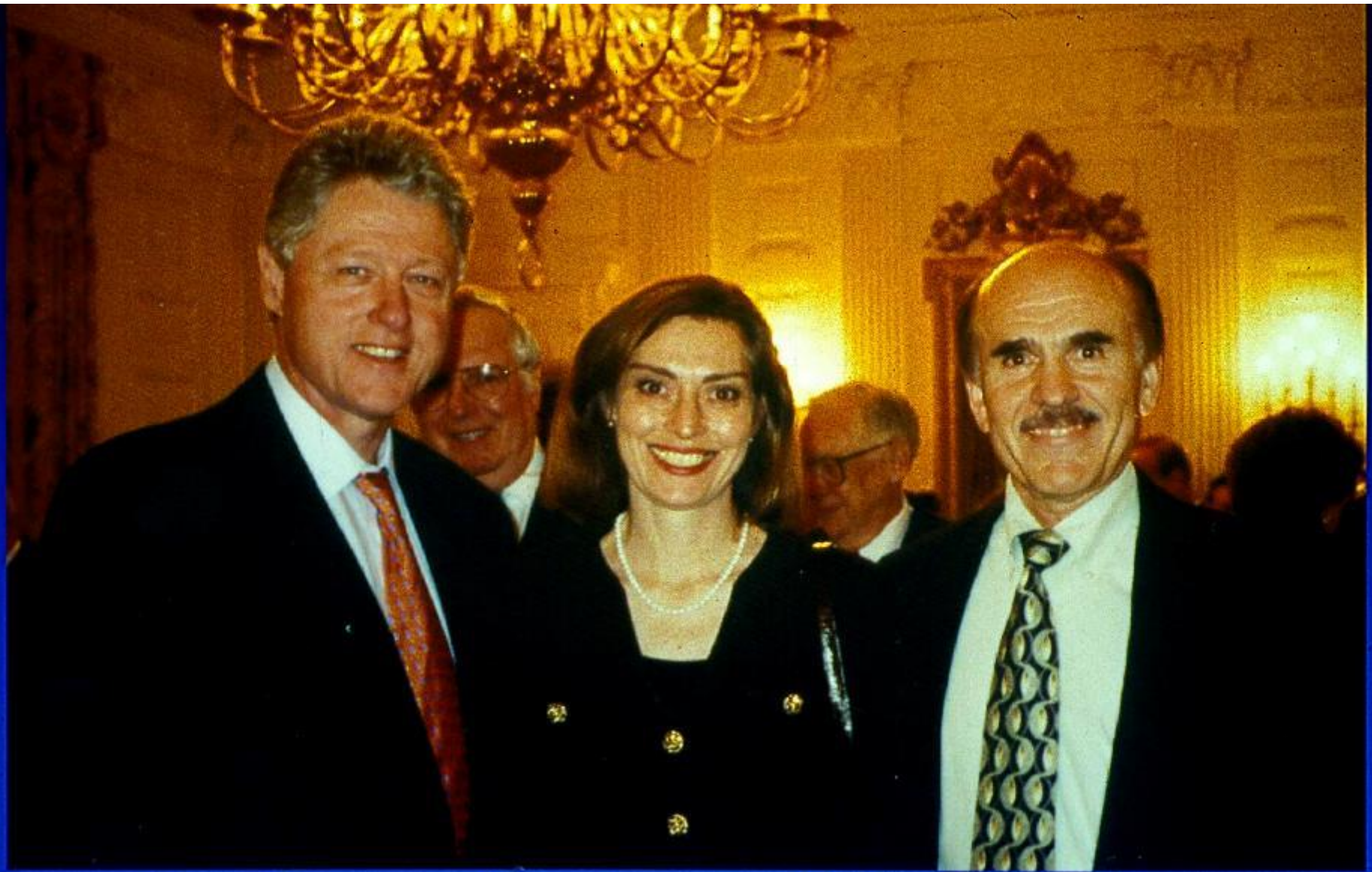
October 12, 1998











Drs. Sharon and Lou Ignarro with President Clinton



Dr. Sharon Williams Ignarro with President Clinton







The three Nobel Laureates in Medicine-1998

