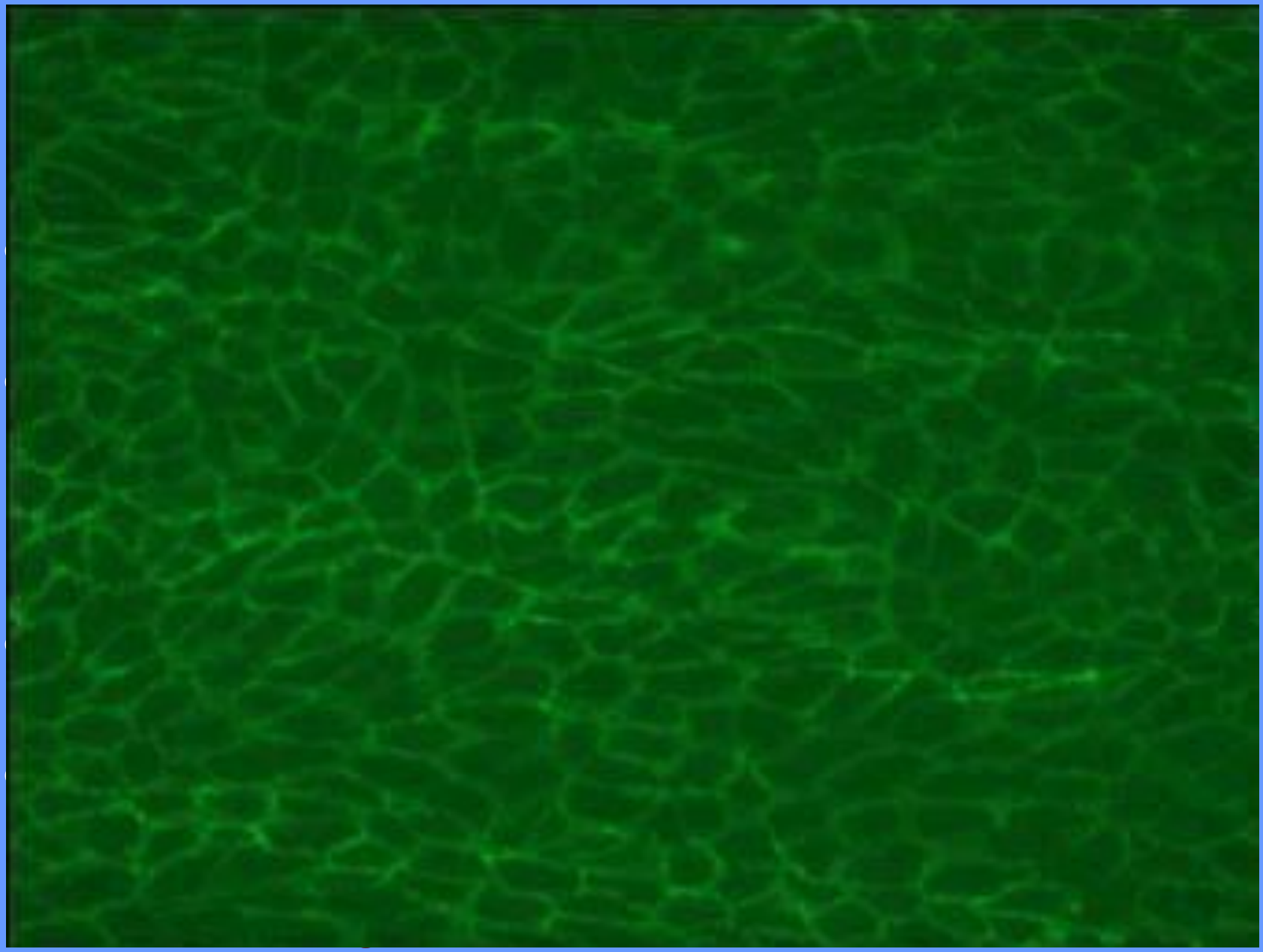
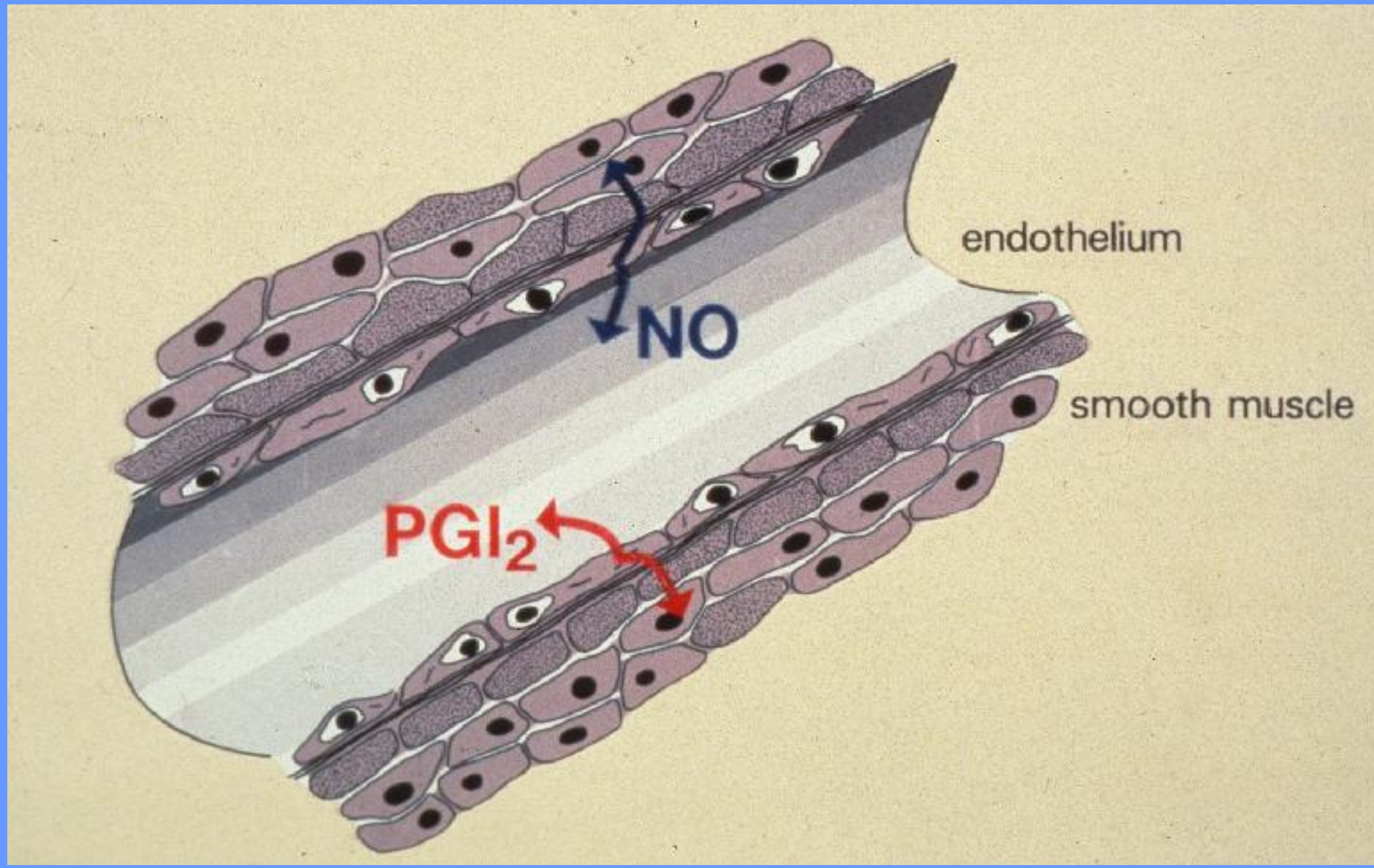


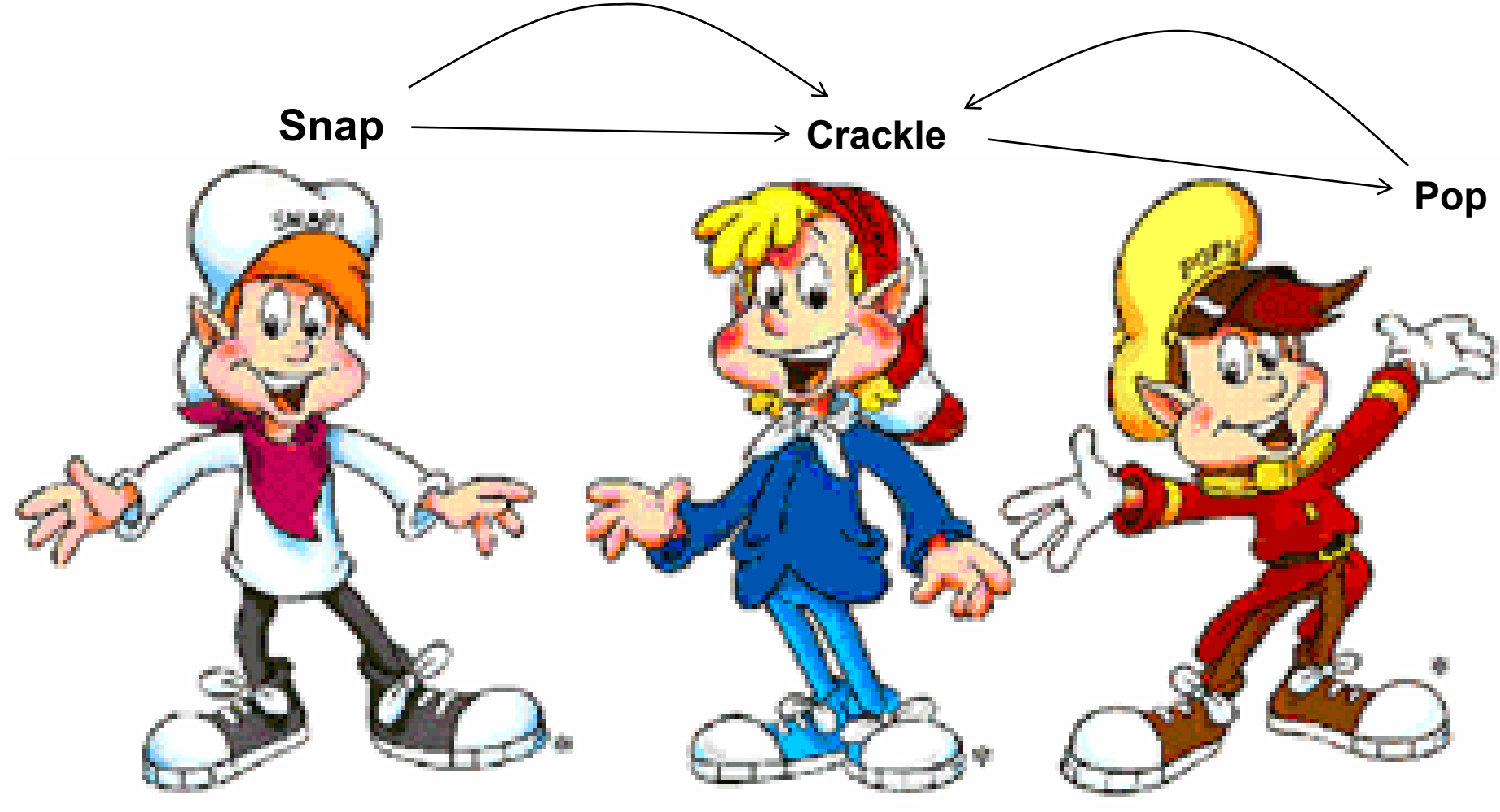
Prostacyclin and NO – fundamental mediators in the vasculature



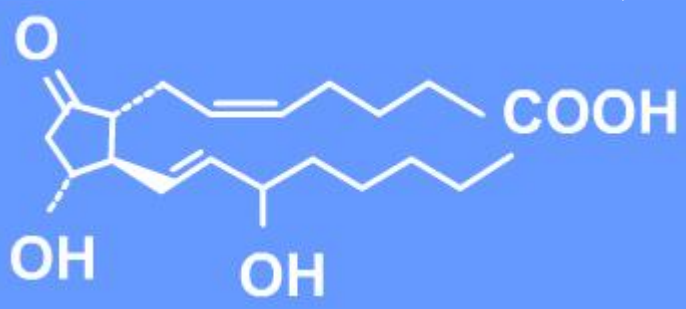
Bioassay profile of different vasoactive substances

TISSUE	PGE_2	$PGF_{2\alpha}$	PGG_2 PGH_2	TXA_2	PGX
Rat stomach strip					
Chick rectum					
Rat colon					
Cat jejunum strip					
Rabbit aorta					
Rabbit coeliac artery					

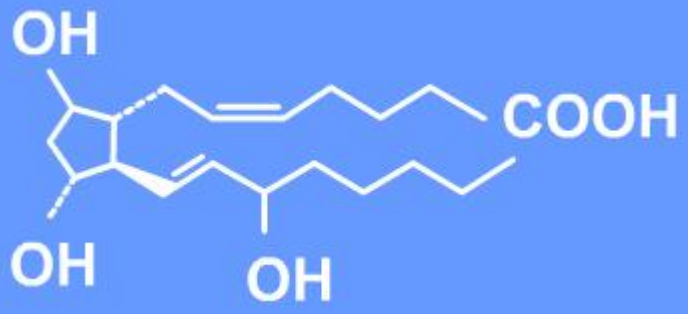
One great advantage of bioassay is that it measures biological activity


Snap
Crackle
Pop

Arachidonic acid



Prostaglandin $F_{2\alpha}$



Prostaglandin E_2

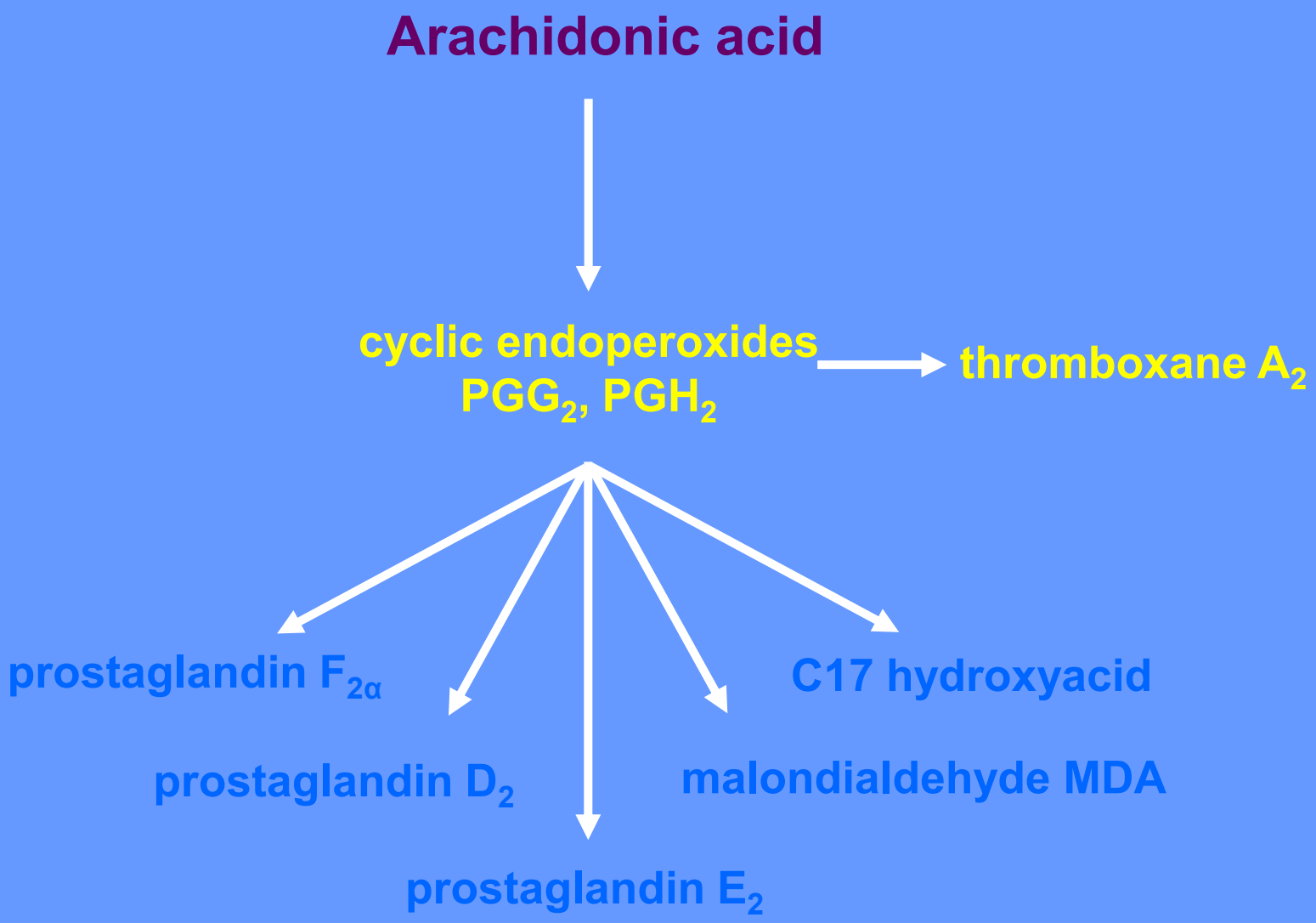
Metabolic pathway of arachidonic acid, 1971

This explained the mechanism of action of aspirin-like drugs

…and at least one of their side effects – the gastric damage

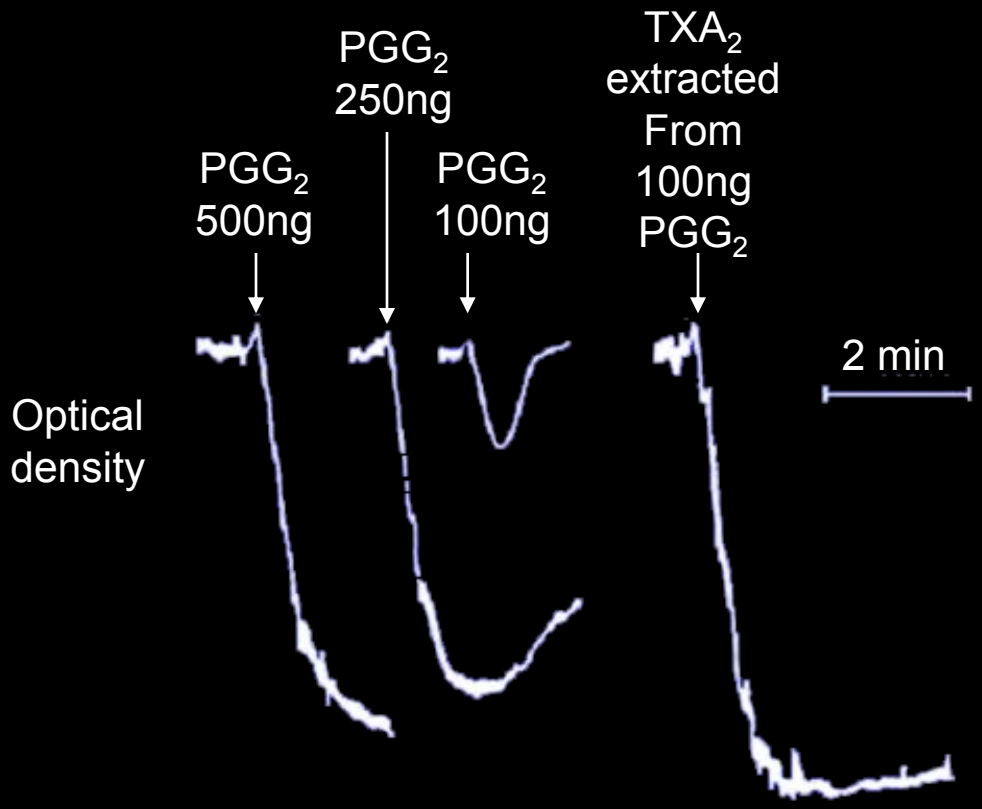
Experiences with aspirin (acetyl salicylic acid) in the nonspecific prophylaxis of coronary thrombosis

Craven (1953) Mississippi Valley Med. J. 75: 38 - 44



Metabolic pathway of arachidonic acid, 1975

Platelet aggregation induced by PGG_2 and TXA_2



Needleman *et al*, (1976) Nature 261: 558 - 560

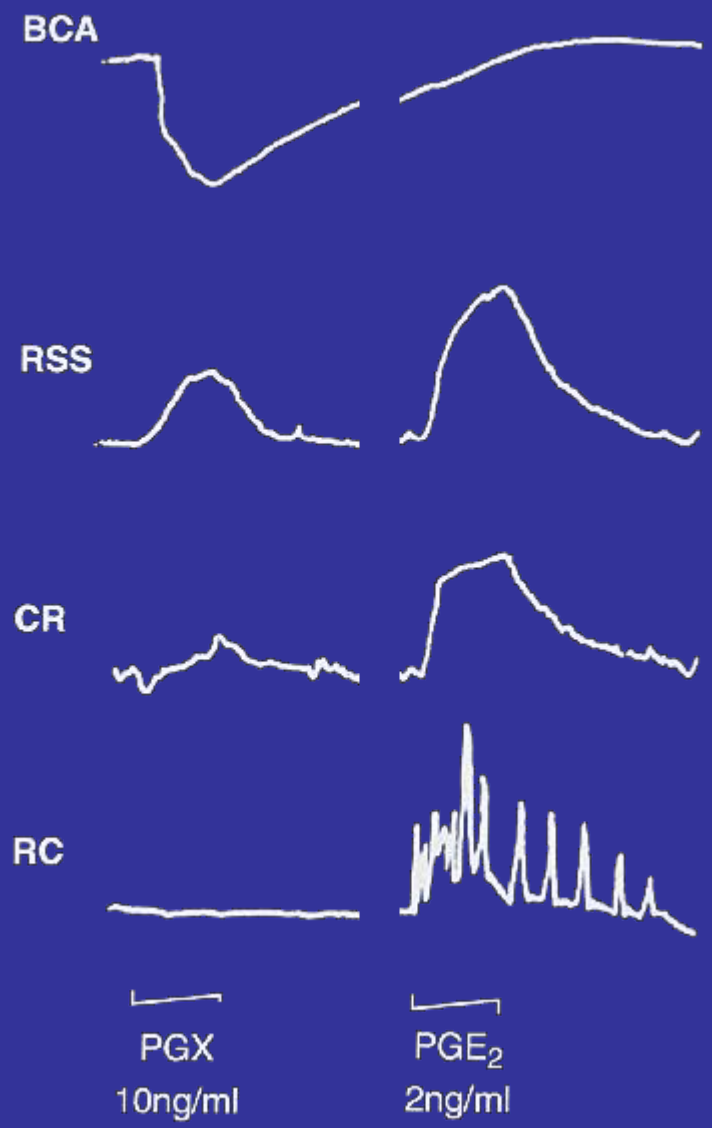
Arachidonic acid

cyclic endoperoxides
PGG_2, PGH_2 → **thromboxane A_2**

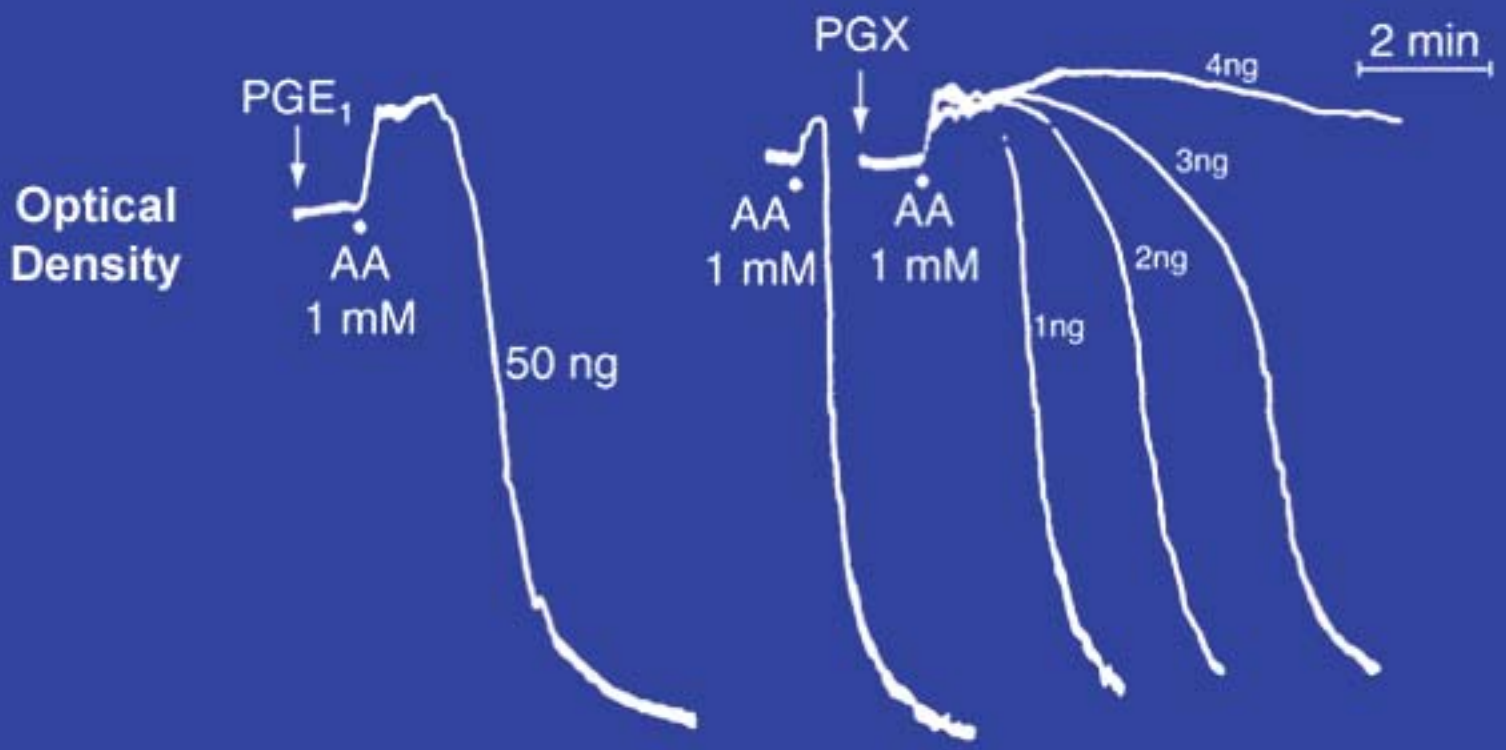
Metabolic pathway of arachidonic acid in platelets

Is the vasoconstrictor thromboxane A_2 also made by the vessel wall?

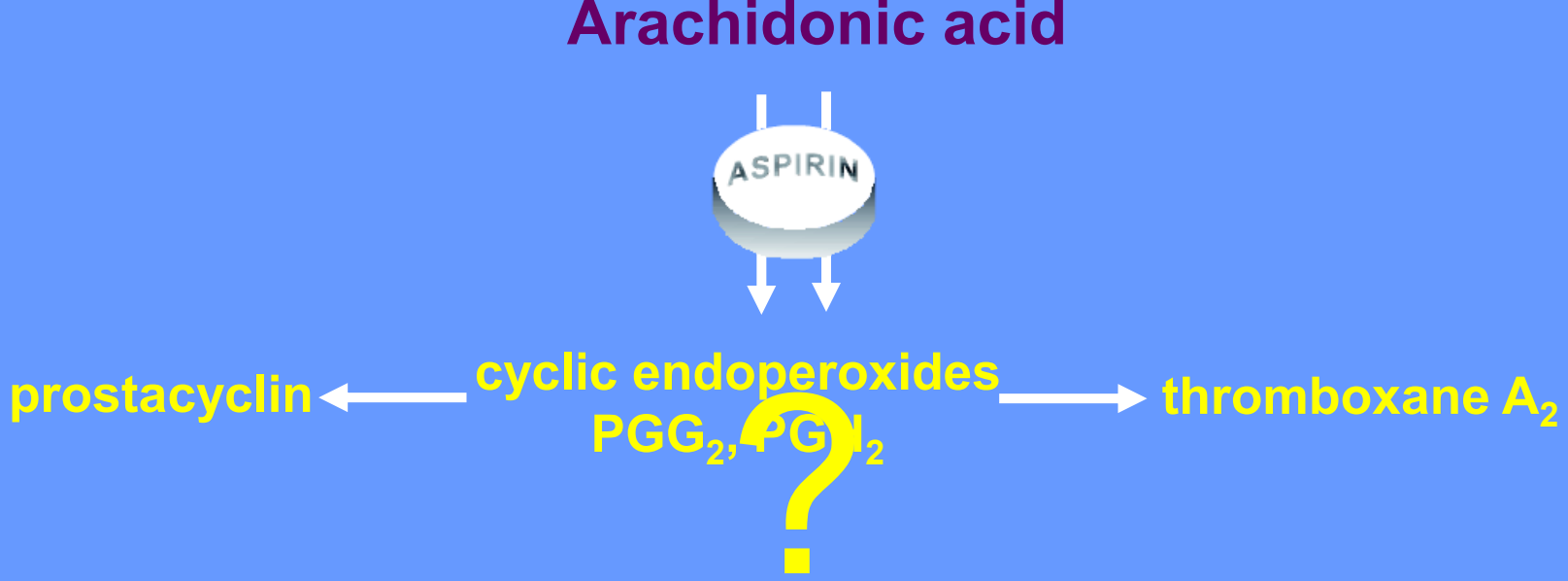
Differential bioassay of PGE_2 and vessel wall extract



Anti-aggregatory activity of PGE_1 and PGX on human platelets



Moncada *et al.* (1976) Nature 263: 663-665



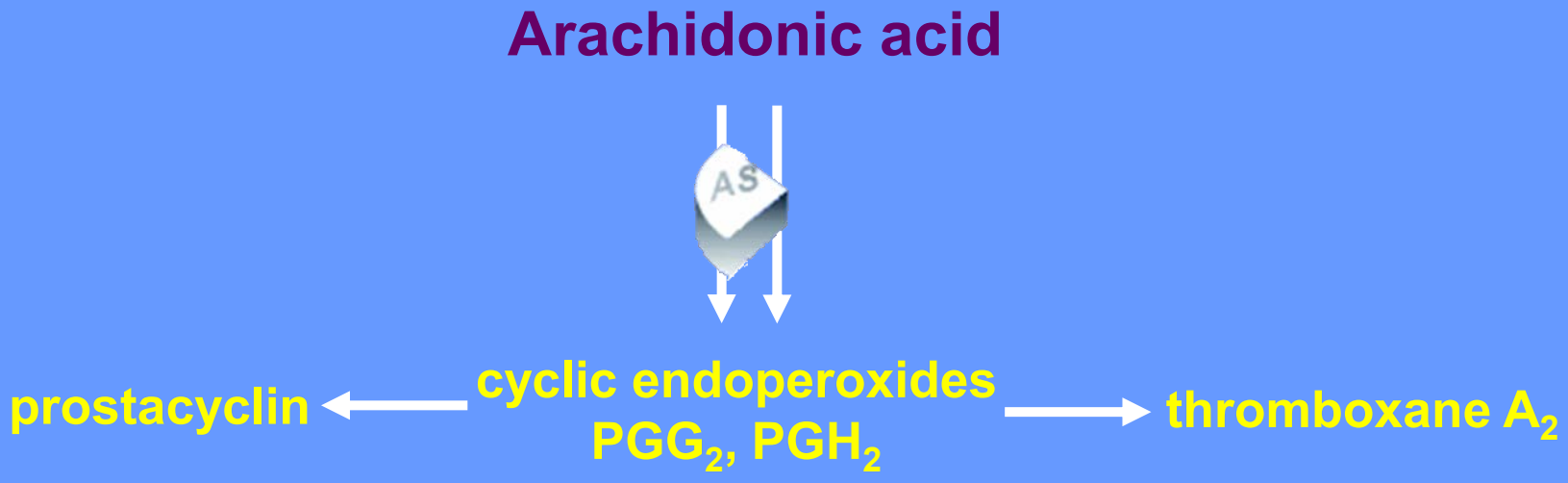
Metabolic pathway of arachidonic acid in platelets and the vessel wall

Aspirin selectively inhibits platelets

- platelet cyclooxygenase is very sensitive to aspirin*

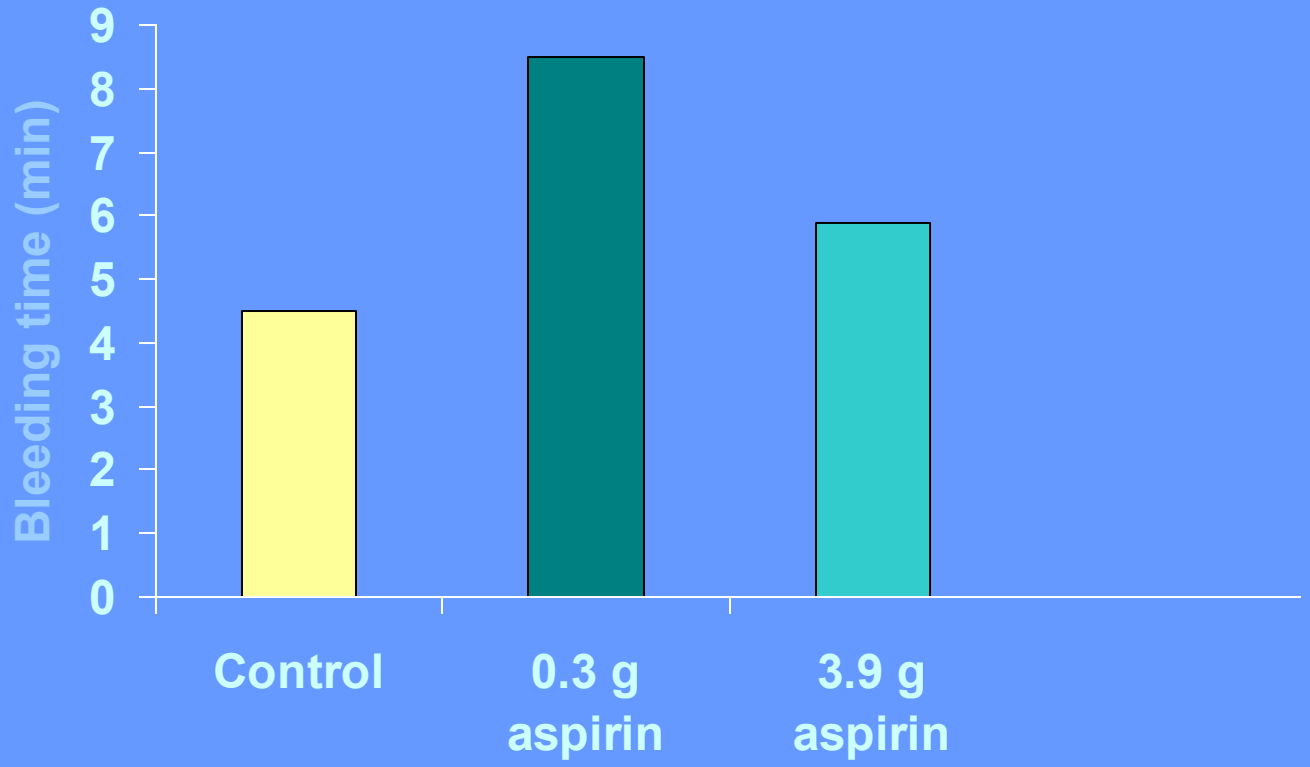
- inhibition of platelet cyclooxygenase lasts for the whole lifetime of the platelet

*Burch et al (1978) J. Clin. Invest. 61: 314-319



Effect of low - dose aspirin on the metabolic pathway of arachidonic acid in platelets and the vessel wall

Effect of low and high dose aspirin on bleeding time in healthy volunteers



O"Gradyand Moncada (1978) Lancet 312:780

Clinical trials show that aspirin:

- prevents stroke in patients with atherosclerosis or TIA
- reduces risk of myocardial infarction in unstable angina
- reduces mortality in acute myocardial infarction
- prevents occlusion of vein grafts
- reduces risk of metastasis in cancer patients

Don‟tuse aspirin for primary prevention of cardiovascular disease

Barnett et al (2010) Brit. Med. J. 340: 920 - 922

It will be difficult

to beat “old aspirin”

Cyclooxygenases (1990)

COX-1: physiological processes

COX-2: inflammatory responses

Inhibition of COX-2 results in:

- inhibition of prostacyclin
- cardiovascular side effects

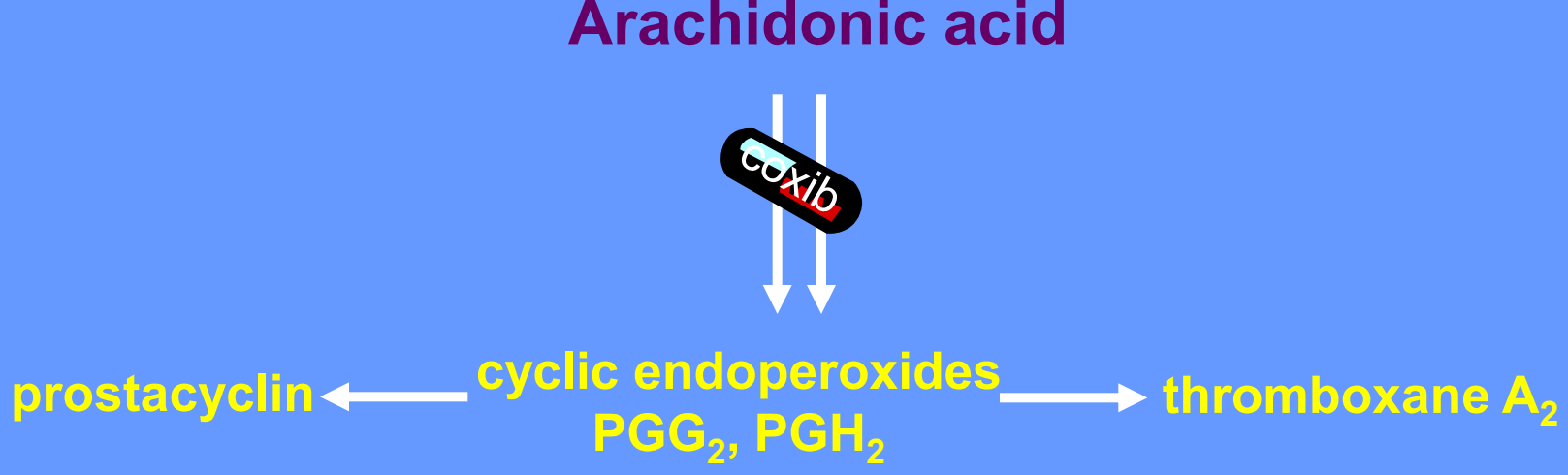
McAdam *et al*. (1999) Proc. Natl. Acad. Sci. USA 96: 272 - 277

Vioxx settlement to total $4.85bn

The maker of Vioxx has agreed to pay $4.85bn to settle legal claims that the controversial drug caused many users to suffer strokes and heart failure.

Vioxx was withdrawn from sale in 2004

BBC News Channel, Monday March 12th 2007



Effect of a COX-2 inhibitor on the metabolic pathway of arachidonic acid in platelets and the vessel wall

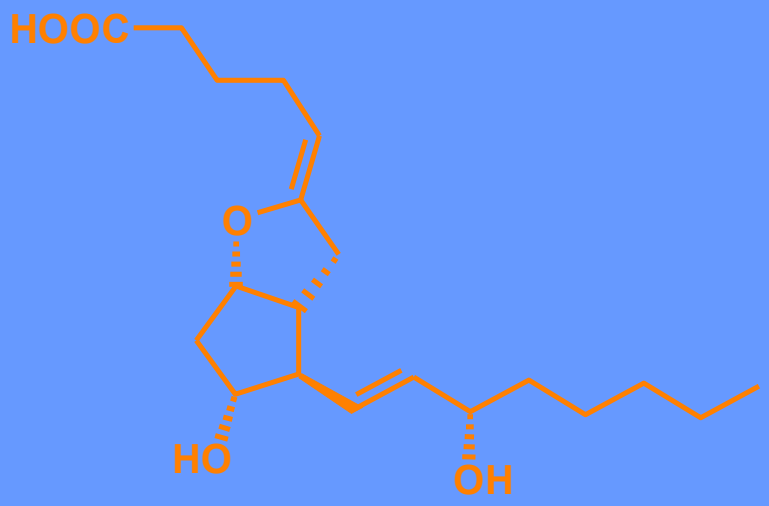
Cardiovascular risk of COX inhibitors

Drug	Relative risk vs nonuser
Naproxen	0.97
Meloxicam	1.25
Indomethacin	1.30
Ibuprofen	1.07
Diclofenac	1.40
Rofecoxib (>25 mg)	2.19
Rofecoxib (<25mg)	1.33
Celecoxib	1.06

From: White (2007) Hypertension 49: 408-418

COX-2 inhibitors may be beneficial in:

- cancer – colon, breast, prostate, lung
- Alzheimer's disease
- Parkinson's disease
- schizophrenia
- major depression
- ischaemic brain injury
- diabetic peripheral nephropathy



Prostacyclin

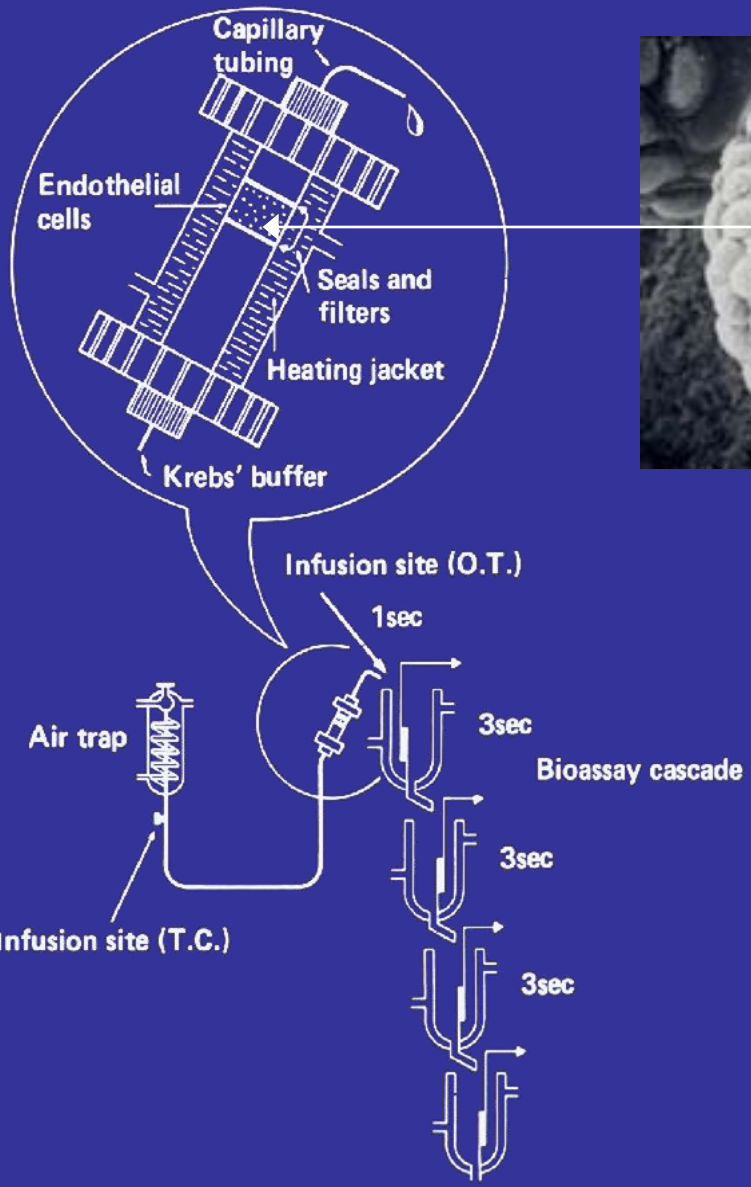
Clinical uses of prostacyclin:

- Primary pulmonary hypertension
- Peripheral arterial disease
- Cardiopulmonary bypass
- Organ transplantation

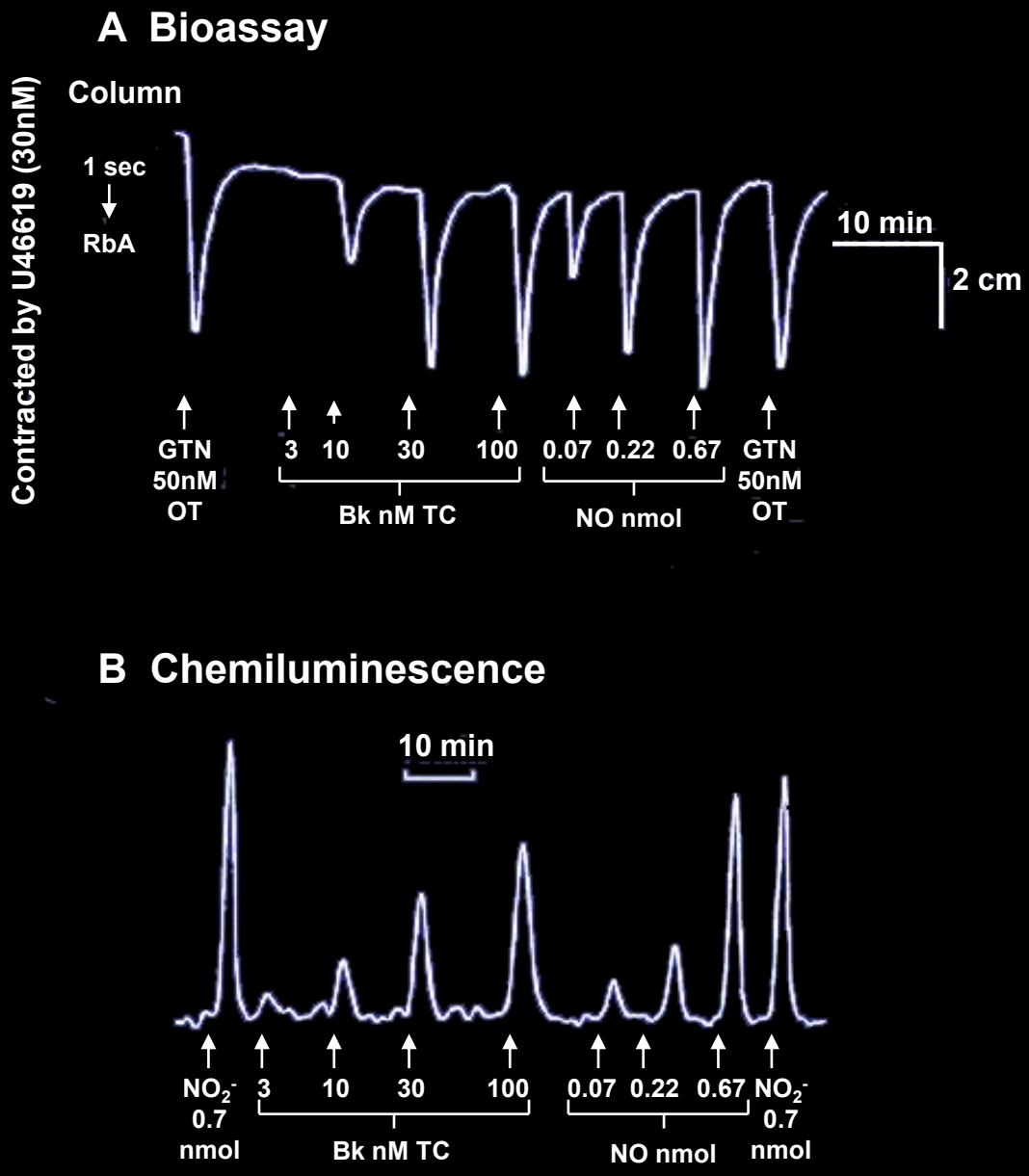
The obligatory role of endothelium in ACh-induced vascular relaxation

Furchgott and Zawadzki, Nature 288, 373-376, 1980

Bioassay of EDRF released from endothelial cells



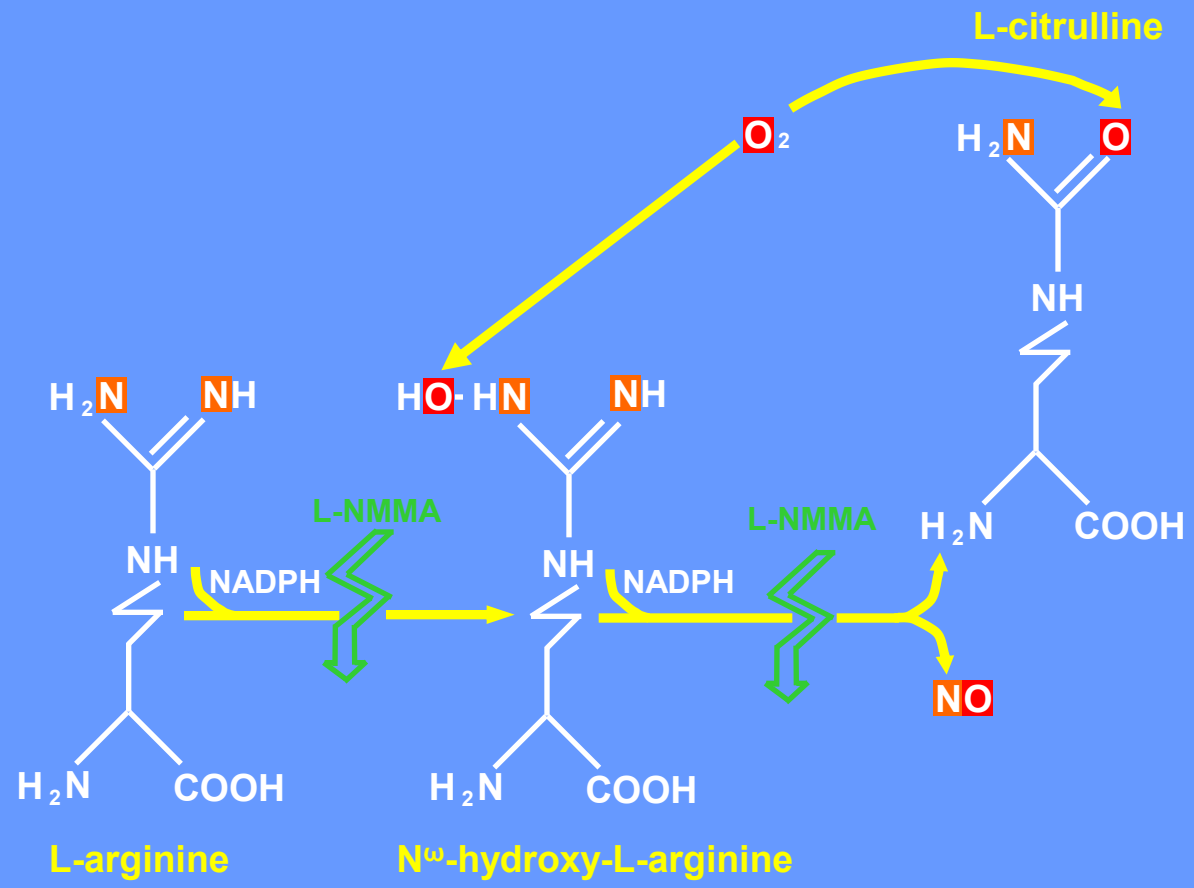
Detection of endogenous and exogenous NO



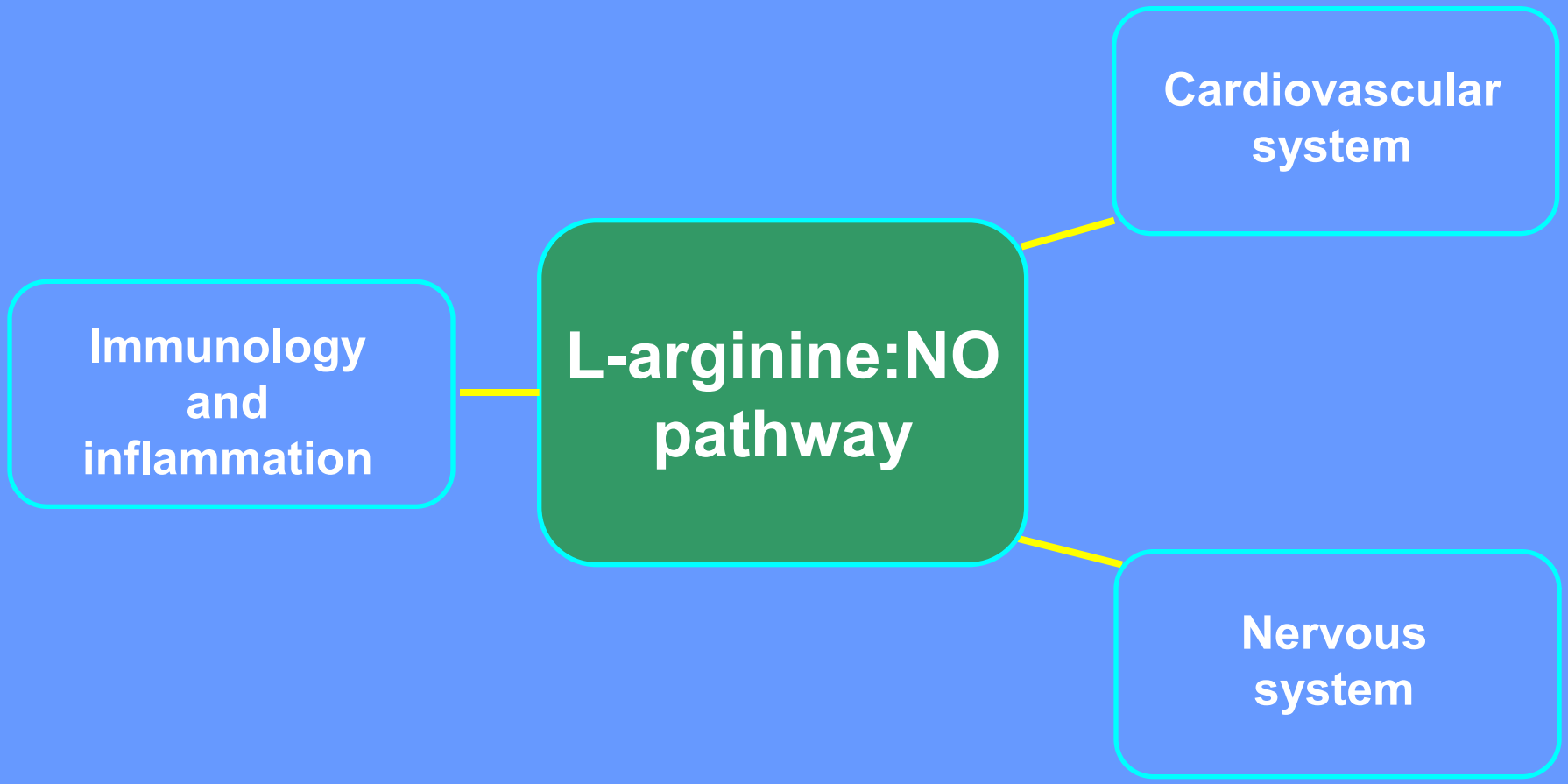
Palmer *et al* (1987) Nature 327: 524 - 526

“You were very persuasive; but unconvincing! I am sceptical for the simple reason that the formation of nitrogen oxides demands some pretty heavy thermodynamic considerations. Nitric oxide is produced in the upper atmosphere through the energic intervention of lightning!”

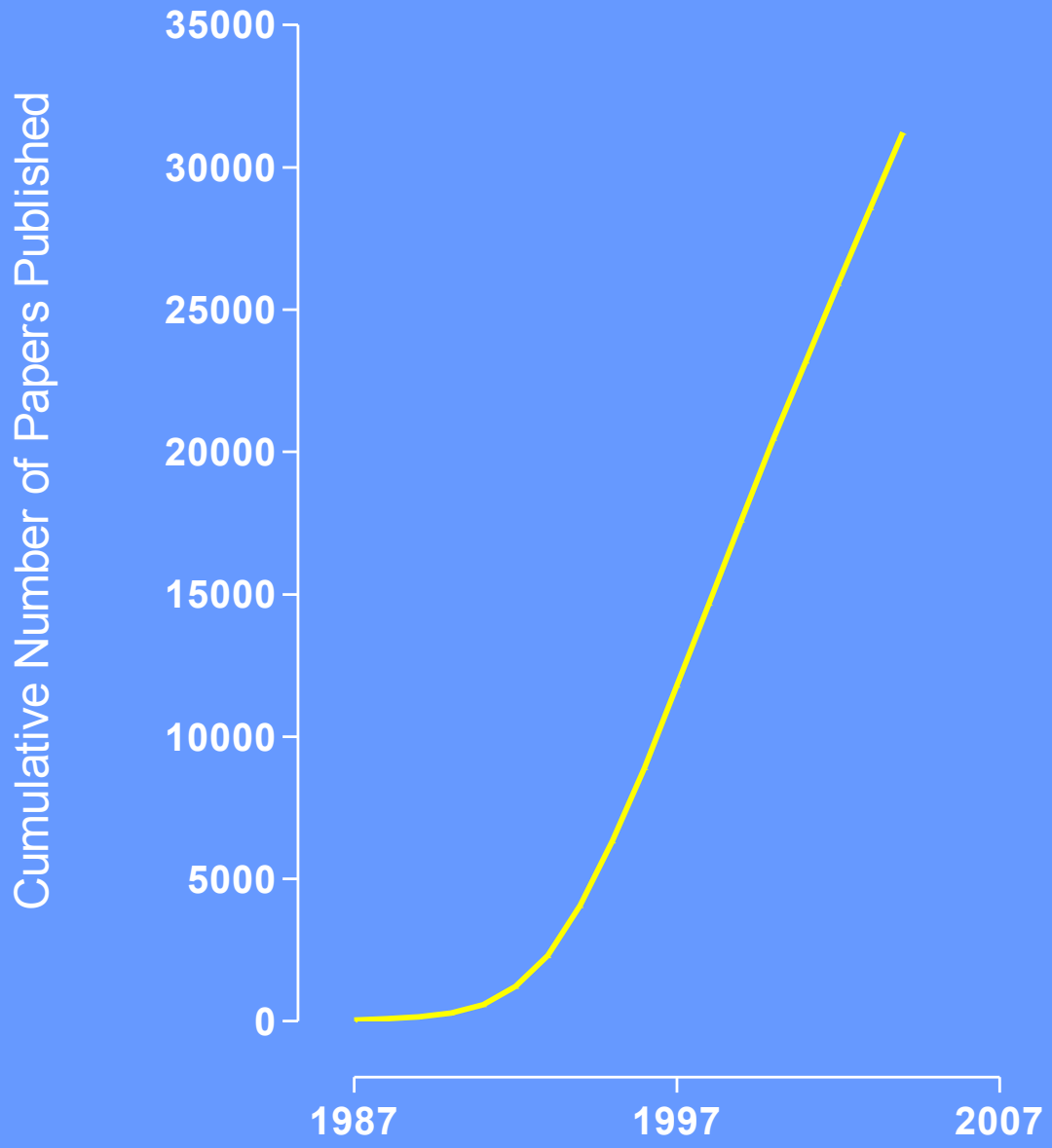
The L-arginine:NO pathway

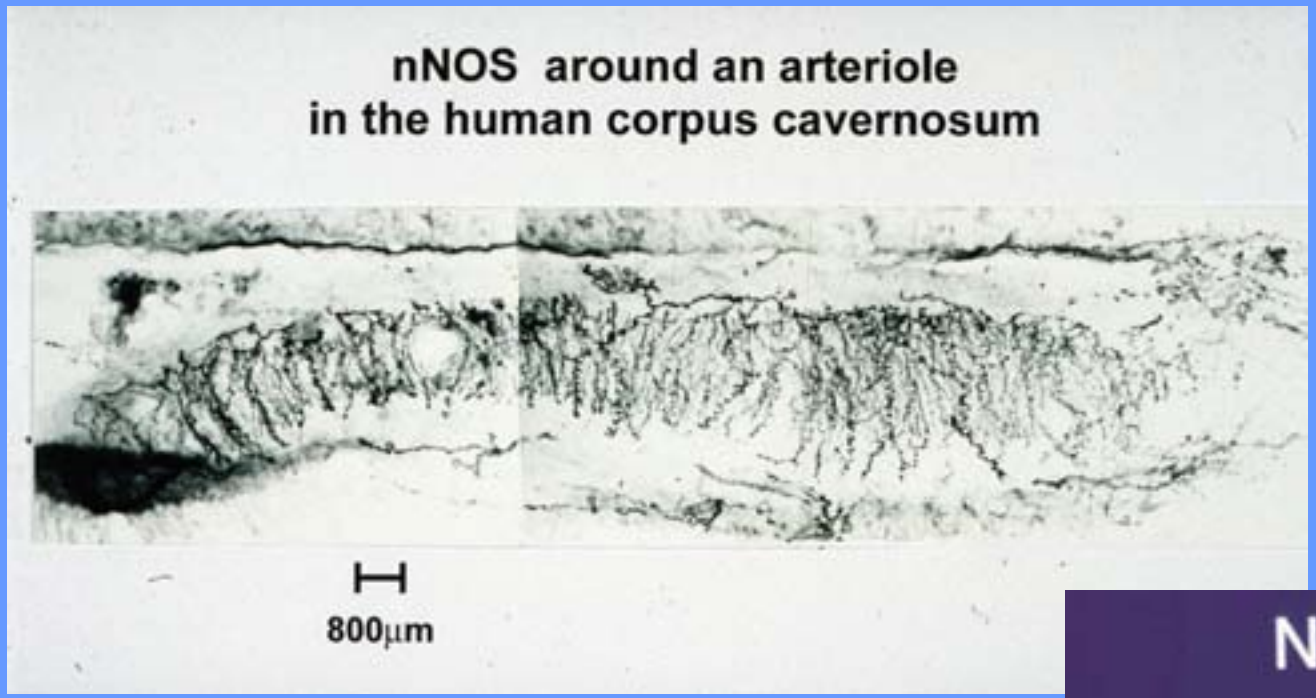


Biology of the L-arginine: NO pathway

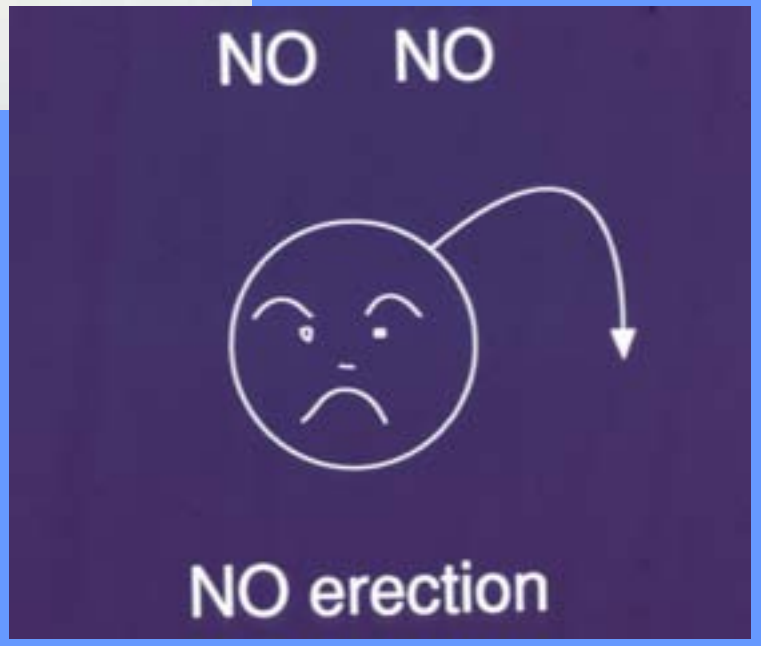


Publications with „nitric oxide“in the title

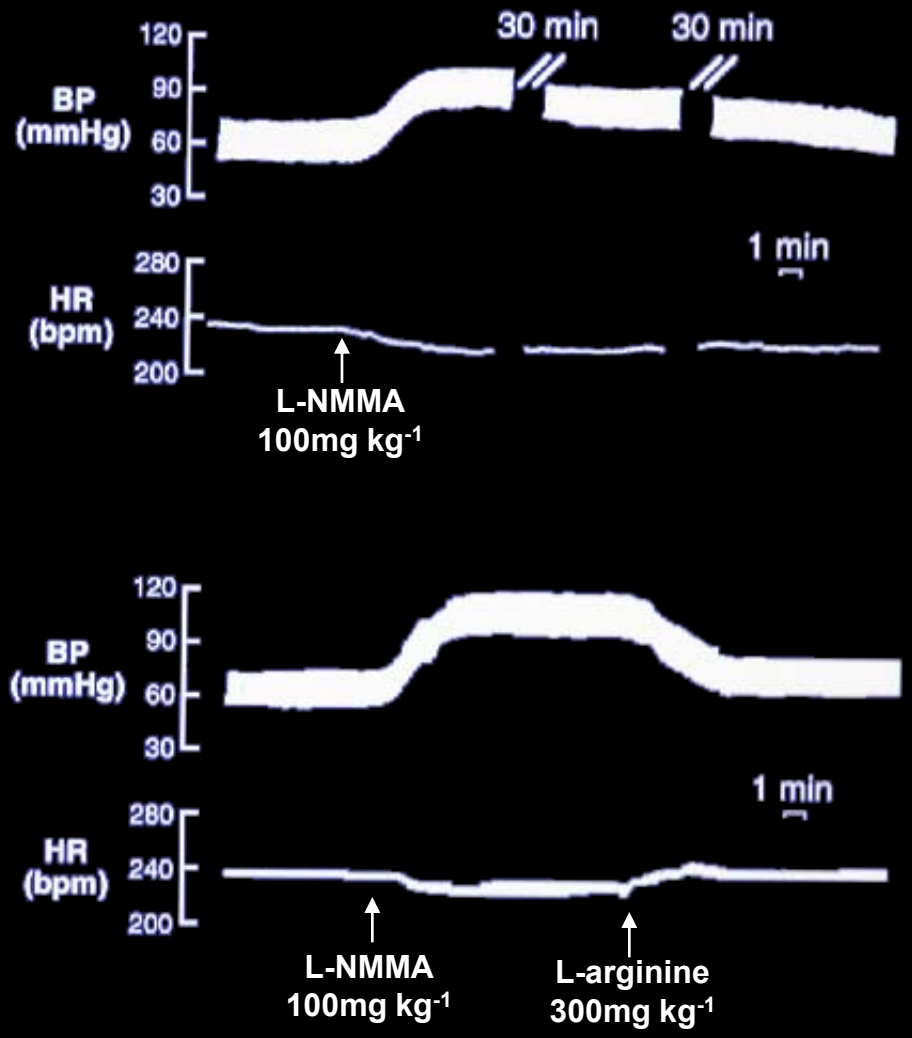




The action of nitric oxide
In the corpus cavernosum



Effect of L-NMMA (100mg kg^{-1}) on blood pressure and heart rate



Rees *et al,* (1989) Proc. Natl. Acad. Sci. USA 86: 3375 - 3378

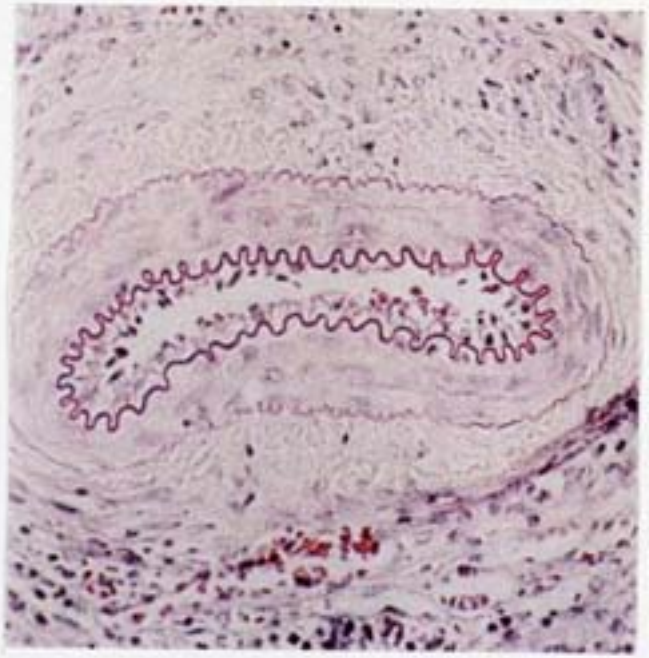
The cardiovascular system is in a state of active vasodilatation

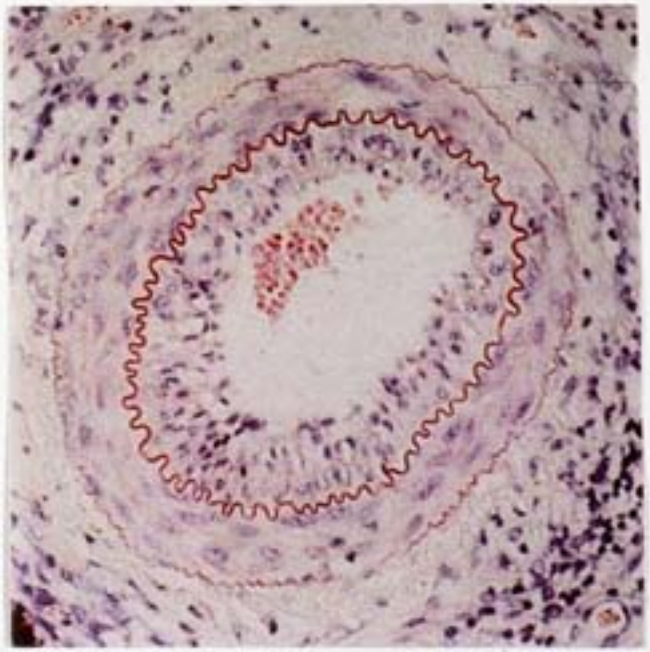
Nitric oxide inhibits

- Platelet aggregation
- Smooth muscle cell proliferation

Lack of vascular nitric oxide contributes to hypertension, vasospasm and atherosclerosis

Response of wild-type (L) and eNOS mutant (R) mice to cuff injury





Endothelial dysfunction :

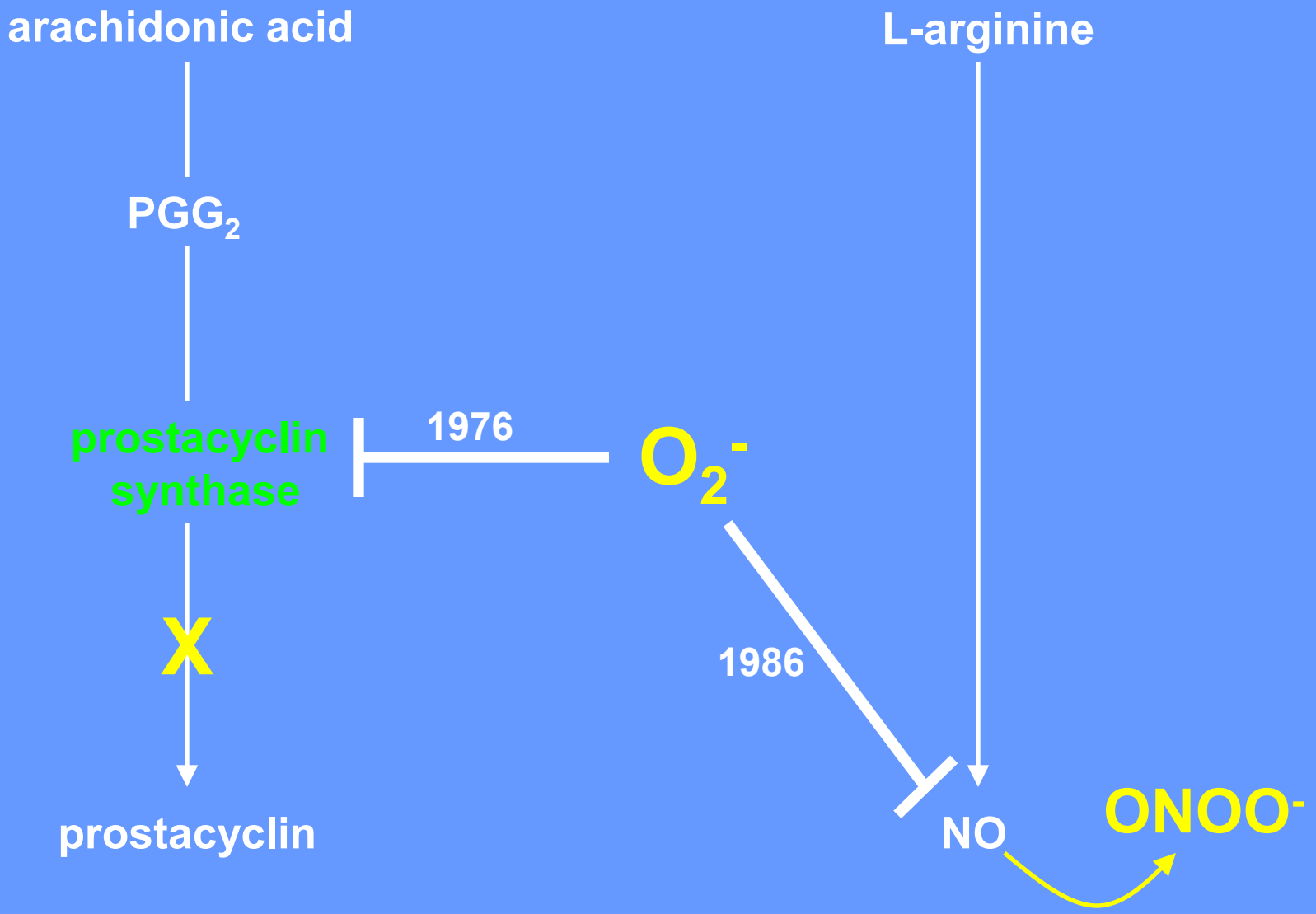
predicts disease in patients with a family history of essential hypertension or risk factors for atherosclerosis

Taddei *et al* (1996) Circulation 94: 1298 - 1303

Reddy *et al* (1994) J. Am. Coll. Cardiol. 23: 833 - 843

Oxidative stress: a most significant factor in cardiovascular disease

Oxidative stress, prostacyclin and NO



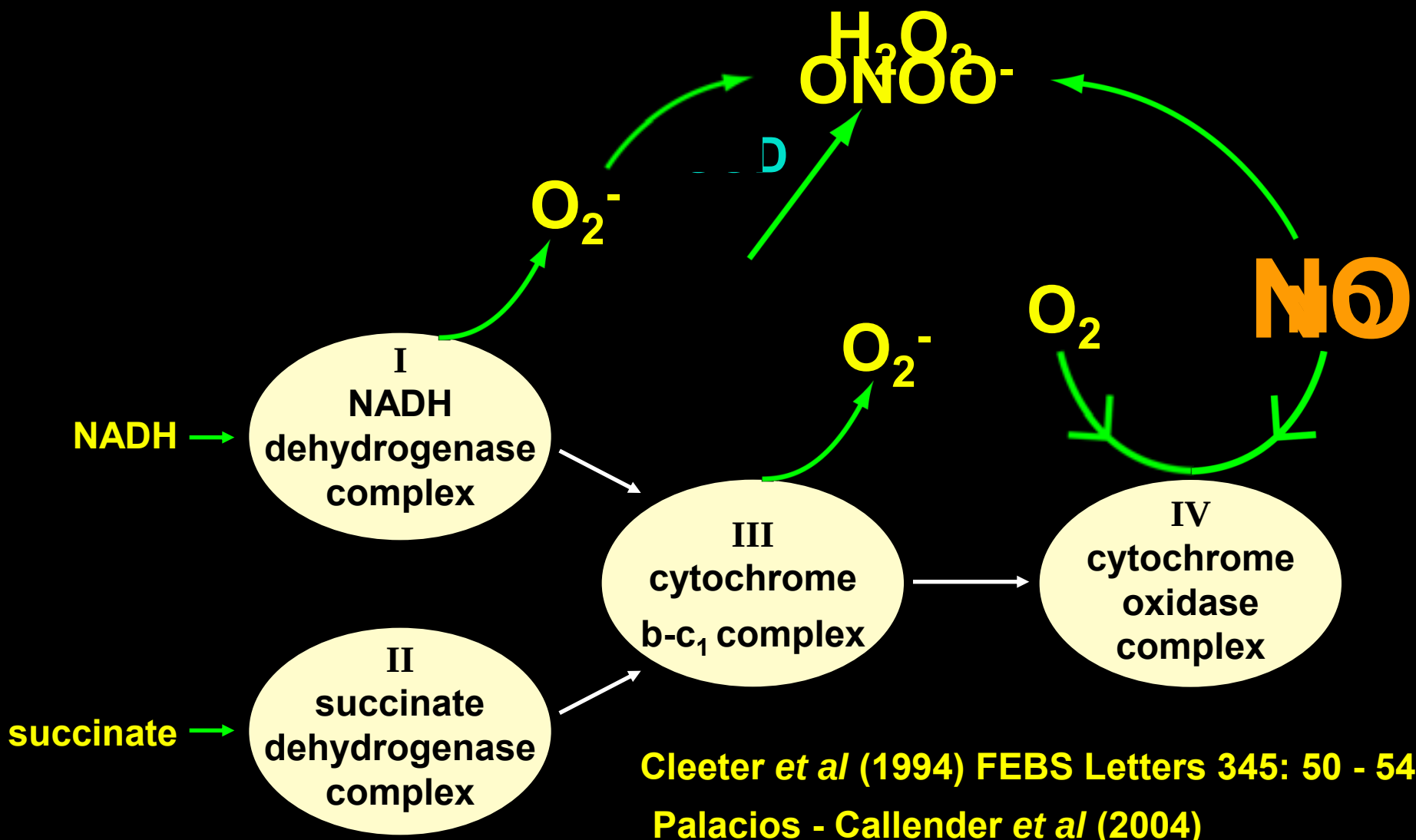
Conditions in which $ONOO^-$ has been implicated

- atherosclerosis
- hyperlipidaemia
- hypertension
- myocarditis
- chronic renal failure
- septic shock
- diabetes
- angiotensin II-mediated vascular disorders
- cigarette smoking

Where do the reactive oxygen species come from?

- NADPH oxidases
- xanthine oxidase
- uncoupled endothelial NO synthase
- mitochondrial electron transport

Nitric oxide and ROS in the respiratory chain
Formation of peroxynitrite



Cleeter *et al* (1994) FEBS Letters 345: 50 - 54

Palacios - Callender *et al* (2004)
Proc. Natl. Acad. Sci. USA 101: 7630-7635