Precious Knowledge: The Linear Concentration-Response Non-Threshold Model as the Golden Ratio

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Annual Conference: Dose Response 2013
Amherst, Massachusetts

Jaap,

this is an interesting title, but didn’t we already attend this conference last year?

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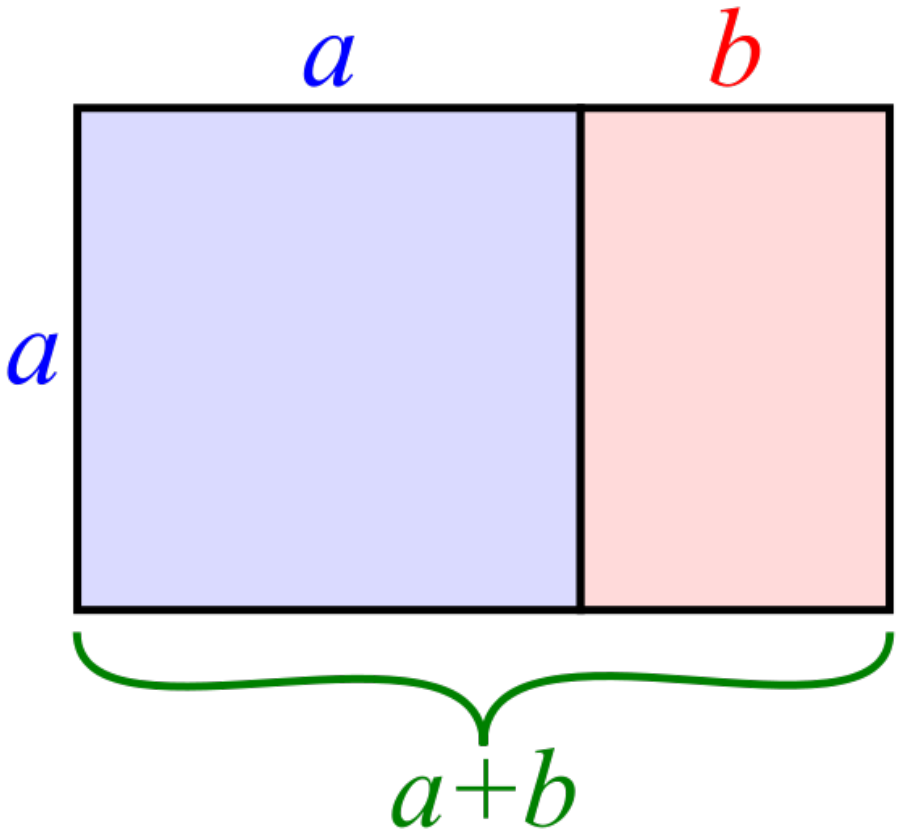
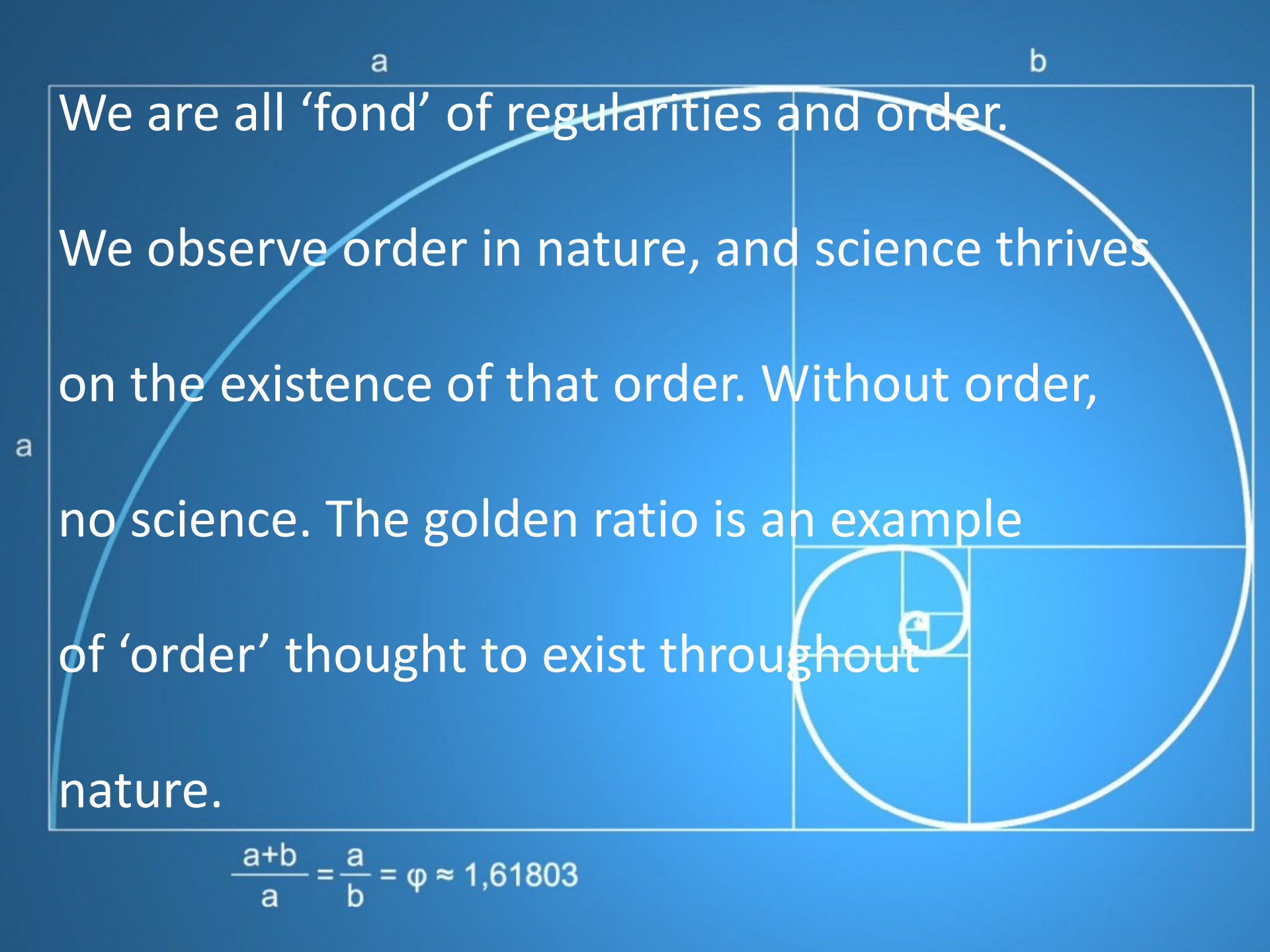


The **golden ratio** is associated with the **Fibonacci sequence** (0, 1, 1, 2, 3, 5, 8, 13, 21, 34, 55, etc.) wherein any number in the sequence (larger than 3) divided by its predecessor has an approximate value of 1.618. Moreover, each number in the sequence represents the sum of the two numbers that come before it.

$$(a+b)/a = a/b = \text{phi} = 1.618$$

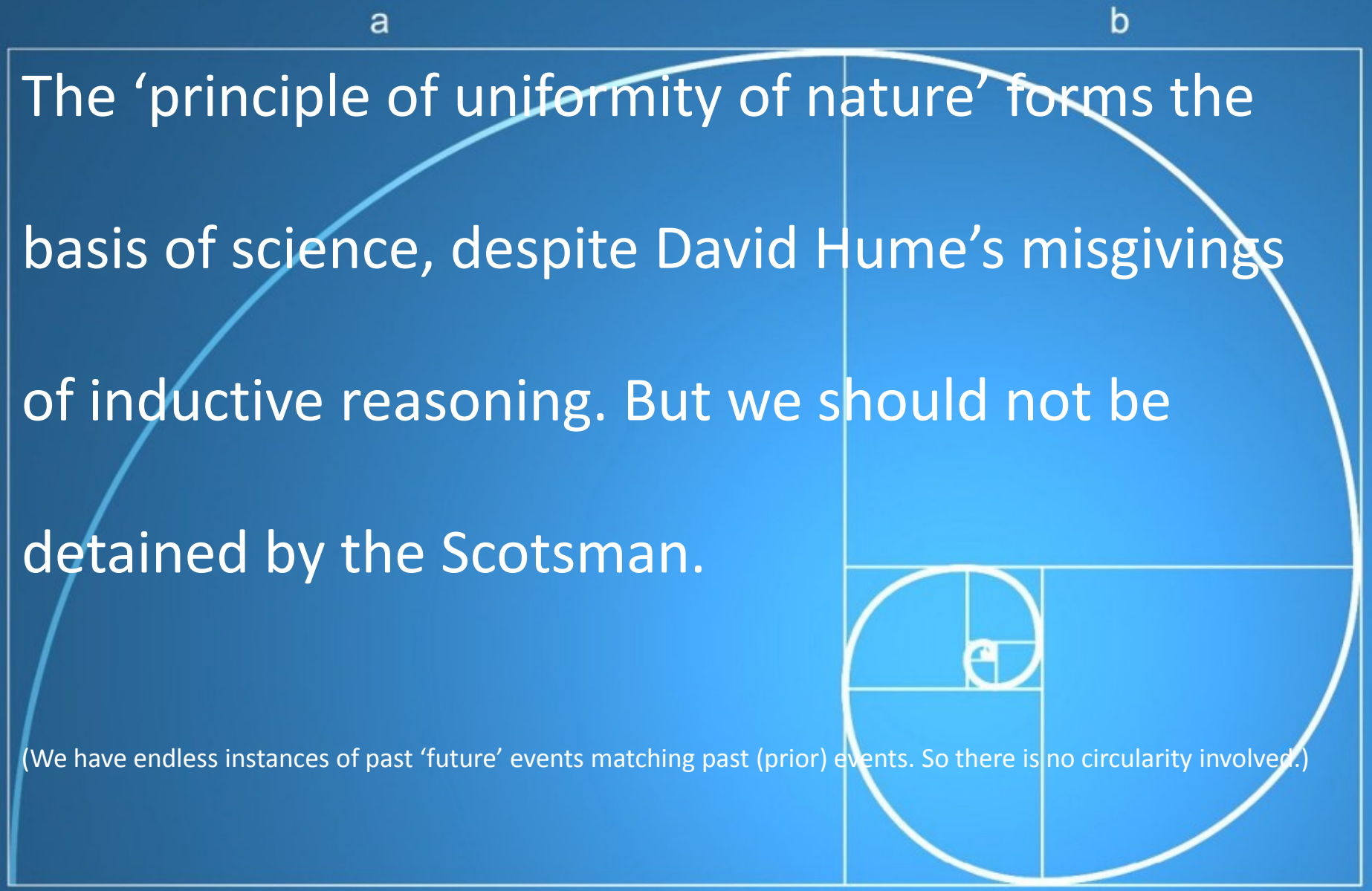
Leonardo Pisano Bigollo – Fibonacci
(c. 1170 – c. 1250)



We are all ‘fond’ of regularities and order.

We observe order in nature, and science thrives on the existence of that order. Without order, no science. The golden ratio is an example of ‘order’ thought to exist throughout nature.

$$\frac{a+b}{a} = \frac{a}{b} = \varphi \approx 1{,}61803$$



The ‘principle of uniformity of nature’ forms the basis of science, despite David Hume’s misgivings of inductive reasoning. But we should not be detained by the Scotsman.

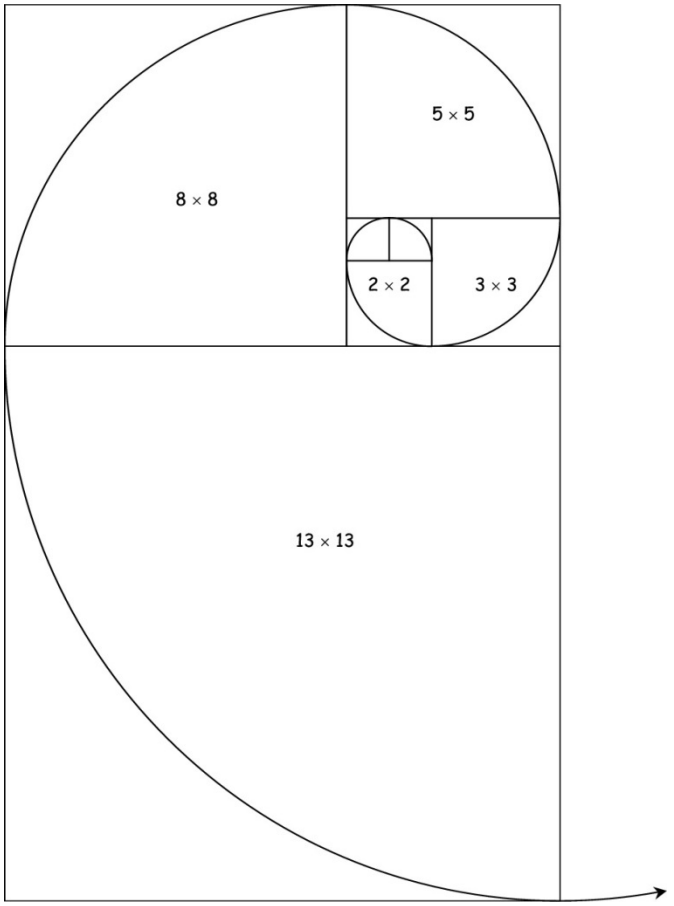
(We have endless instances of past ‘future’ events matching past (prior) events. So there is no circularity involved.)

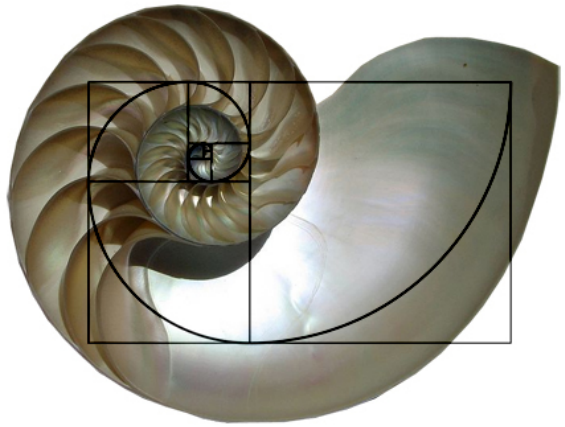
$$\frac{a+b}{a} = \frac{a}{b} = \varphi \approx 1{,}61803$$

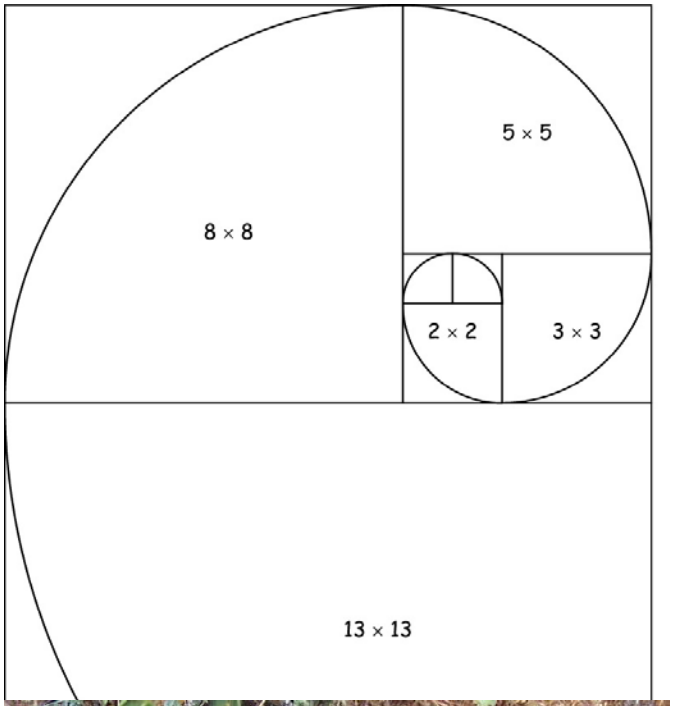
Aalt,

Is the Golden Ratio truly a property of nature?

The Fibonacci sequence can be used to graph an infinite logarithmic spiral based on units equated to each number in the sequence.



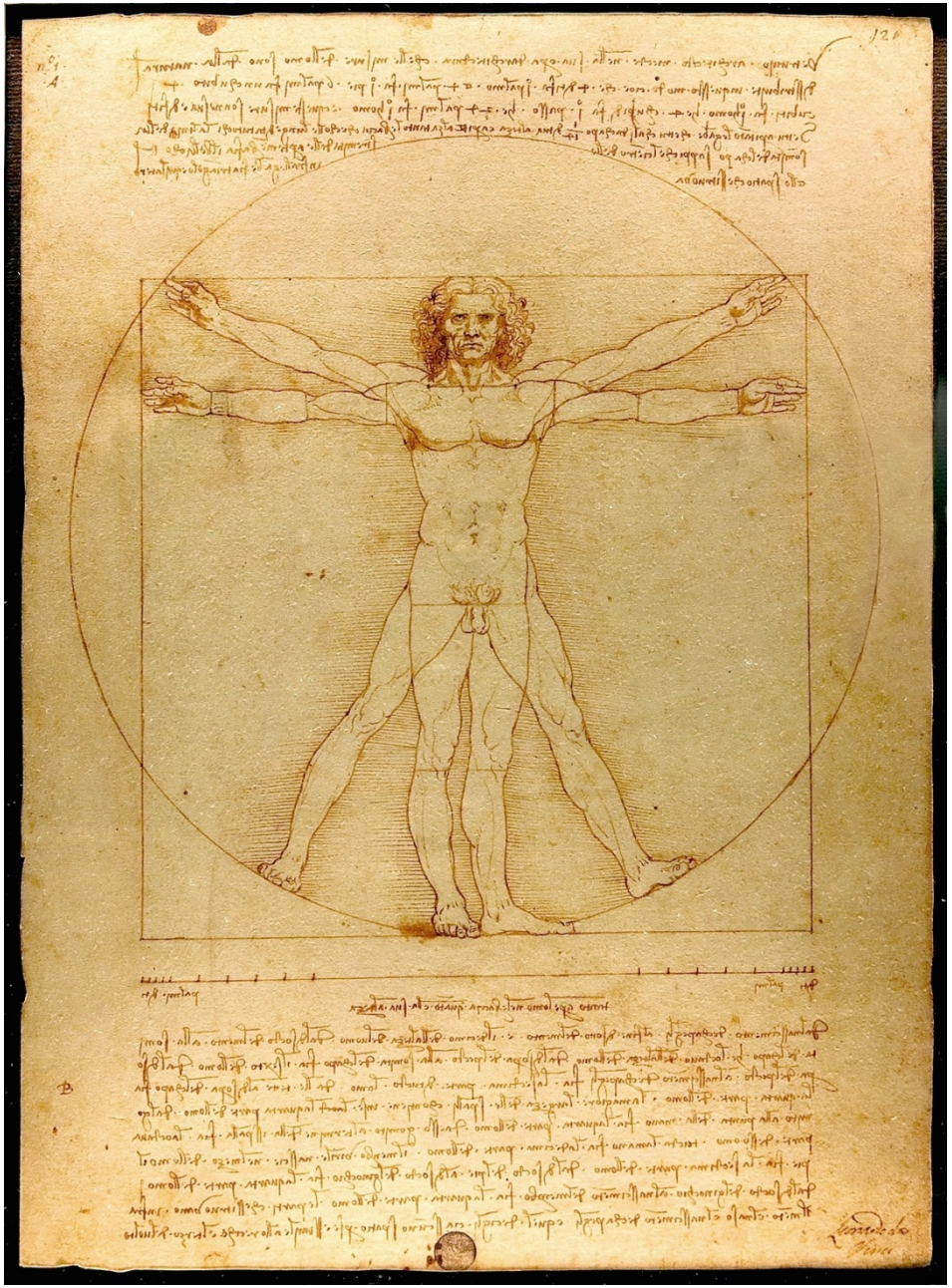




Similarly, sunflowers have a Golden Spiral seed arrangement. This provides a biological advantage because it maximizes the number of seeds that can be packed into a seed head.

Jaap,

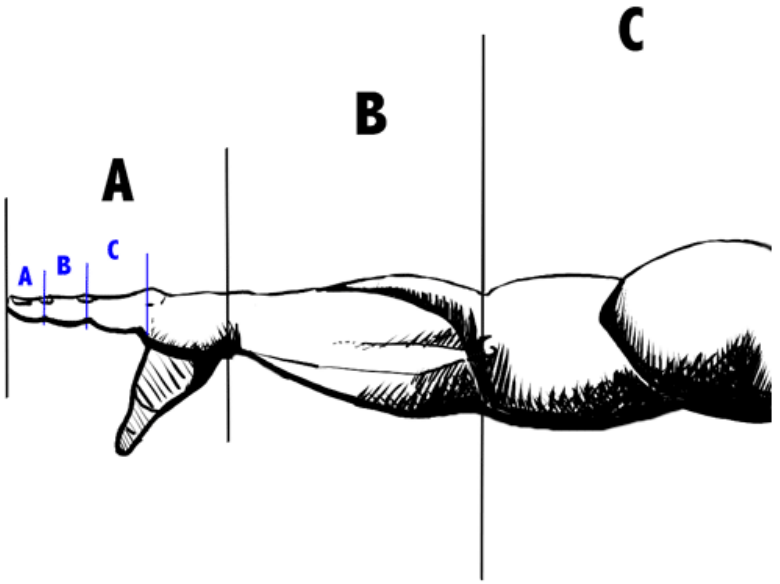
Is the Golden Ratio also found in humans?
That would be a surprising notion, is it not?



Vitruvian Man by Leonardo da Vinci

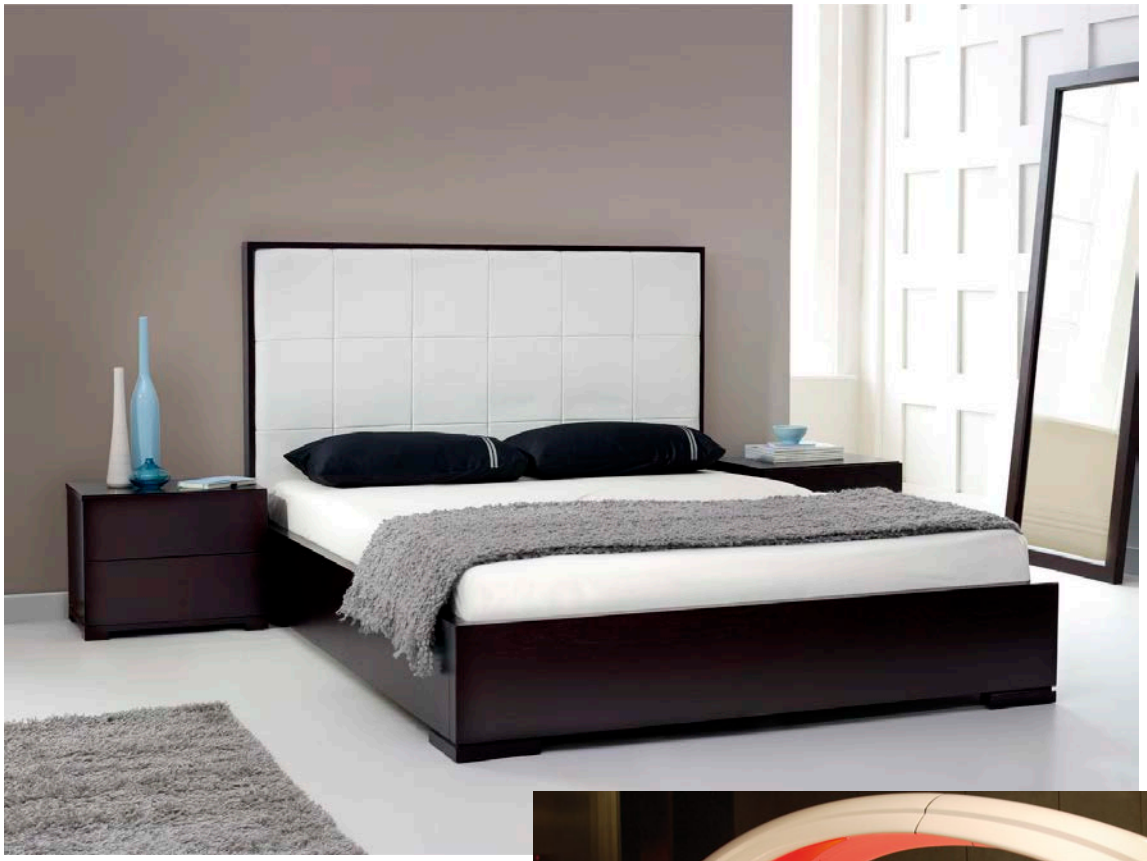
It is widely believed that Leonardo Da Vinci's *Vitruvian Man* was proportioned according to the golden ratio. E.g.: the height from toes to navel and from the navel to the top of the head is in golden ratio.

The Golden Ratio is seen in the proportions in the sections of a human arm:



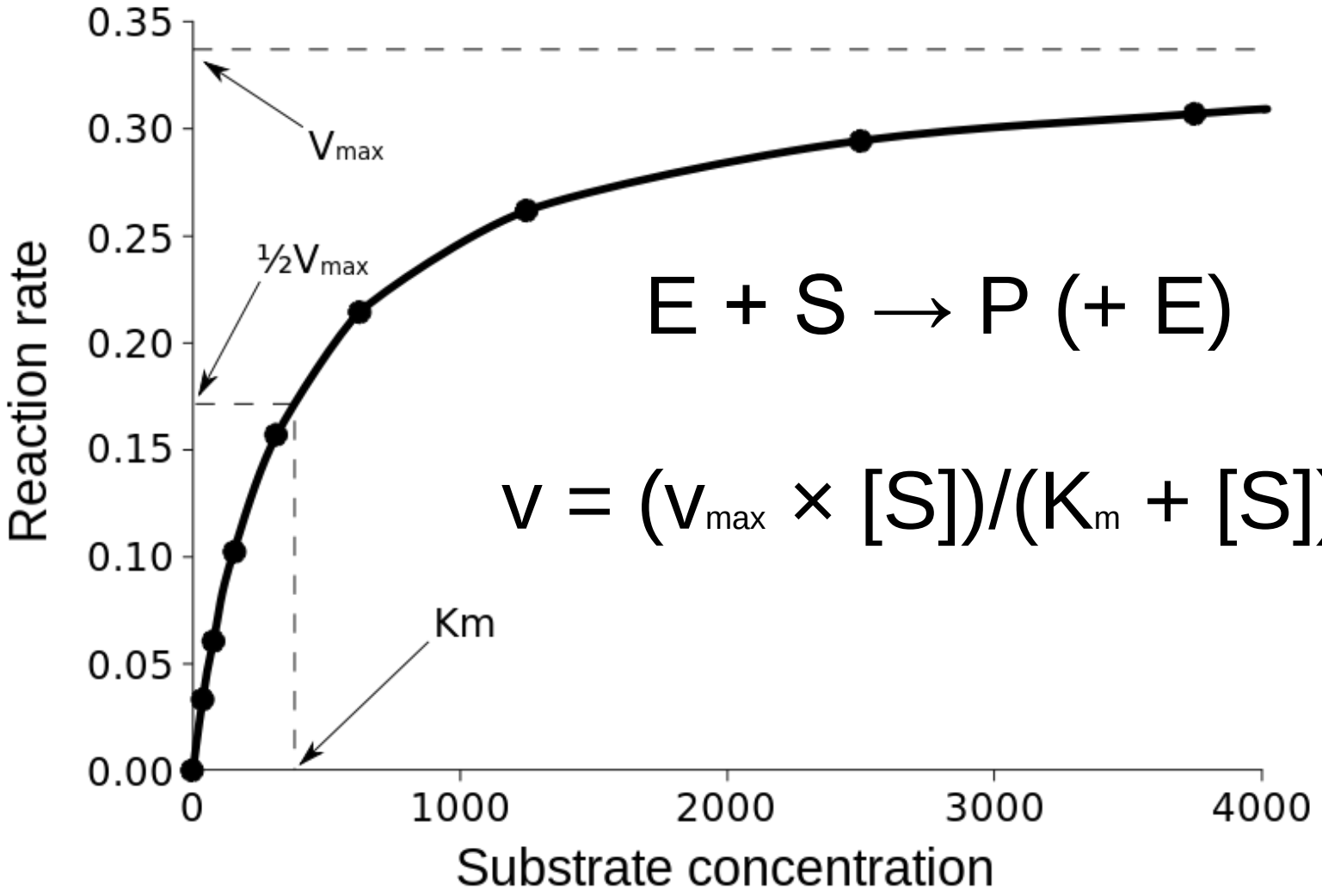
But Aalt,

How is all this related to our topic?
This all seems very esoteric and out place in a scientific conference, does it not?



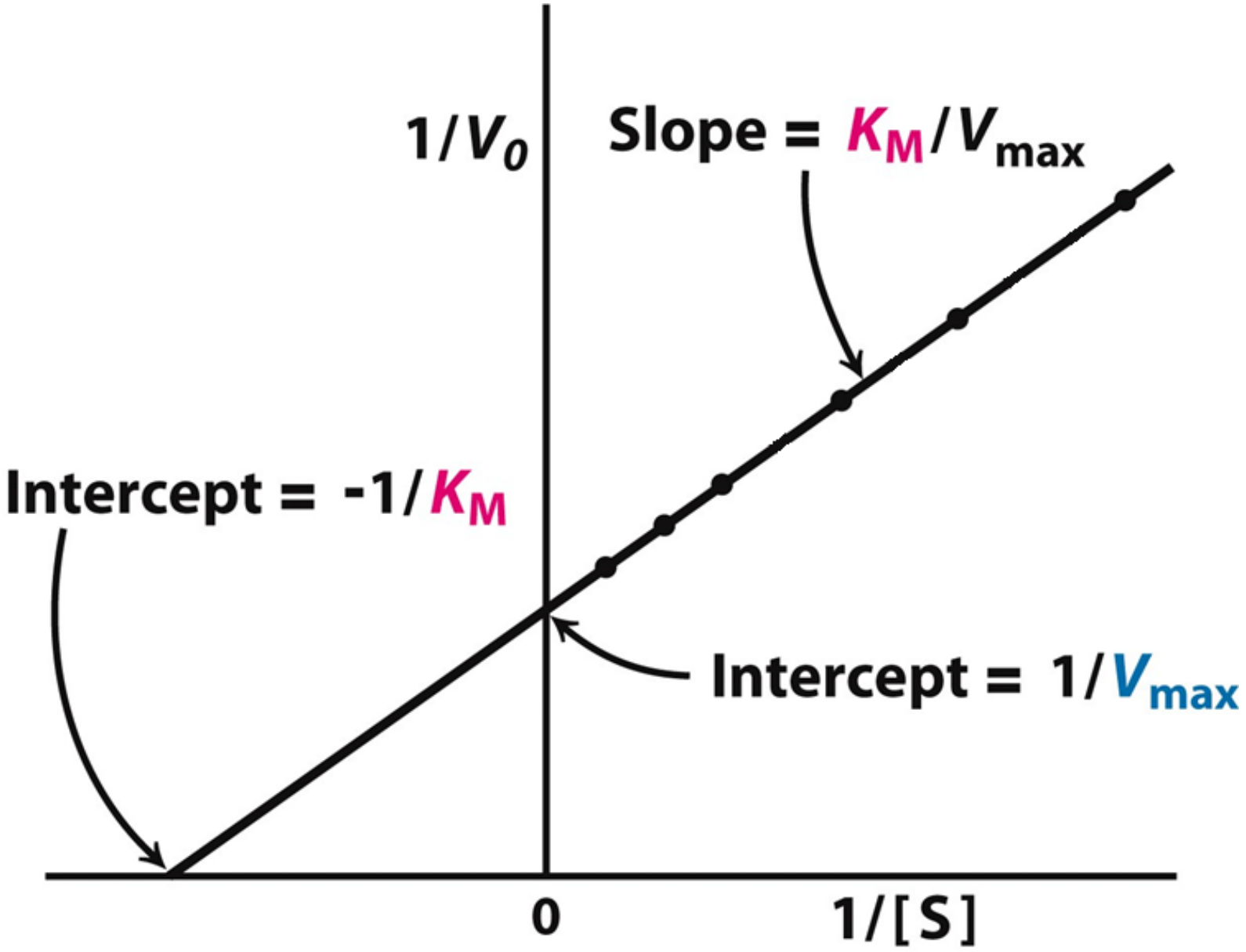
Straight lines and curves

Enzyme kinetics



$$E + S \rightarrow P\ (+ E)$$

$$v = (v_{max} \times [S])/(K_m + [S])$$



Lineweaver-Burk plot

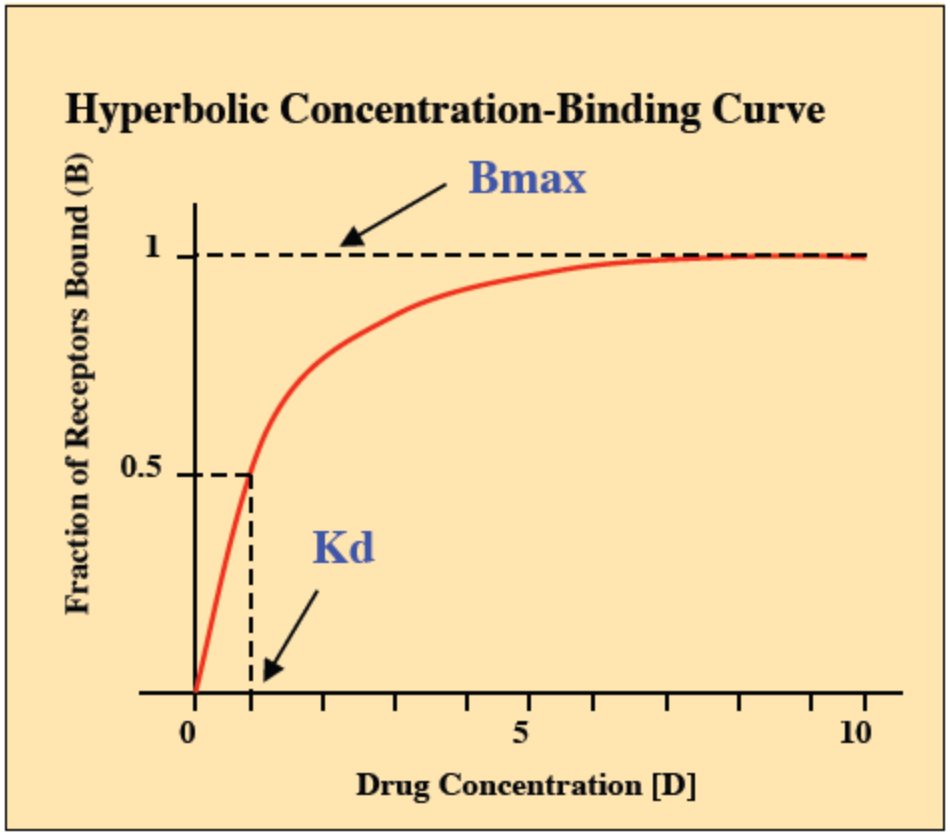
Jaap,

Do you see my point?

Aalt,

Yes I do. Biochemistry works this way. But, do we have the same approach in pharmacology?

Relationship of Drug Concentration and Receptor Binding



$$B = \frac{B\max \times [D]}{[D] + Kd}$$

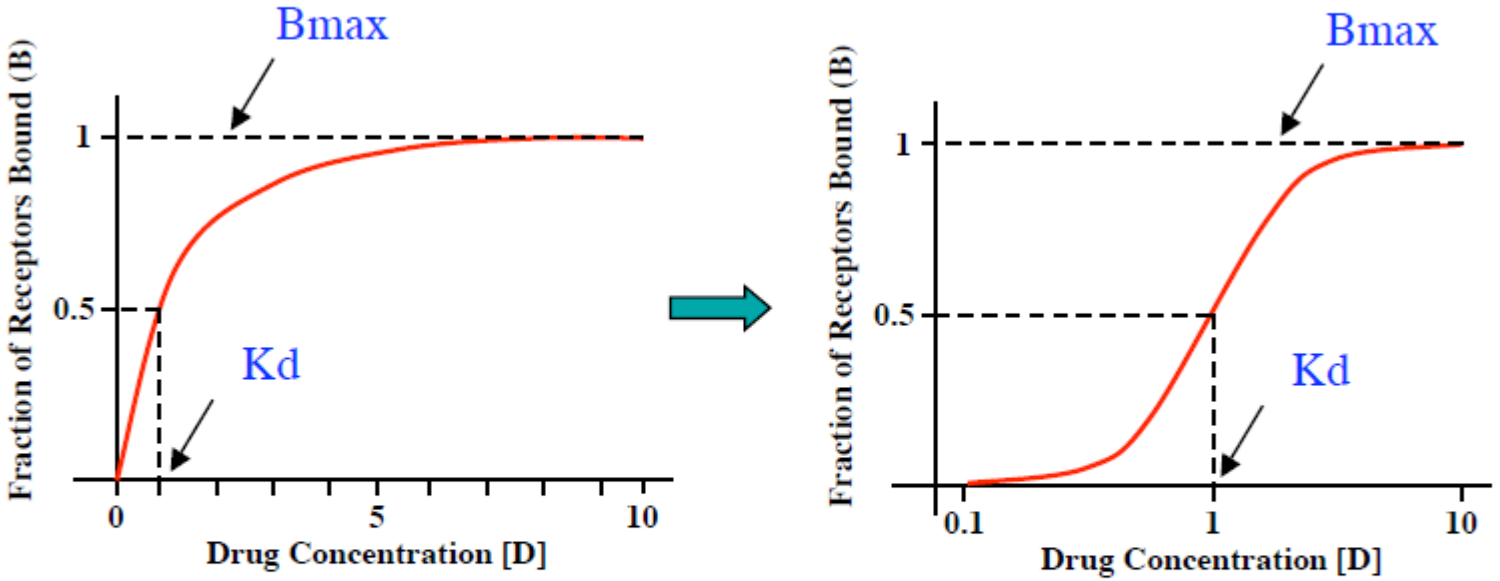
B -Fraction of available receptors bound

Bmax -Maximal binding of receptors (=1)

[D] -Concentration of drug

Kd -Equilibrium Dissociation Constant
-Drug concentration at which 1/2 of available receptors are bound
-Measure of affinity of drug/receptor interaction

Sigmoidal Receptor Binding Curves



-Semi-logarithmic transformation
-Common representation of pharmacological data
-Expands concentration scale at low concentration (where binding is changing rapidly)
-Compresses concentration scale at high concentrations (where binding is changing slowly)
-Does not change value of Bmax and Kd

Jaap,

Is this all clear to you?

Yes, Aalt. But I would actually underscore this by referring to recent developments in toxicology and pharmacology!!

Jaap,

Are you referring to your work on nitrate?

In 1945 the ‘blue baby syndrome’ is associated with the nitrate concentration in water.

Blue babies had stomach-intestinal infections

Well water mixed with baby food contained besides nitrate
also the E. coli

The EU Nitrate Directive: 50 mg/L

Nitrate itself isn't that toxic

- LD50 for small mammals is 2 – 10 g/kg

- Dosages between 5 and 8 g p.o. is without consequences in volunteers
- Even 7 g i.v. is without consequence

The ADI for nitrate is 3,65 mg/kg body weight/day

Oxidation of nitrite (NO_2^-) in the erythrocyte, gives nitrate (NO_3^-) and methemoglobine

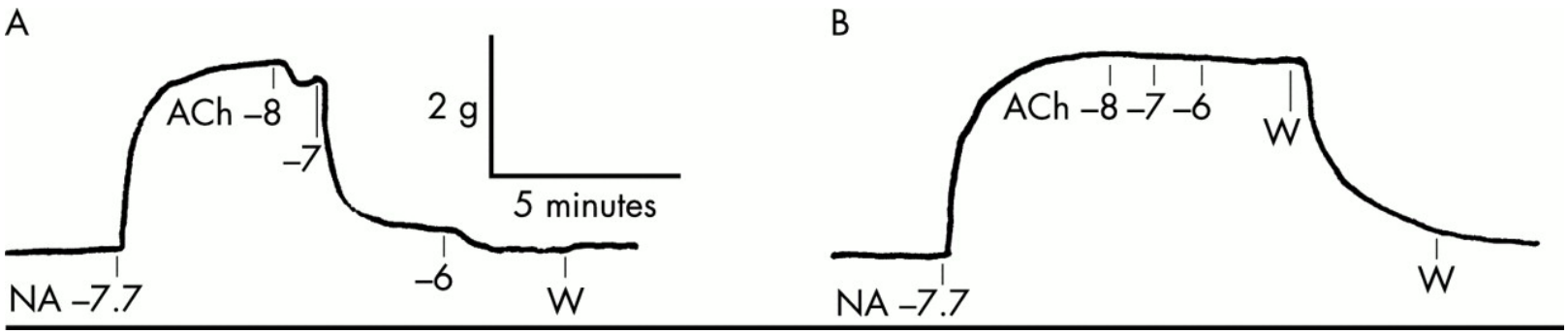
$$4NO_2^- + 4HbO_2 + 4H^+ \longrightarrow$$

$$4NO_3^- + 4\text{Met-Hb} + 2H_2O + O_2$$

Aalt,

But we use nitrates in medicine. So, although it might not be a real burden, how can it function as medicine?

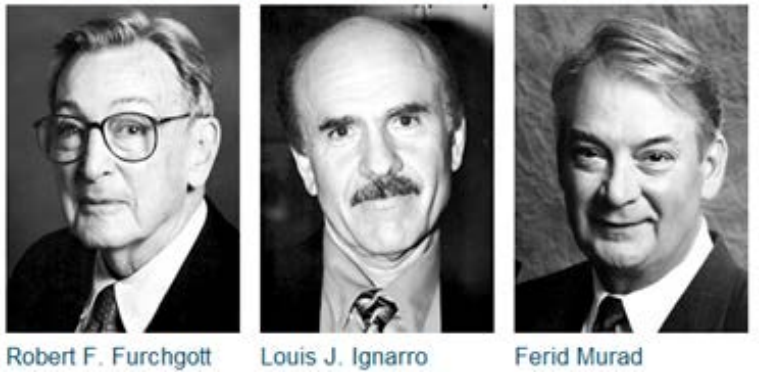
Acetylcholine mediated relaxation of rabbit aorta



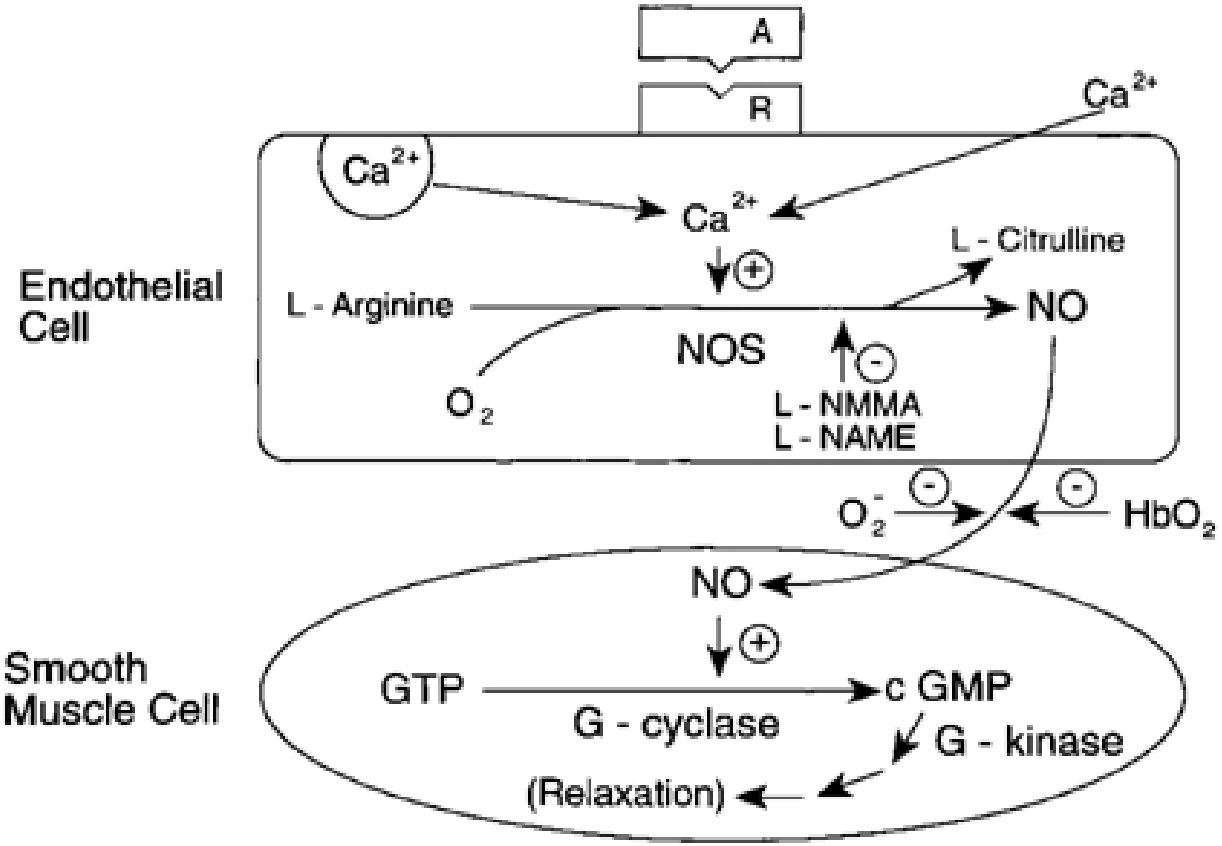
with endothelium

without endothelium

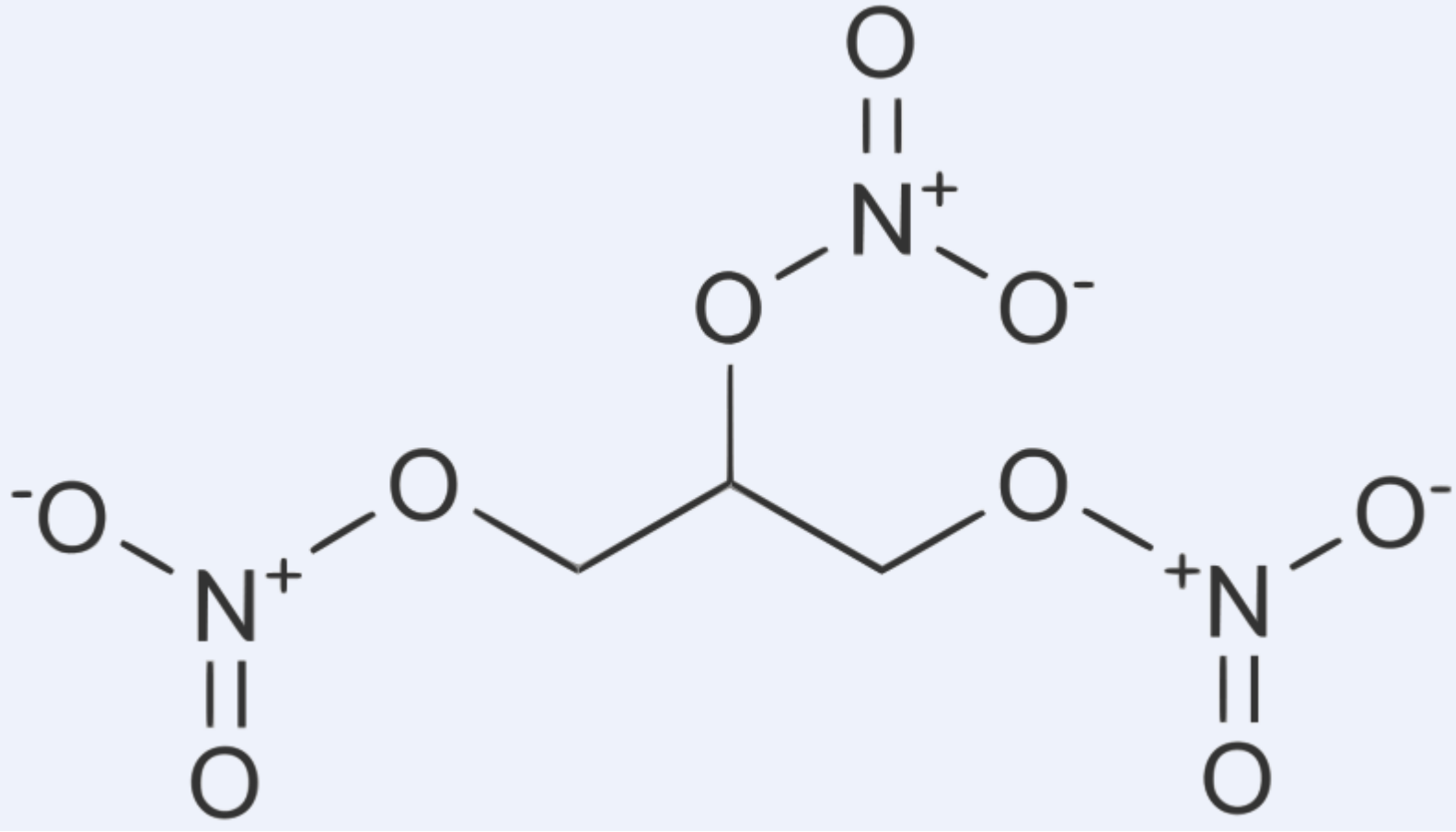
The Nobel Prize in Physiology or Medicine 1998
Robert F. Furchgott, Louis J. Ignarro, Ferid Murad

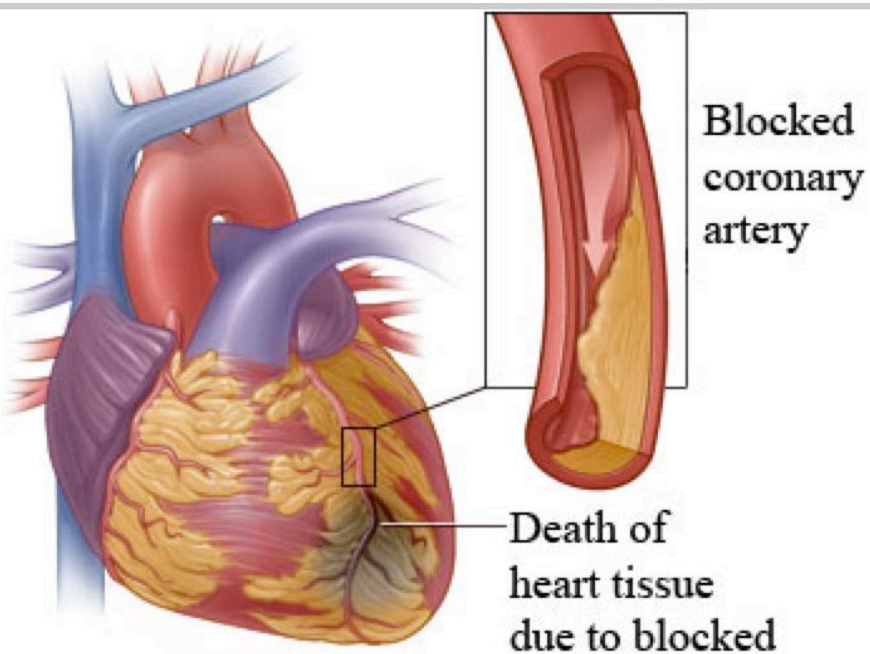


Endothelium dependent relaxation



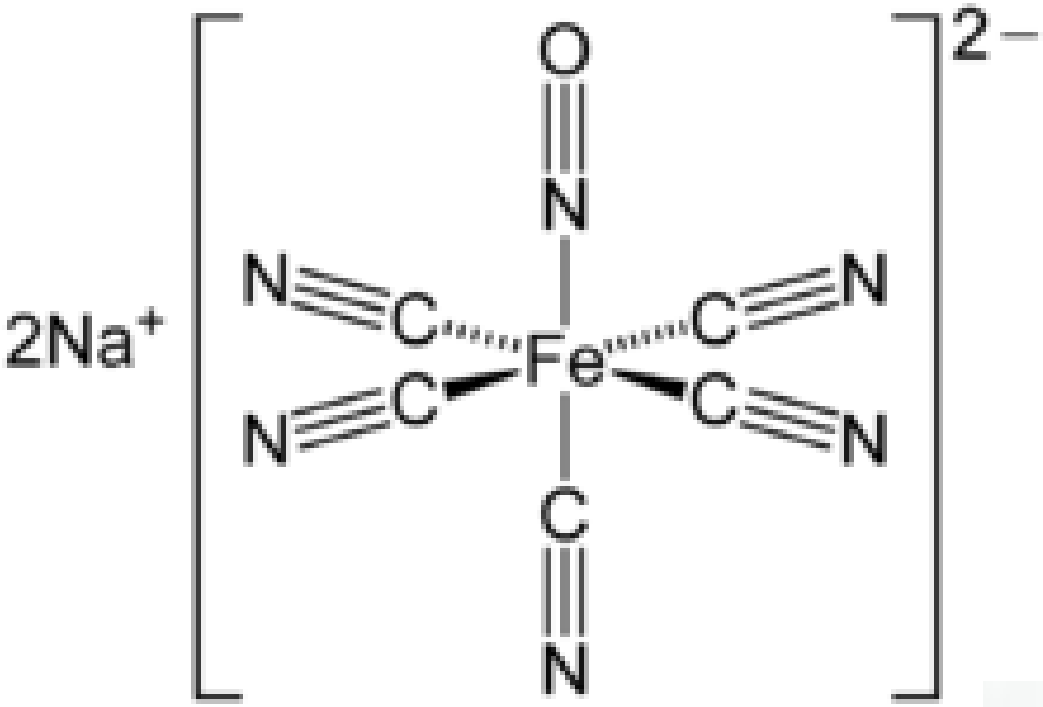
Nitroglycerine produces NO•





Nitroglycerine under the tongue

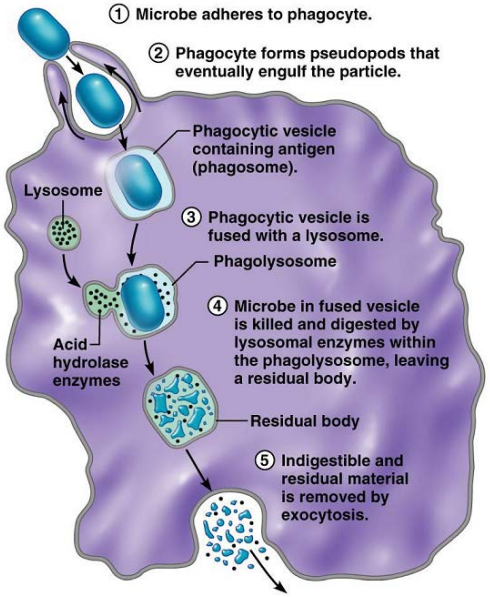
Sodium nitroprusside



Jaap,

Before we run off with the benefits of nitrate and its related compounds, what about the long-standing history of its risks?

Inflammatory cells produce NO and nitrite



NADPH oxidase

O_2

$O_2\bullet^-$ + NO• ⟶ $OONO^-$

arginine

NO synthase

NO• + O_2 ⟶ NO_2^-

+

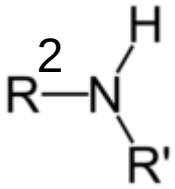
citrulline

Formation of nitrite by auto-oxidation of NO

$$4NO\bullet + O_2 + 2H_2O \longrightarrow 4NO_2^- + 4H^+$$

But Aalt,

My mother always warned me about nitrate in vegetables. So …?

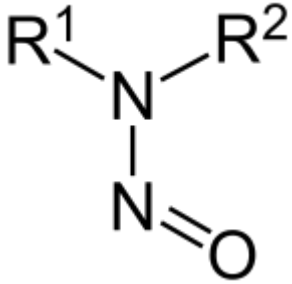


Secondary amines
(from proteins)

NO_2^-

nitrite

Especially in acid
environment



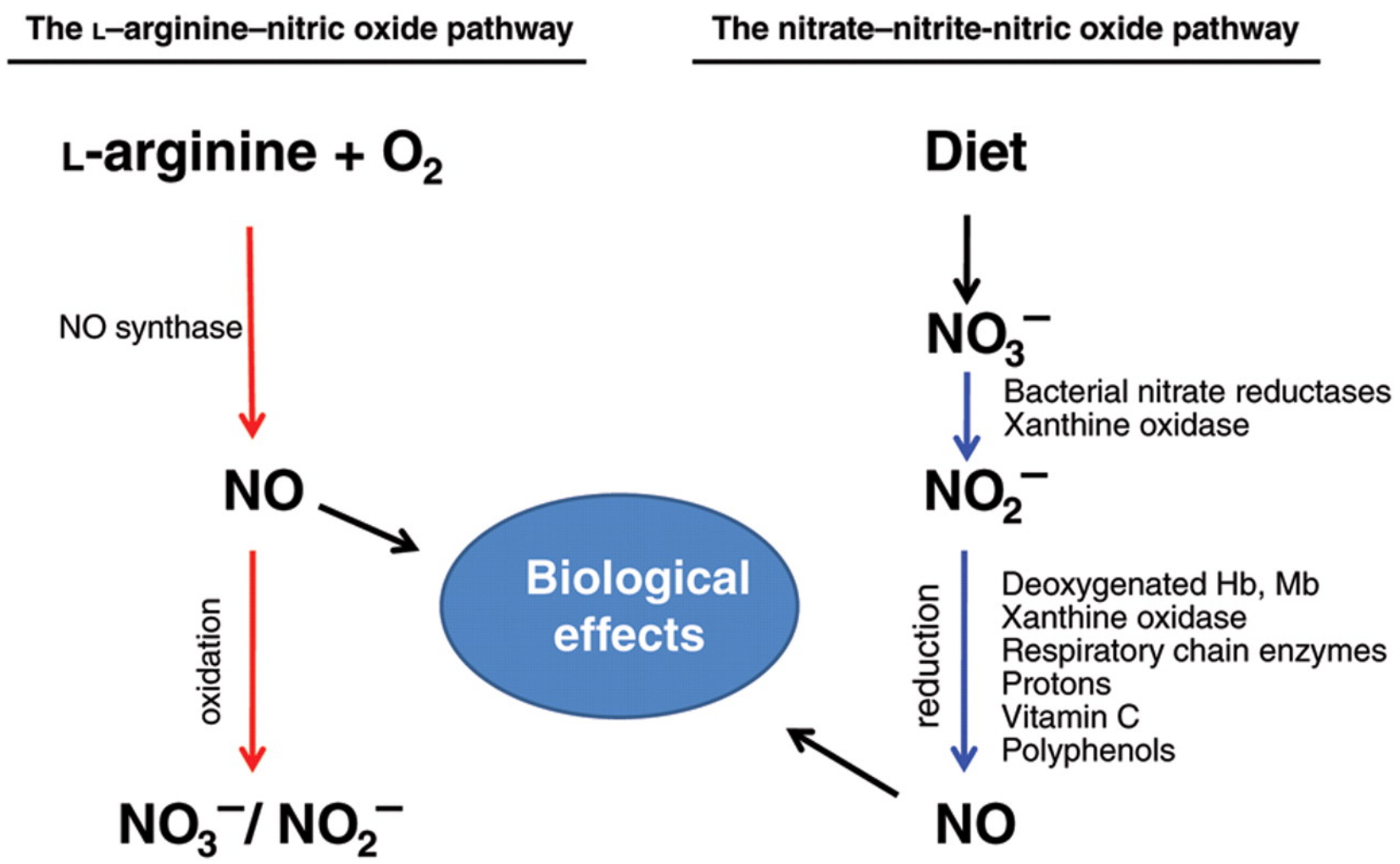
nitrosamines

(carcinogenic)

But Jaap,

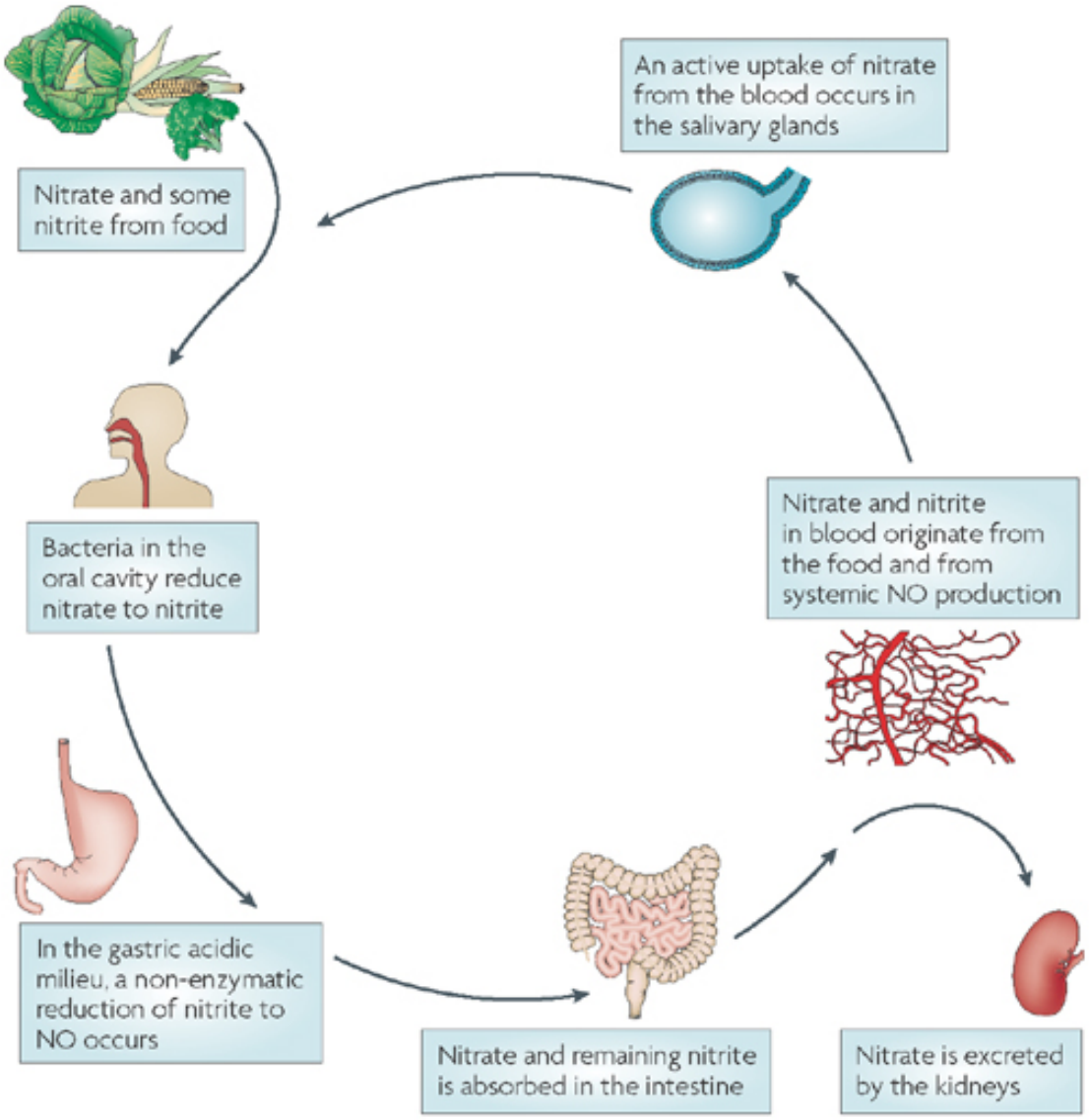
Couldn’t nitrate have, against all ‘common knowledge’, have benefits?

Two parallel pathways for NO formation in mammals



Lundberg J O et al. Cardiovasc Res 2011;89:525-532

Intestinal – saliva cycle of nitrate



Nitrate

↓

Nitrite

↓

NO

Effects of fruit and vegetable consumption on plasma antioxidant concentrations and blood pressure: a randomised controlled trial

The falls in blood pressure in our study (4·0 mm Hg systolic and 1·5 mm Hg diastolic) would be expected to produce small clinical effects, but would substantially reduce cardiovascular disease at the population level. A reduction of 2 mm Hg in diastolic blood pressure results in a decrease of about 17% in the incidence of hypertension, 6% in the risk of coronary heart disease, and 15% in the risk of stroke and transient ischaemic attack.[26]

Jaap, Jaap, Jaap

Could you show me the slide again?!

Effects of fruit and vegetable consumption on plasma antioxidant concentrations and blood pressure: a randomised controlled trial

The falls in blood pressure in our study (4·0 mm Hg systolic and 1·5 mm Hg diastolic) would be expected to produce small clinical effects, but would substantially reduce cardiovascular disease at the population level. A reduction of 2 mm Hg in diastolic blood pressure results in a decrease of about 17% in the incidence of hypertension, 6% in the risk of coronary heart disease, and 15% in the risk of stroke and transient ischaemic attack.[26]

Aahhh, I see what you mean. Nitrate is not just bad or good. It is both, underscoring non-linearity!!

Jaap,

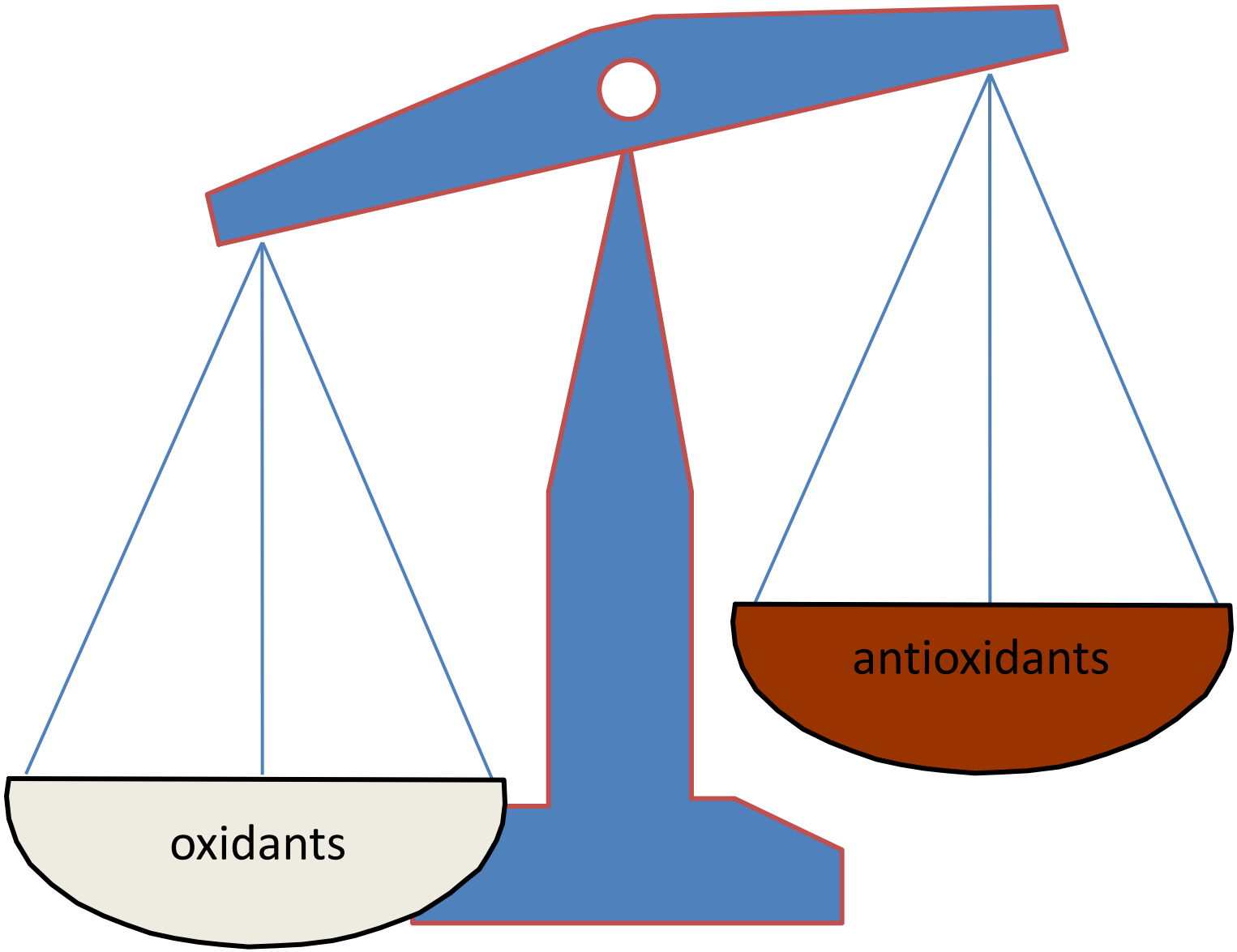
But wait, there is more!!! Show that slide again.

Effects of frult and vegetable consumptlon on plasma antloxldant concentratlons and blood pressure: a randomlsed controlled trlal

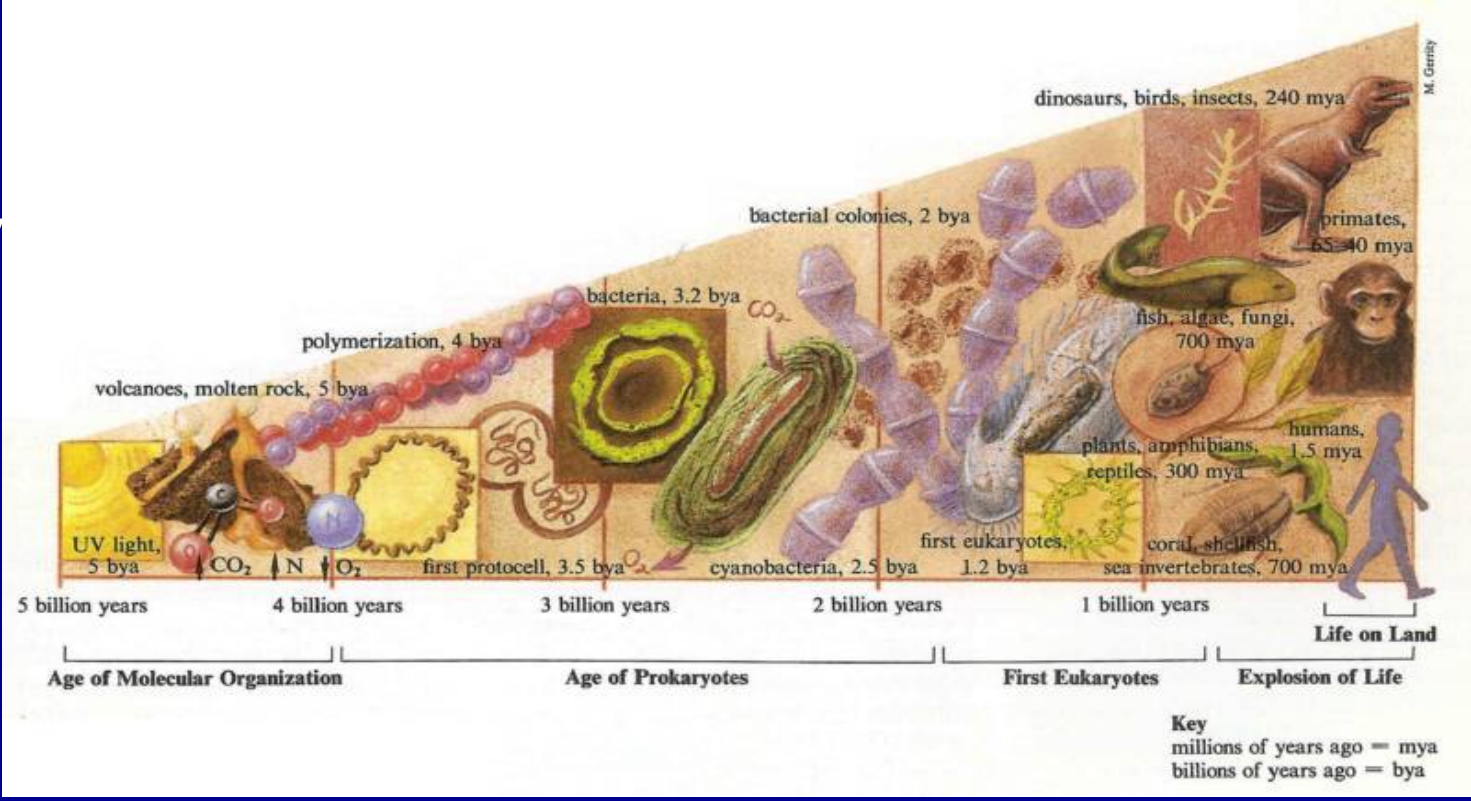
antioxidant

The falls in blood pressure in our study (4·6 mm Hg systolic and 1·5 mm Hg diastolic) would be expected to produce small clinical effects, but would substantially reduce cardiovascular disease at the population level. A reduction of 2 mm Hg in diastolic blood pressure results in a decrease of about 17% in the incidence of hypertension, 6% in the risk of coronary heart disease, and 15% in the risk of stroke and transient ischaemic attack.[26]

Oxidative stress



Evolutionary adaptation to oxygen



Million years ago	
3500	Intense solar radiation bombards the surface of the earth. Anaerobic life begins.
>2500	Blue green algae acquire the ability to split water and release oxygen.
1300	Oxygen levels in the atmosphere reach 1%. More complex cells with nuclei (eukaryotes) begin to evolve. Emergence of multicellular organisms.
500	Oxygen levels in the atmosphere reach 10%. Ozone layer screens out much UV light and facilitates emergence of life forms from the sea.
65	Primates appear.
5	Humans appear. Atmospheric oxygen levels reach 21%.

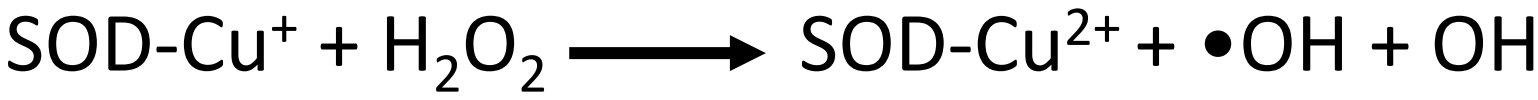
superoxide dismutase (SOD)

Mn SOD mitochondria
Cu/Zn SOD cytoplasma

$$SOD\text{-}Cu^{2+} + O_2^{\cdot -} \longrightarrow SOD\text{-}Cu^{+} + O_2$$

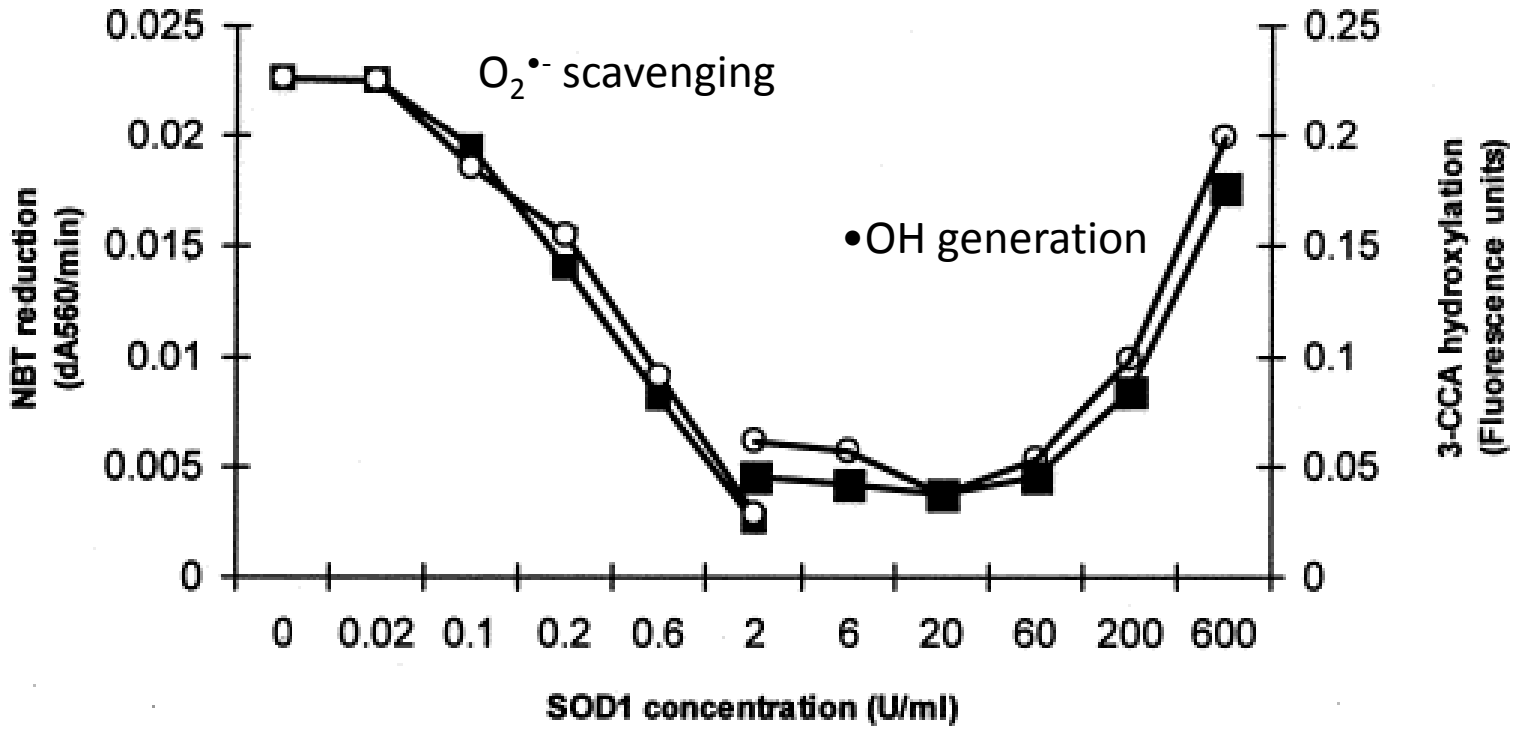
$$SOD\text{-}Cu^{+} + O_2^{\cdot -} + 2H^{+} \longrightarrow SOD\text{-}Cu^{2+} + H_2O_2$$

$$\text{Overall: } 2O_2^{\cdot -} + 2H^{+} \longrightarrow O_2 + H_2O_2$$



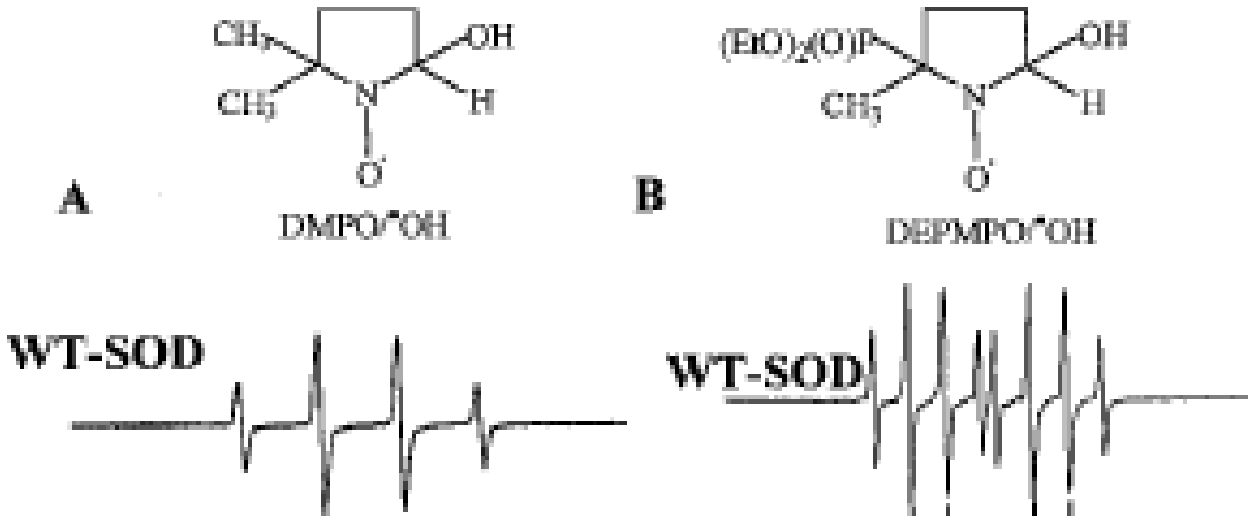
R.J. Singh et al., PNAS 95, 6675 (1998)

Superoxide scavenging and hydroxyl radical formation by SOD1 (closed squares) and PC-SOD (open circles)



G.J.M. Den Hartog et al., Chem. Biol. Interact. 2003

Formation of DMPO/•OH and DEPMPO/•OH adducts by SOD and H_2O_2



$SOD\text{-}Cu^{+} + H_2O_2 \longrightarrow SOD\text{-}Cu^{2+} + \bullet OH + OH^{-}$

R.J. Singh et al., PNAS 95, 6675 (1998)

Jaap,

Do you see my point? Adaptation to oxygen with enzymes enables us to develop and survive under toxic stress of oxygen.

However, and here again some form of non-linearity crops up, the adaptation itself carries the ambiguity of good and bad.

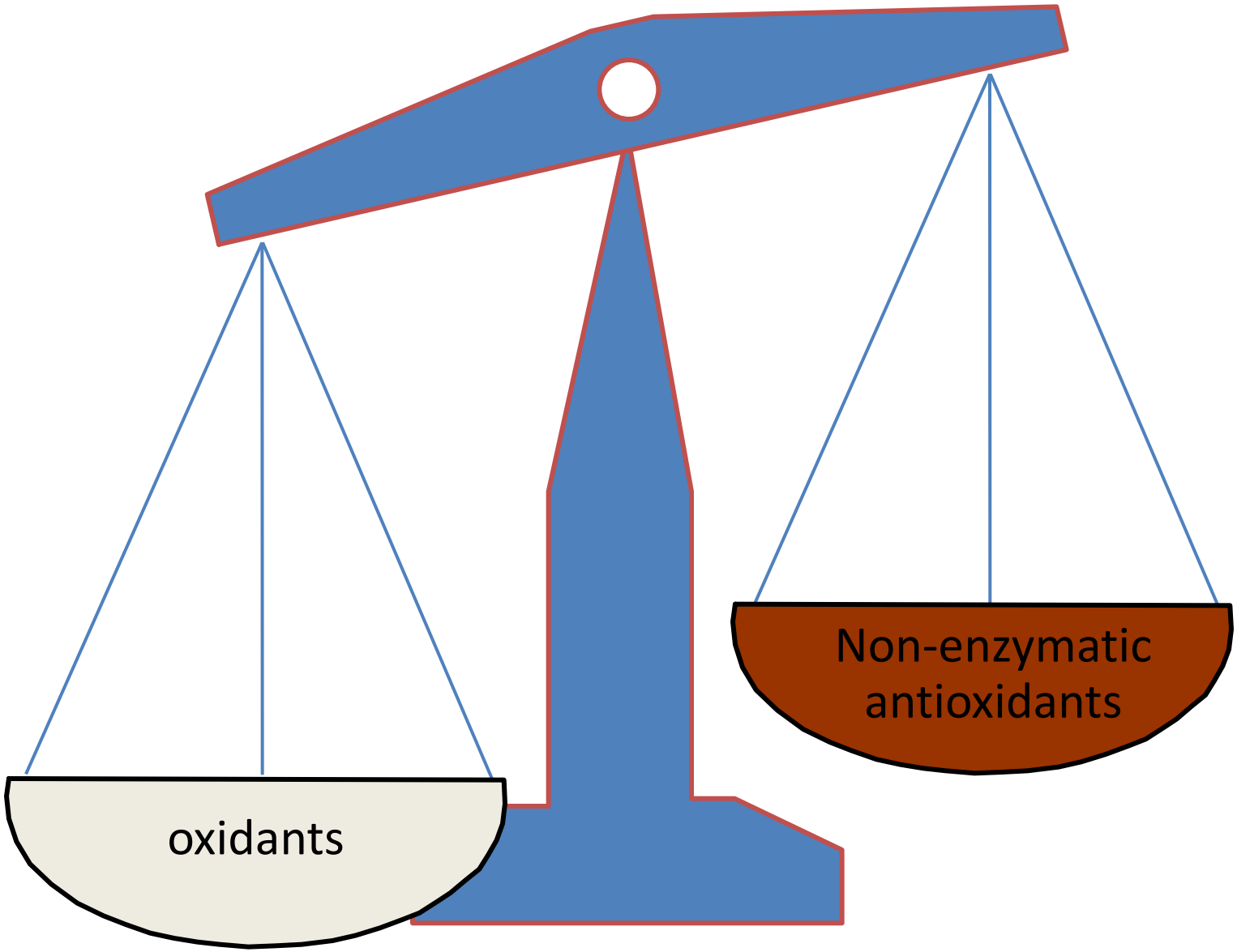
Aalt,

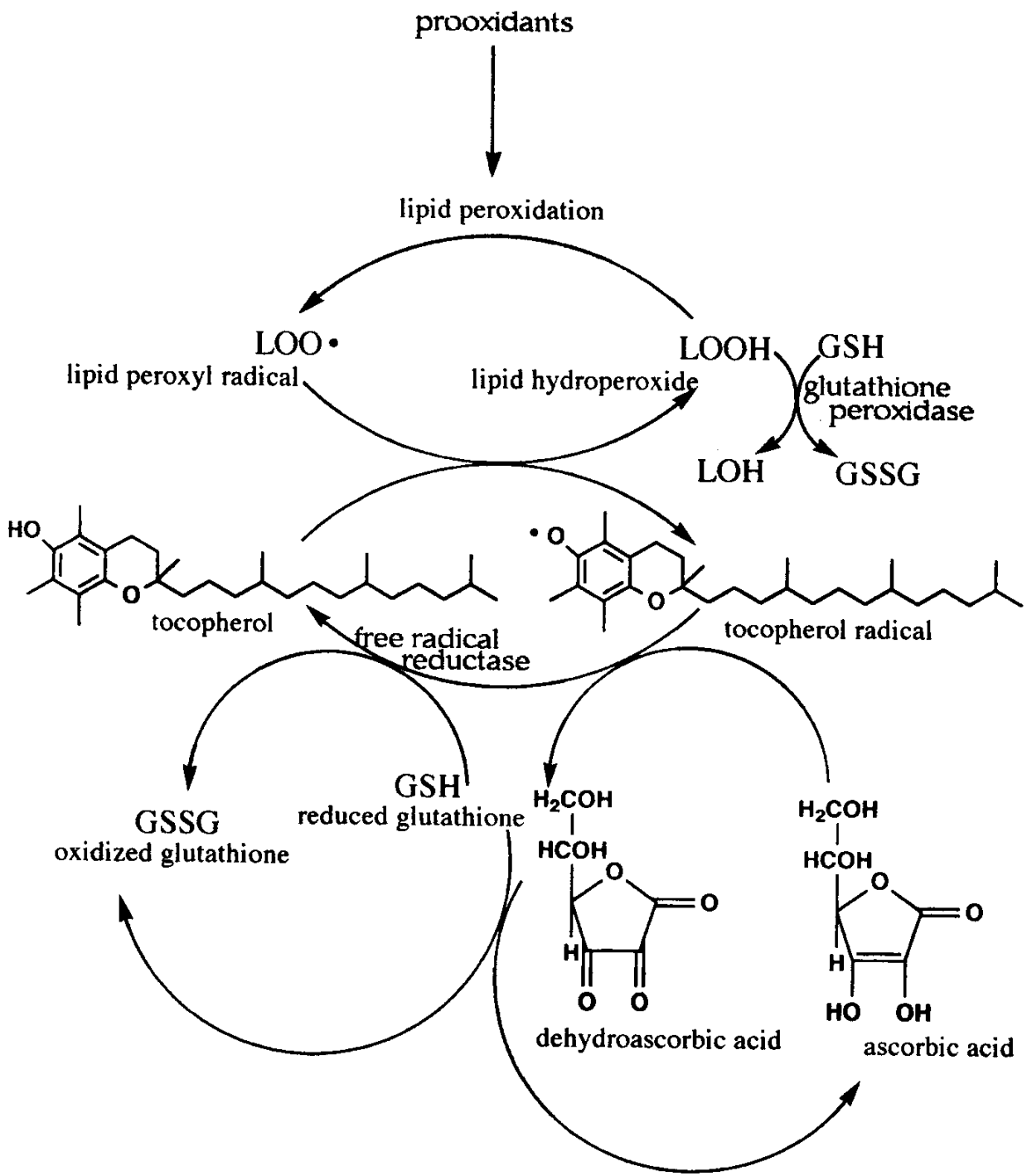
We were not discussing enzymatic antioxidants, is it not?

Jaap,

You’re absolutely right. Pray, continue.

Oxidative stress




prooxidants
lipid peroxidation
LOO•
lipid peroxyl radical
LOOH
lipid hydroperoxide
GSH
glutathione peroxidase
LOH
GSSG
HO
O
tocopherol
• O
O
tocopherol radical
free radical reductase
GSSG
oxidized glutathione
GSH
reduced glutathione
H2COH
HCOH
O
O
H
O O
dehydroascorbic acid
H2COH
HCOH
O
O
H
HO OH
ascorbic acid

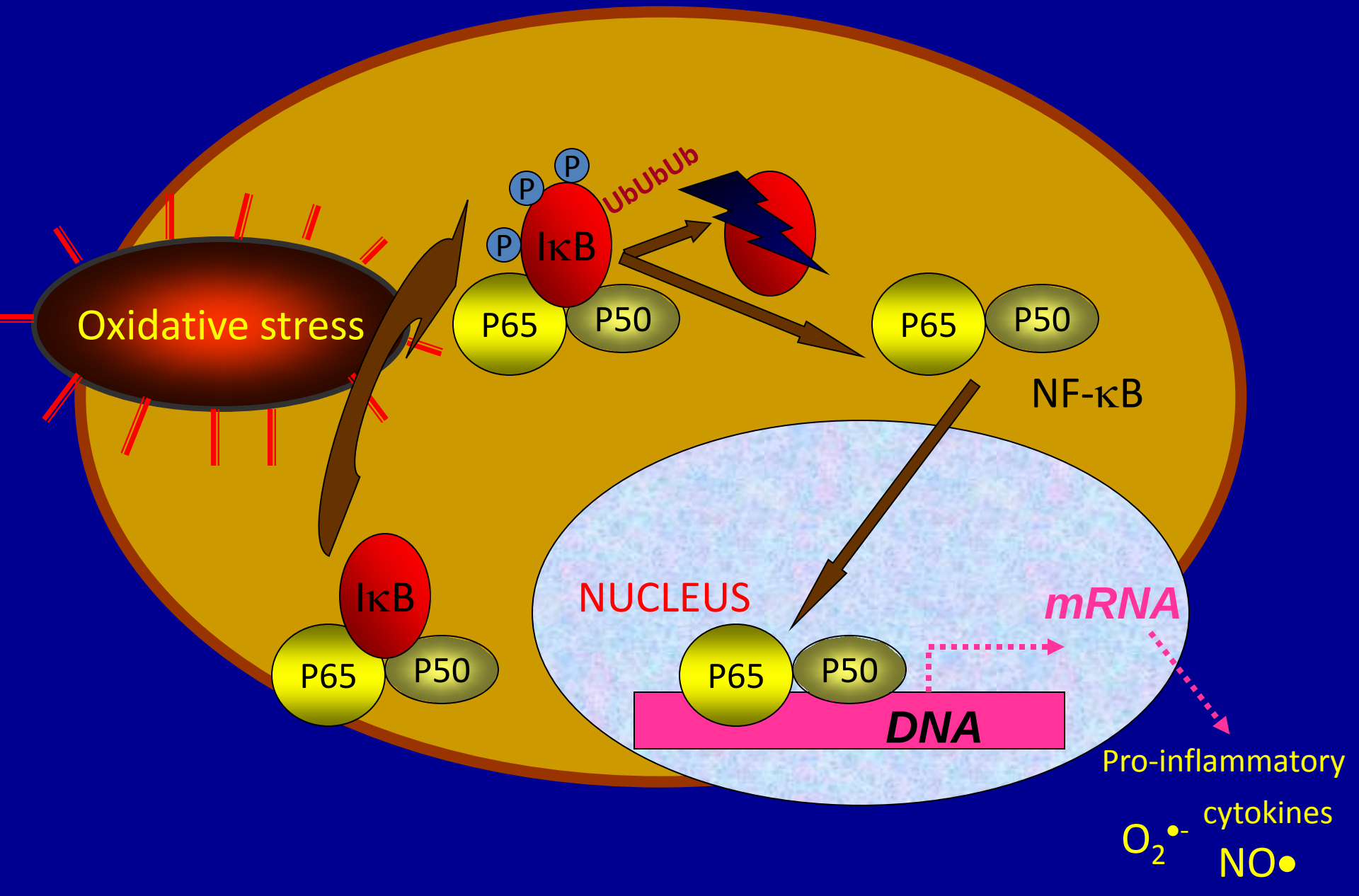
Aalt,

All clear to you?

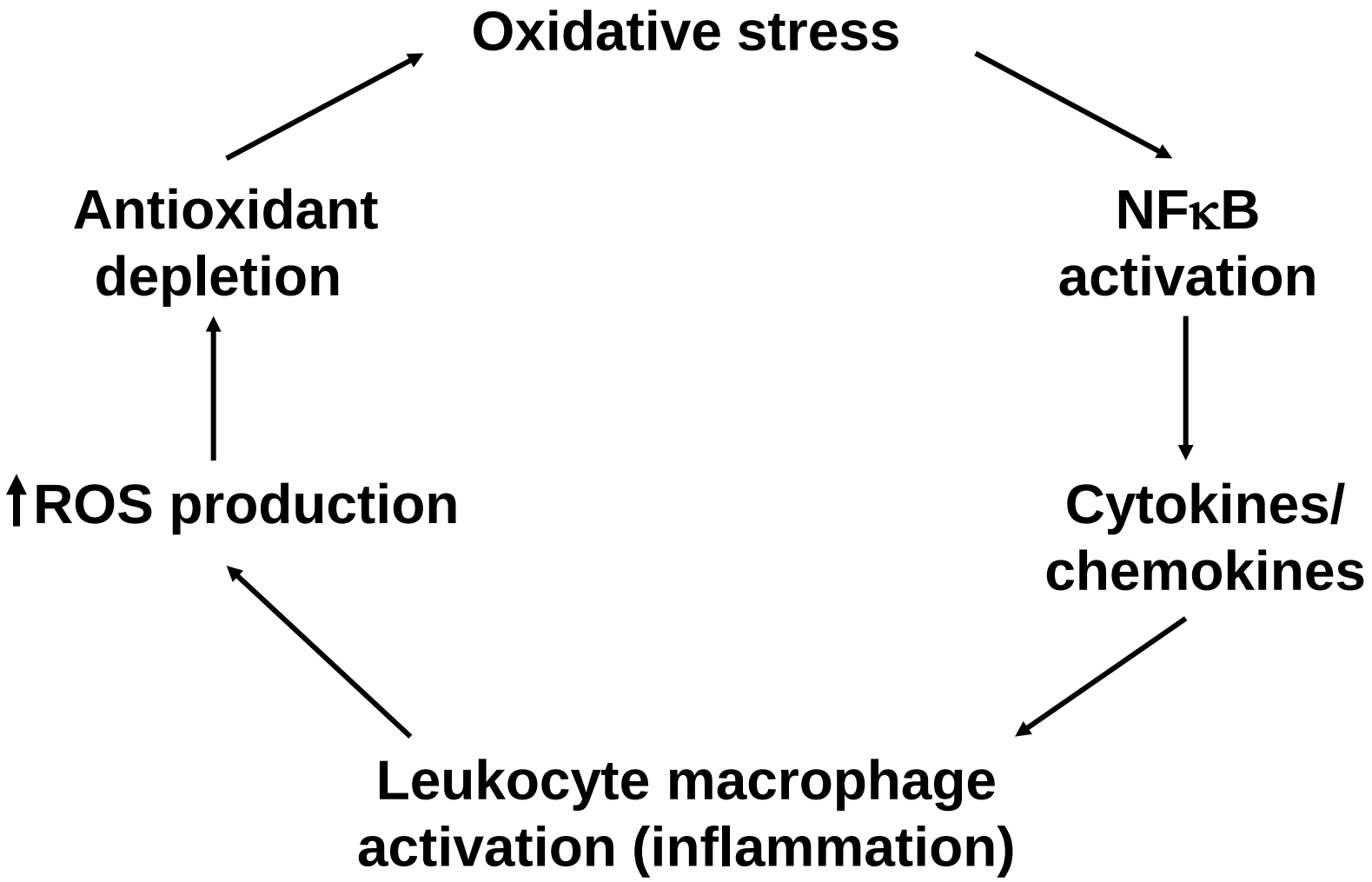
Jaap,

Quite. And quite interesting. But let me up the ante for you.

NF-κB activation by oxidative stress



Oxidative stress and inflammation



Jaap,

Do you catch my drift?

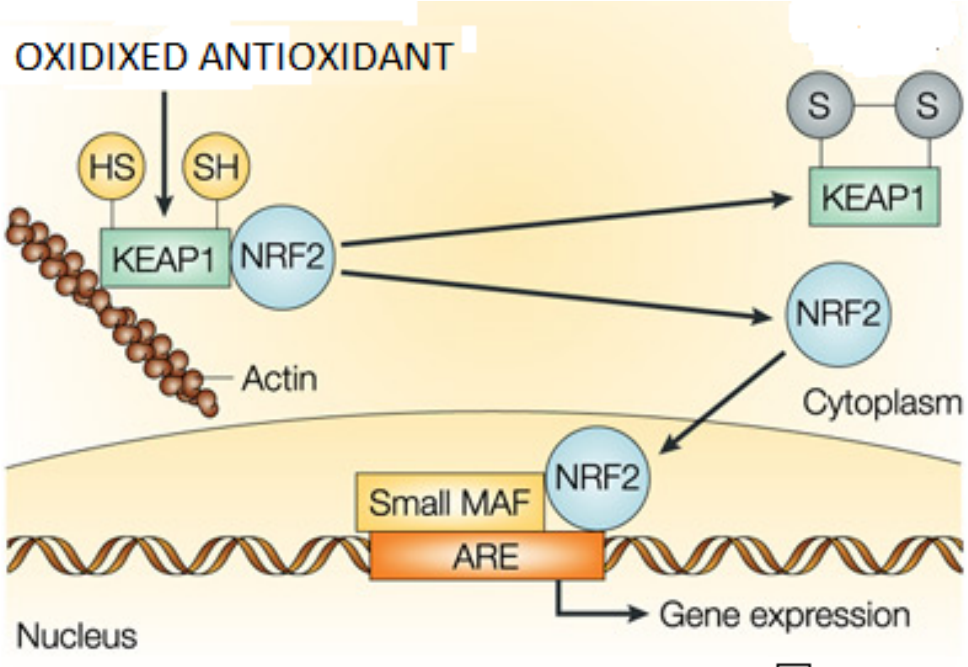
Aalt,

I believe I do. Let me wrap this up. What you are saying is that the adaptation itself can result in a run-away physiology. This is more than just two-sided aspects of compounds.

Jaap,

But wait, there is more.

ANTIOXIDANT ⇨ OXIDIXED ANTIOXIDANT



⇩

ANTIOXIDANT ENZYMES (LIKE SOD)

Jaap,

Can we wrap this up together? What is the take-home message, if any?

J: Science always tries to impose linearity on physiological systems, the Golden Ratio of our age.

A: Compounds such as nitrate are harmful and beneficial to human health.

J: Adaptation, intrinsically non-linear, has given life the potential to develop and survive.

A: Enzymatic oxygen-defence is characterised by both positive and negative effects (SOD).

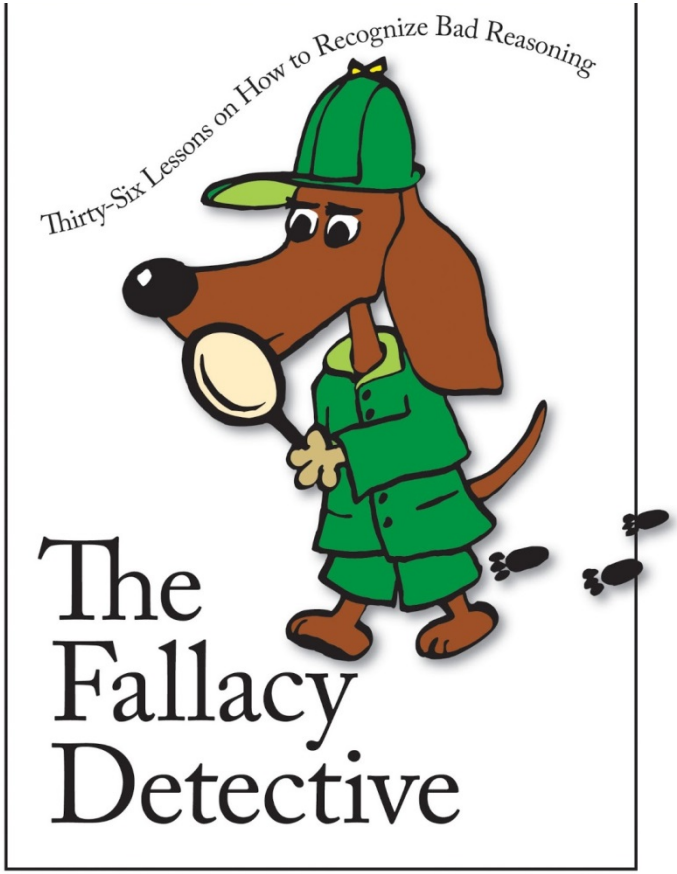
J: Oxygen damage leads to inflammation and thereby amplification of physiological damage (NFkB).

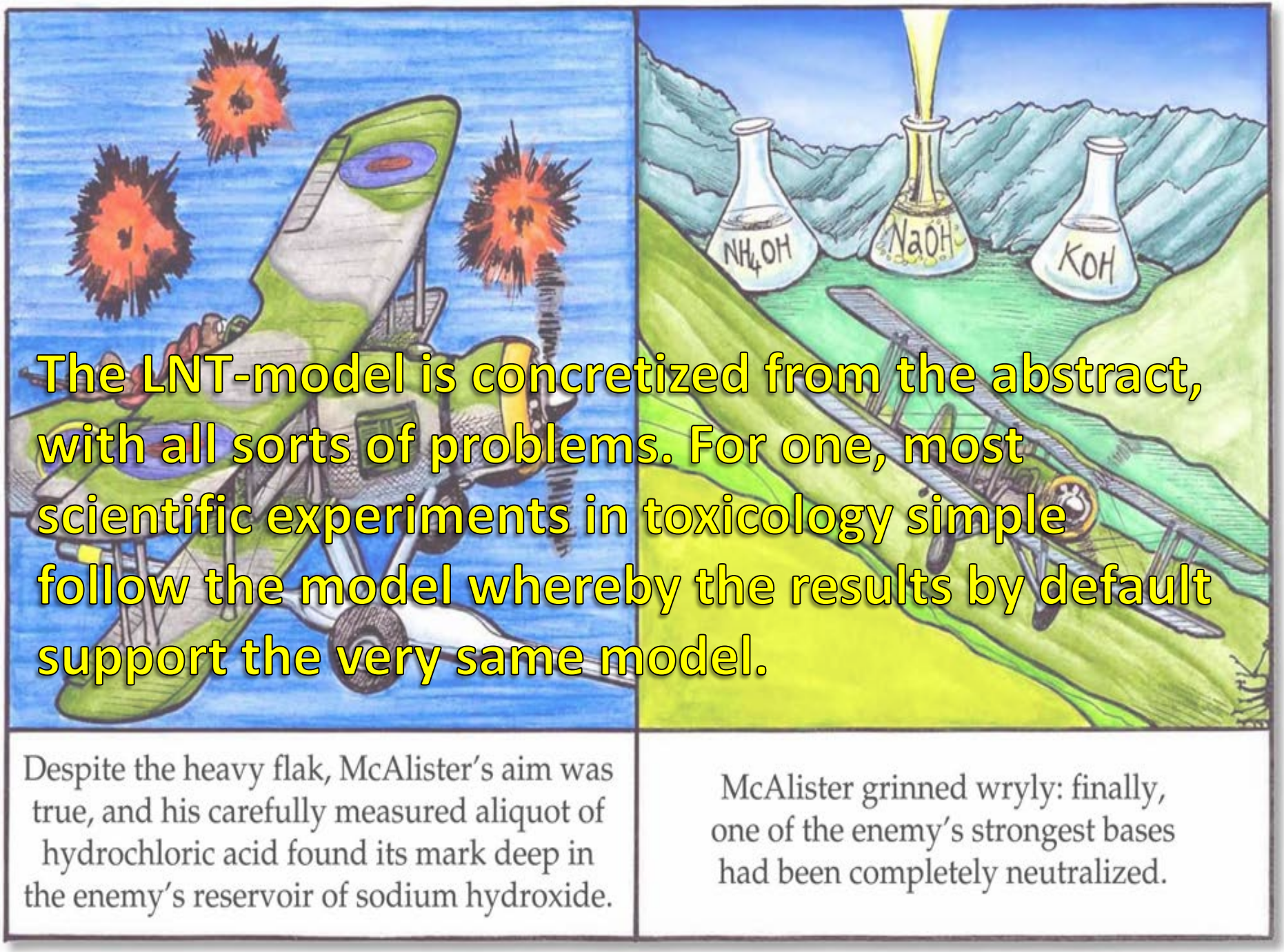
A: Oxidised antioxidants enhance the enzymatic antioxidant system.

A: Jaap, is there anything left for the Golden Ratio?

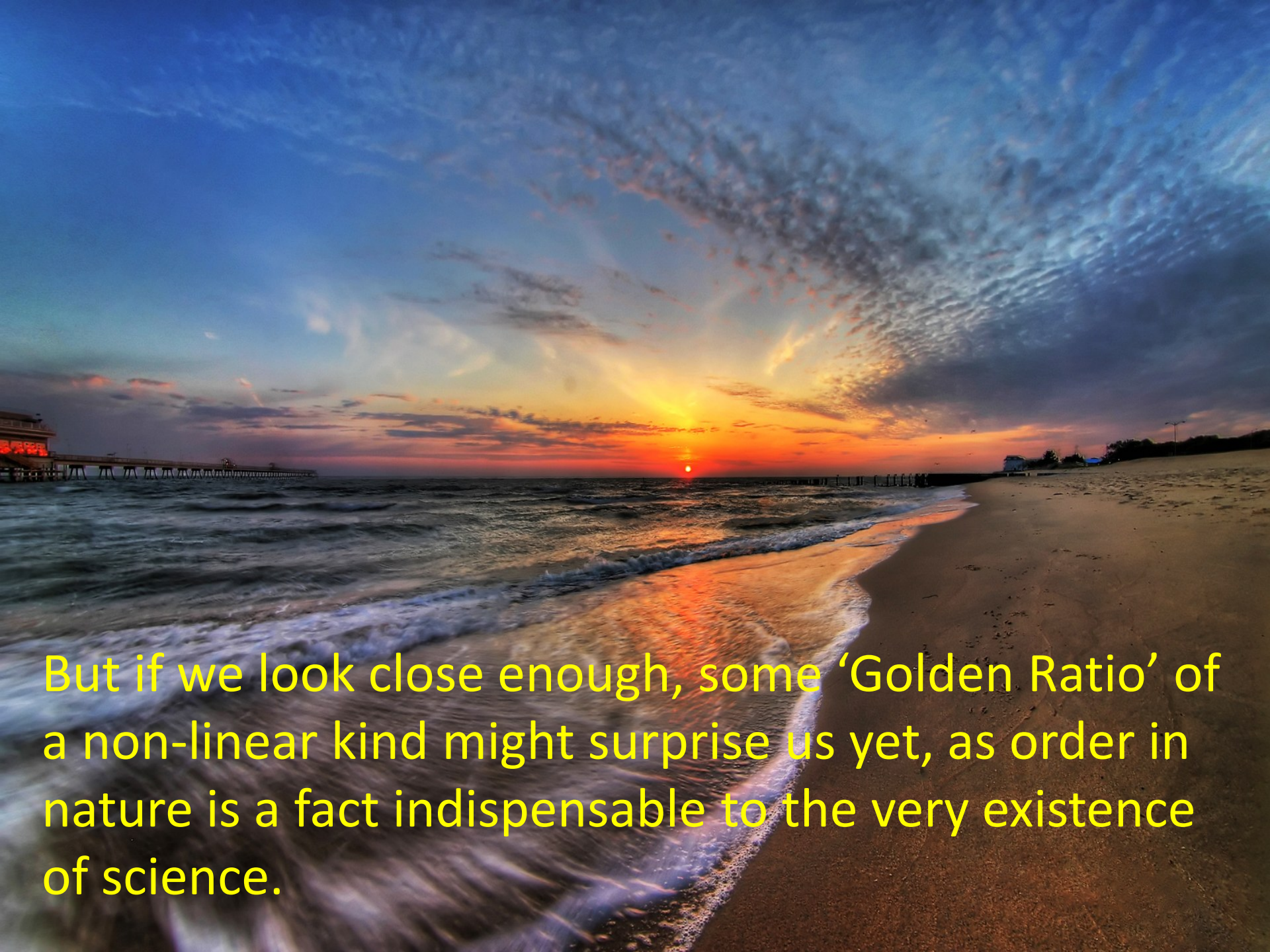
The reification fallacy (misplaced concreteness): Treating abstractions (the LNT-model) as actual existing entities …

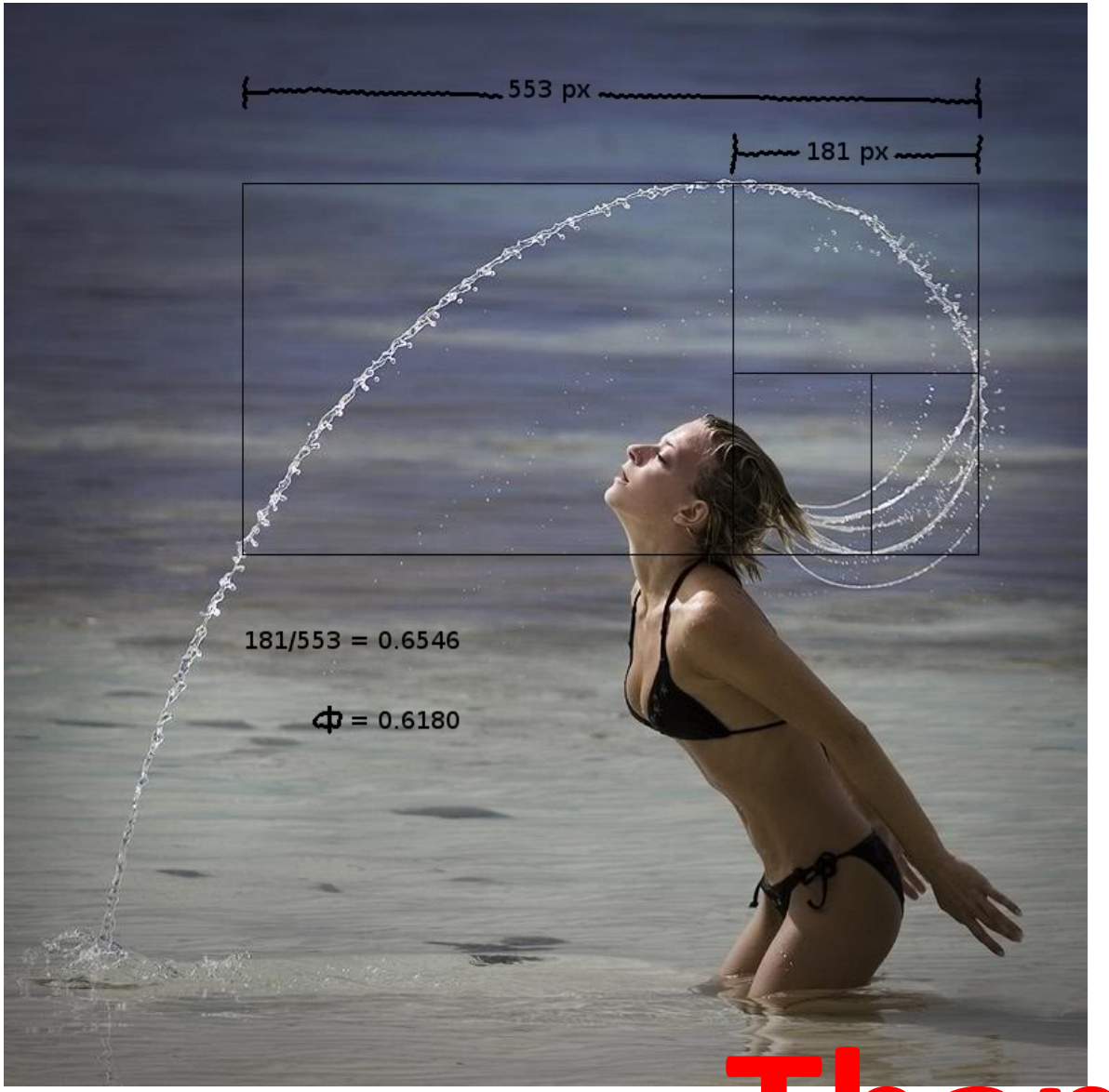
… or regarding them as causally efficacious and ontologically prior *and* superior to their referents.





The LNT-model is concretized from the abstract, with all sorts of problems. For one, most scientific experiments in toxicology simple follow the model whereby the results by default support the very same model.


But if we look close enough, some ‘Golden Ratio’ of a non-linear kind might surprise us yet, as order in nature is a fact indispensable to the very existence of science.



Thank You!