

But where does the Pharmaceutical Industry go ?

# ... and Universities in all that business ?



<http://www.facm.ucl.ac.be>

<http://www.farm.ucl.ac.be/cfcl>

<http://www.uclouvain.be/en-ldri.html>



<http://www.umons.be>

Paul M. Tulkens, Dr Méd.

Professeur Invité

*Louvain Drug Research Institute*

Secteur des Sciences de la Santé

Université catholique de Louvain

Chargé de cours émérite

Service de Biochimie humaine

Faculté de Médecine et de Pharmacie

Université de Mons

# But does the Industry know ?



**And has the University a clearer view ? ...**



Université du Havre : escalier de la bibliothèque  
from <http://imagesduhavre.wordpress.com/2010/01/24/bibliotheque-universitaire-du-havre/>

# What is Medicine all about ?

**Doctor**



**Patient**



But the doctor may not know  
unless he has been taught  
and trained...

# What is Medicine all about ?

**Science**

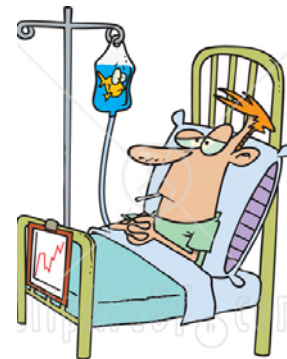
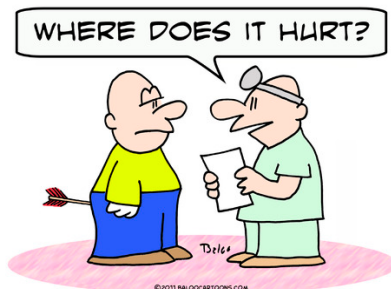


We must use all  
what Science  
offers to treat  
patients

**Doctor**

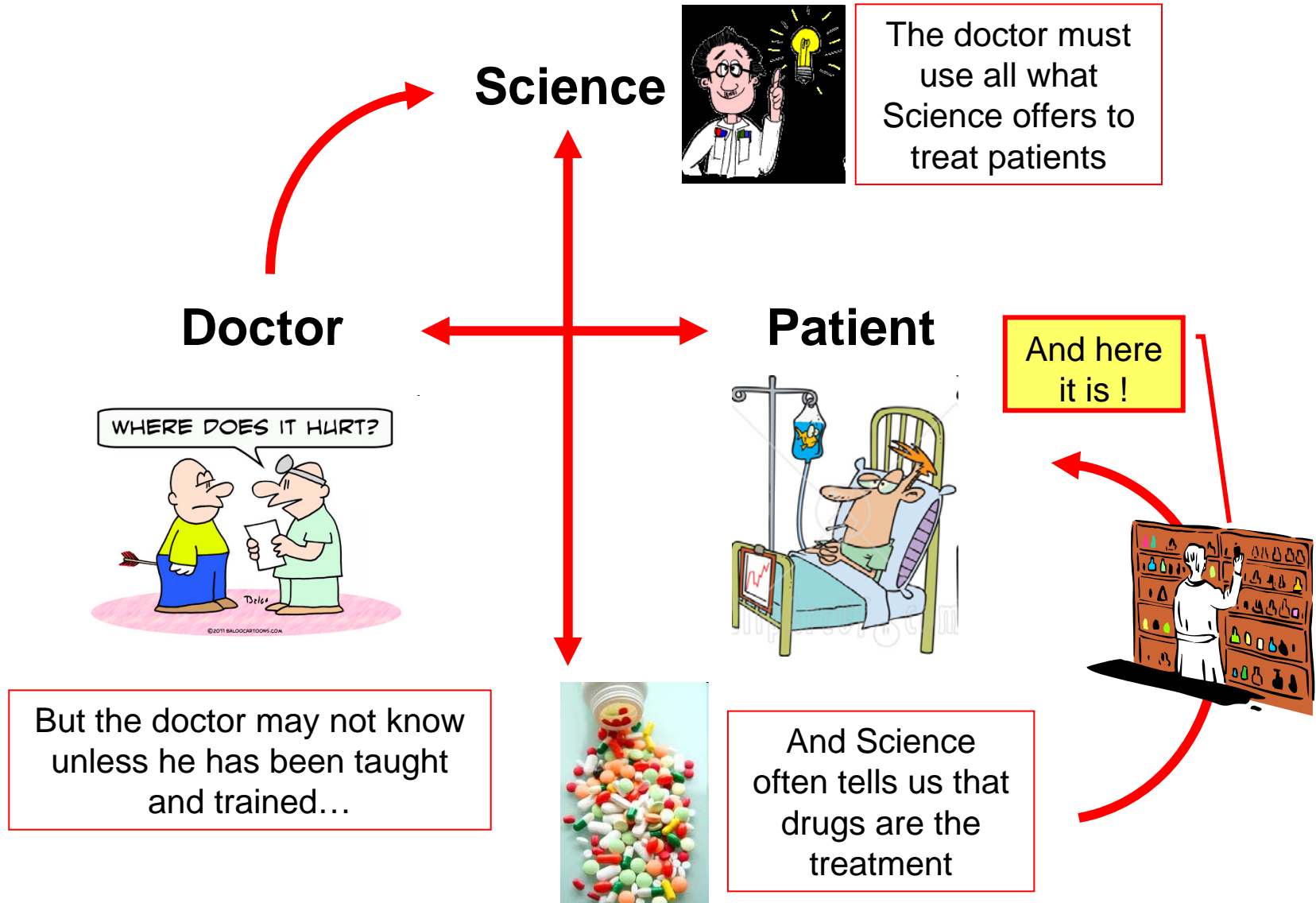


**Patient**



But the doctor may not know  
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# What is Medicine all about ?



# A short history of drug discovery

- Most drugs were for long discovered by accident and from natural sources
- Some were useful but others not, and many were toxic (in the short [rarely] or in the long [frequently] term...



The Helkias was a very effective drug to treat skin diseases and ulcers. It was made of mercuric bichloride which is a powerful antiseptic. This remedy was a great success not only in Belgium but also abroad. Sales stopped shortly before the Second World War, as the dangerous side effects of mercury in the Helkias had caused serious damage, if not fatal.

Source: Hôpital de la Rose, Lessines (<http://www.notredamealarose.com>)



# The impact of pharmacology

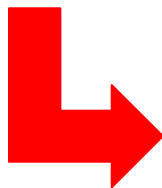
- Drugs must be active and specific for a defined target
  - is the target unique and linked to a specific pathologic state ?
  - what is the nature of the interaction ?
- Their mode of action must be clear
  - simple receptor agonism/antagonism or complex modulation of a physiological function ?
  - altering the essential functions of an invader ?
- Their properties, as drugs must be comprehensively assessed
  - absorption, distribution, metabolism, excretion
  - stability and suitability for the proposed use



# The impact of pharmacotherapy

- Is the drug effective for the disease it is supposed to treat ?
  - for diseases where many drugs exist, but what is their ranking ?
  - for diseases without effective therapy, is the new drug a breakthrough or symptomatic ?
- Is the drug usable in daily practice ?
  - what are the problems linked with administration
  - how important are the side effects
  - how important and difficult are therapy adjustments (monitoring, e.g.)
- What are the alternatives ?
  - another drug ...
  - another treatment ?
- Is the drug really needed ?

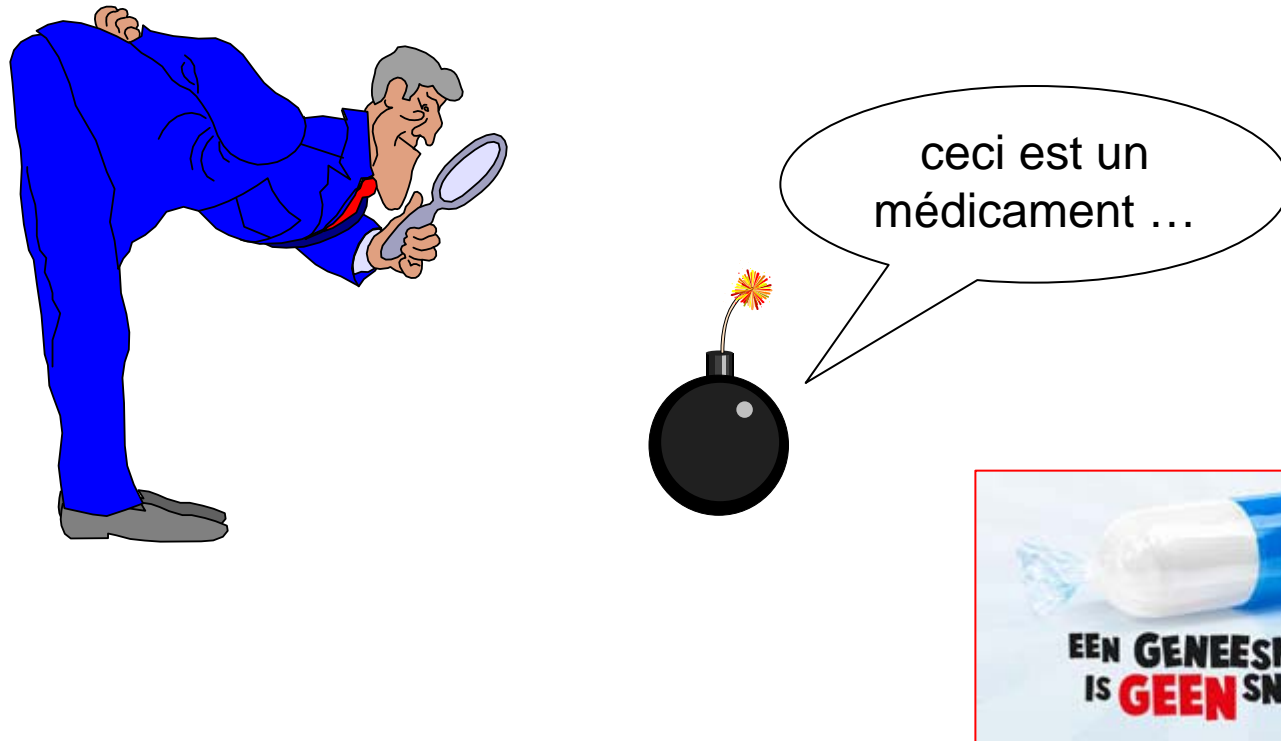
# The impact of the "need for safety"



## Quelques exemples de pharmacovigilance avec retrait ou restriction importante du médicament correspondant ...

- 1880: le **chloroforme** cause des **arrêts cardiaques** ...
- 1946: la **streptomycine** cause de la **surdit  irr versible**
- 1953: la **ph nac tine** cause de la **n photoxicit **
- 1961: la **thalidomide** cause des **malformations cong nitales (phocom lie)**
- 1990: la **t mafloxacine** cause de l'**an mie h molytique ur mique**
- 1998: le **tolcapone** cause de l'**h patotoxicit **
- 2000: la **c rivastatine** cause de la **rhabdomyolyse**
- 2001: le **cisapride** cause des **torsades de pointe**
- 2004: le **rof coxib** cause des **infarctus** ...
- 2007: la **t lithromycine** cause des **insuffisances h patiques**

# Drugs can be dangerous ...



Which means that safety concerns can be quite difficult to address

- at registration (viz. EMA, FDA)
- during product life-time (several examples)

# Can you easily register an "old" but needed drug today ?

## The situation with colistin...

### Re-emergence of colistin in today's world of multidrug-resistant organisms: personal perspectives

July 2008, Vol. 17, No. 7, Pages 973-981 (doi:10.1517/13543784.17.7.973)

[Matthew E Falagas](#)<sup>†1,2,3</sup> MD MSc DSc & [Petros I Rafailidis](#)<sup>1,3</sup> MD MRCP UK  
MSc

<sup>†1</sup>Alfa Institute of Biomedical Sciences (AIBS), 9 Neapoleos Street, 15123  
Marousi, Athens, Greece +30 694 611 0000; +30 210 683 9605;  
[m.falagas@aibs.gr](mailto:m.falagas@aibs.gr)

<sup>2</sup>Tufts University School of Medicine, Department of Medicine, Boston, MA,  
USA

<sup>3</sup>Henry Dunant Hospital, Department of Medicine, Athens, Greece

<sup>†</sup> Author for correspondence

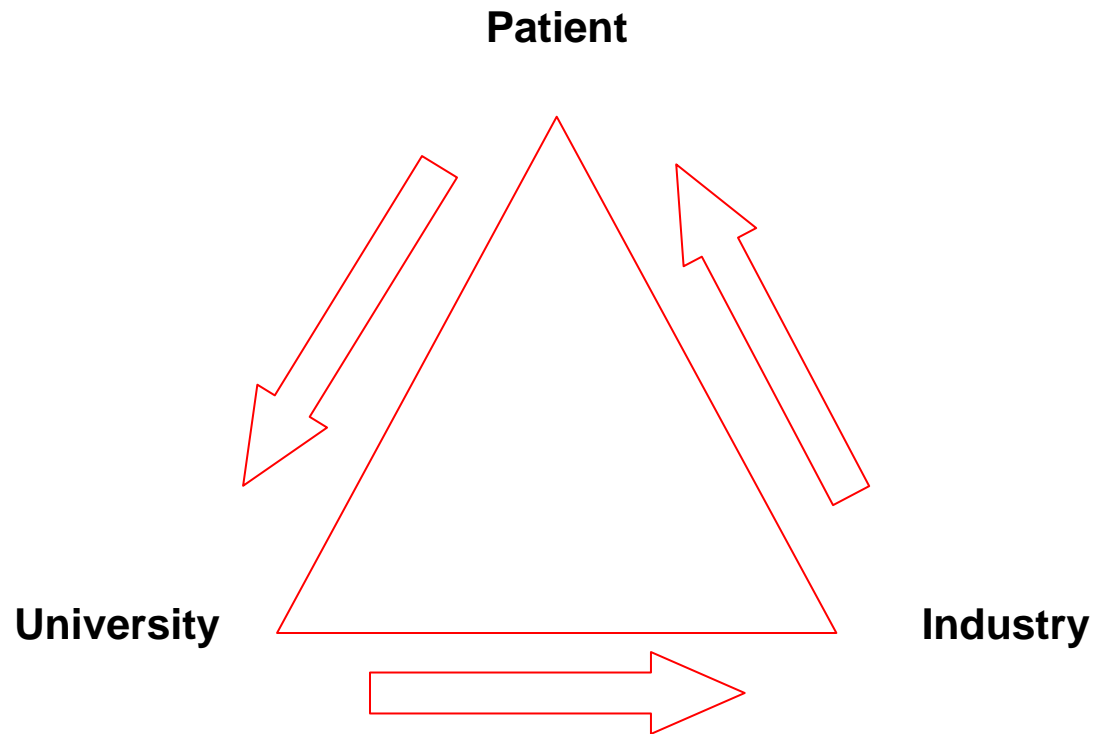
[HTML](#)[PDF \(244 KB\)](#)[PDF Plus \(293 KB\)](#)[Reprints](#)[Permissions](#)

# Can you easily register a drug today ?

**A few problems for colistin ... if you were to ask for registration...**

- Pharmaceutical aspects:
  - uncertainties about the composition and strengths of the medicinal product offerings
- Microbiology:
  - High risk of failures by loss of bacterial susceptibility (regrowth and development of resistance)
- Preclinical safety:
  - Uncertain and incomplete animal safety testing
- Preclinical assessment of efficacy:
  - Incomplete and often unconvincing pharmacokinetics/pharmacodynamic parameters
- Clinical safety:
  - Uncertainties about the true human nephrotoxic potential
- Clinical effectiveness:
  - incomplete clinical development

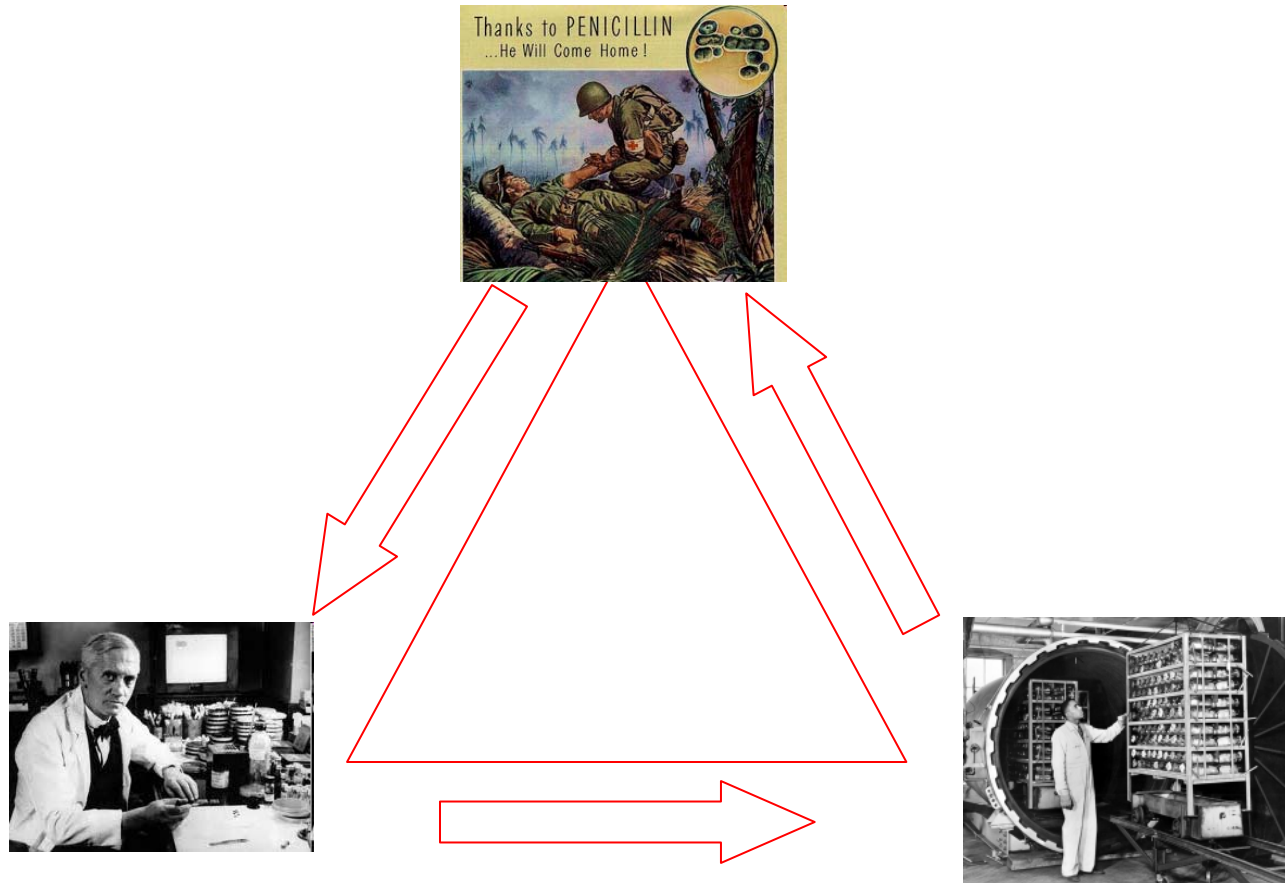
# The current triangle of drug discovery – development – clinical use



**This approach has been very successful !**

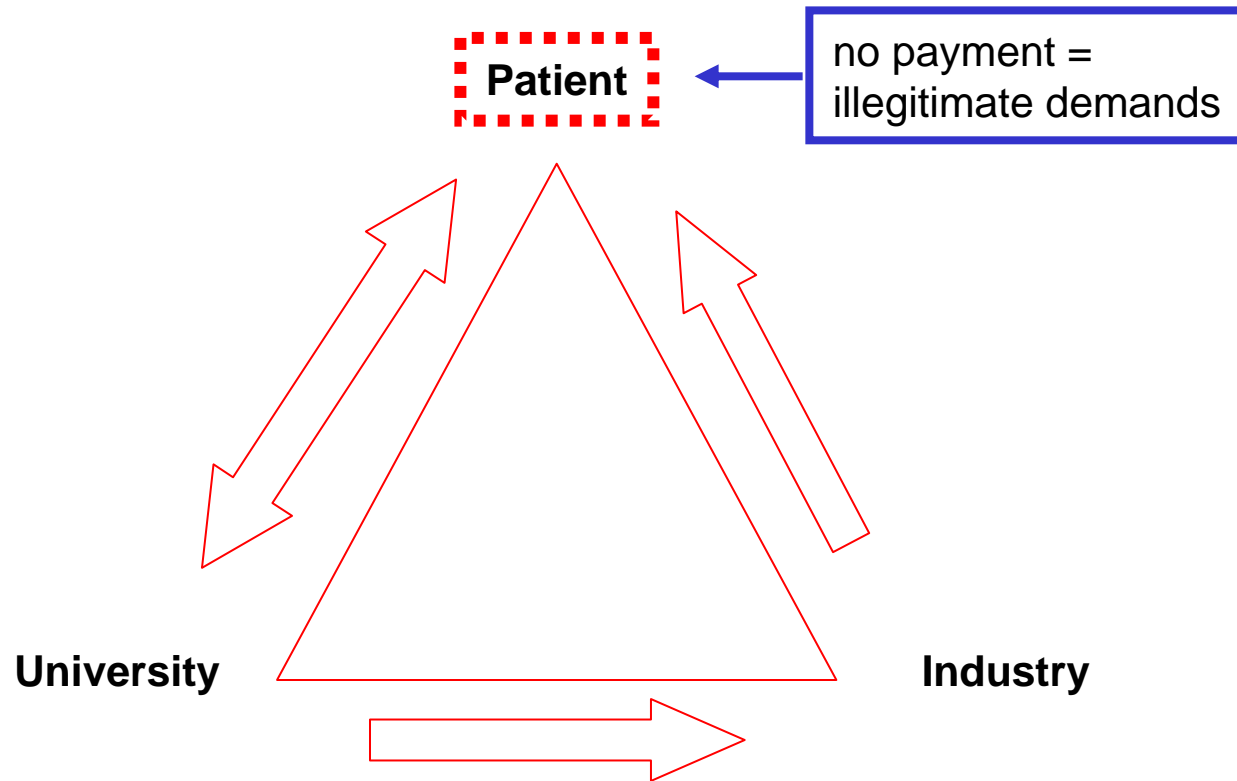


# The current triangle of drug discovery – development – clinical use



**This approach has been very successful !**

# What are the dangers in our current system ?



# Patient's illegitimate demand ?

France...

Le.JR mercredi 9 octobre 2011

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## Mobilisation contre la surconsommation d'antibiotiques

L'assurance-maladie lance une campagne d'information afin de limiter une pratique chère et nocive.

Alexander Fleming, inventeur de la pénicilline en 1929, n'en reviendrait pas. Moins d'un siècle après que ce médecin britannique a ouvert la voie au traitement des maladies infectieuses (tuberculose, diphtérie, choléra, etc.) par les antibiotiques, ces médicaments sont aujourd'hui dangereusement surconsommés.

Pour promouvoir le "bon usage" des antibiotiques et limiter le phénomène de résistance des bactéries, la Caisse nationale d'assurance-maladie (CNAM) lance, en ce mois d'octobre, une vaste campagne d'information et de sensibilisation auprès des médecins et du grand public, conformément au calendrier du plan pluriannuel pour "préserver l'efficacité des antibiotiques" lancé en novembre 2001 par Bernard Kouchner, l'ancien ministre de la santé.

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**.be HEALTH**

Een initiatief van de Federale Overheidsdienst  
"Volksgezondheid, Veiligheid Voedselketen en Leefmilieu"

## antibiotica minder vaak en beter gebruiken

laatste herziening op december 2002

tegang brochure Om meer te weten

TV SPOT

**NEW!** folder

**ANTIBIOTICA**  
minder vaak  
en  
beter  
gebruiken

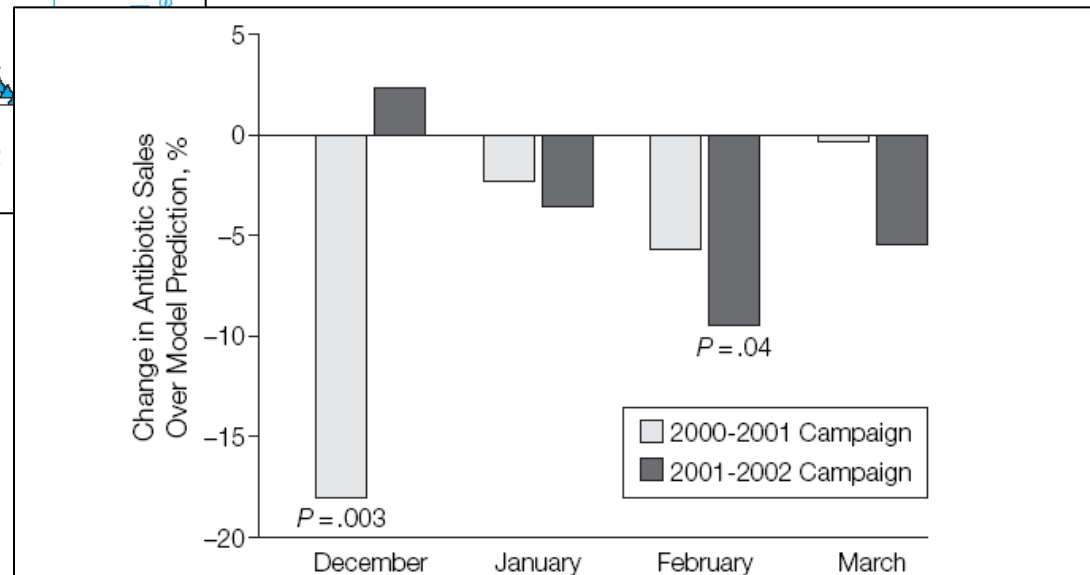
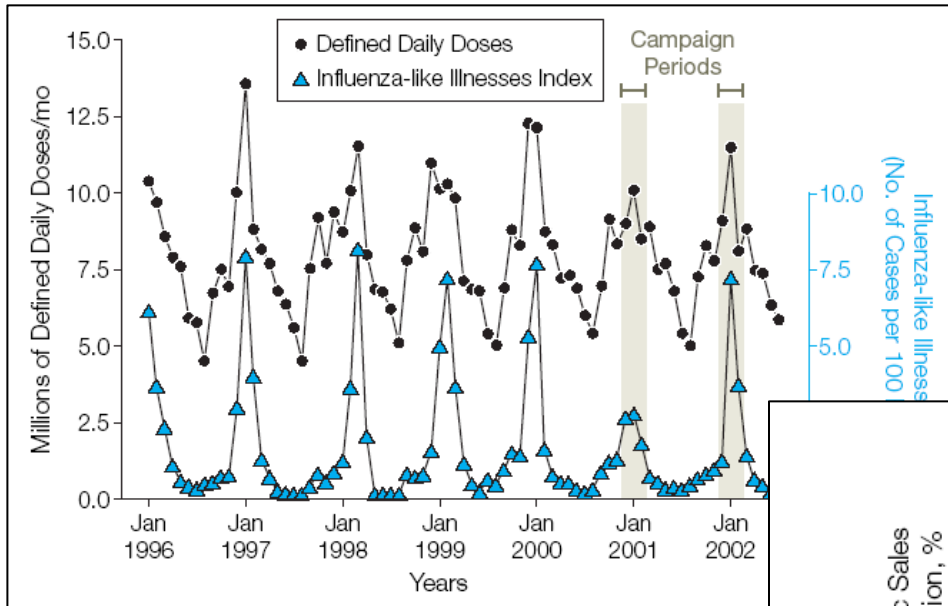
Met de steun van de volgende wetenschappelijke verenigingen:

- Belgische Vereniging voor Kindergeneeskunde
- Wetenschappelijke Vereniging van Vlaamse Huisartsen
- Belgische Vereniging voor Pneumologie
- Koninklijke Belgische Vereniging voor Geneeskunde

Belgium...

The correct use  
of antibiotics

# Decreasing patient's illegitimate demand ?



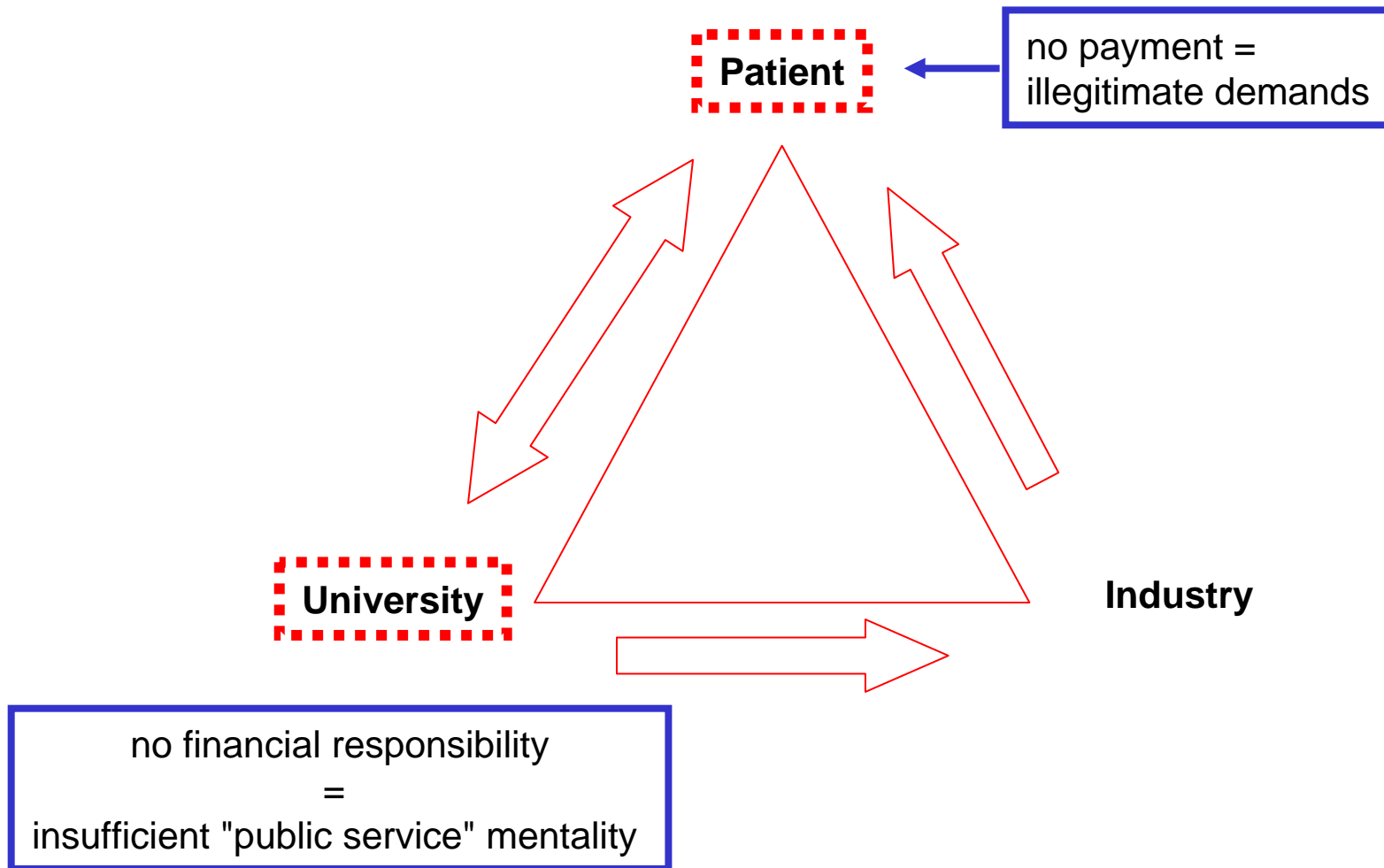
## RESEARCH LETTER

### Association Between Antibiotic Sales and Public Campaigns for Their Appropriate Use

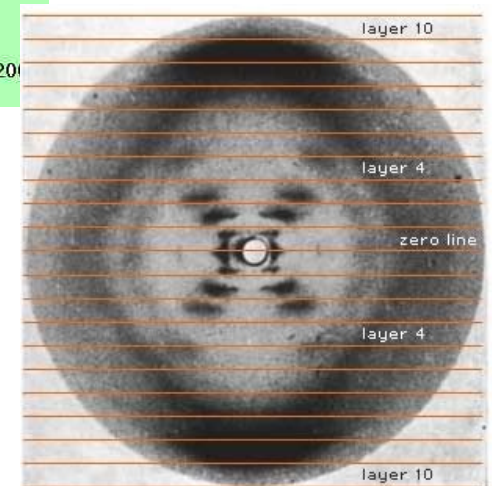
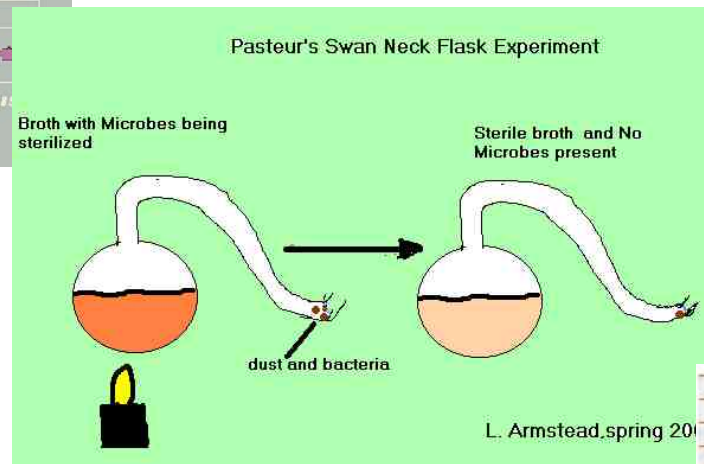
JAMA, November 24, 2004—Vol 292, No. 20 2469

Residual seasonal autoregressive terms: lag period, 12 months; estimated coefficient: 0.83 [SE, 0.06]; constant: 7 459 075 (SD, 431 387) defined daily doses/mo. The  $P$  values are indicated for the months and campaigns for which the changes were statistically significant.

# What are the dangers in our current system ?

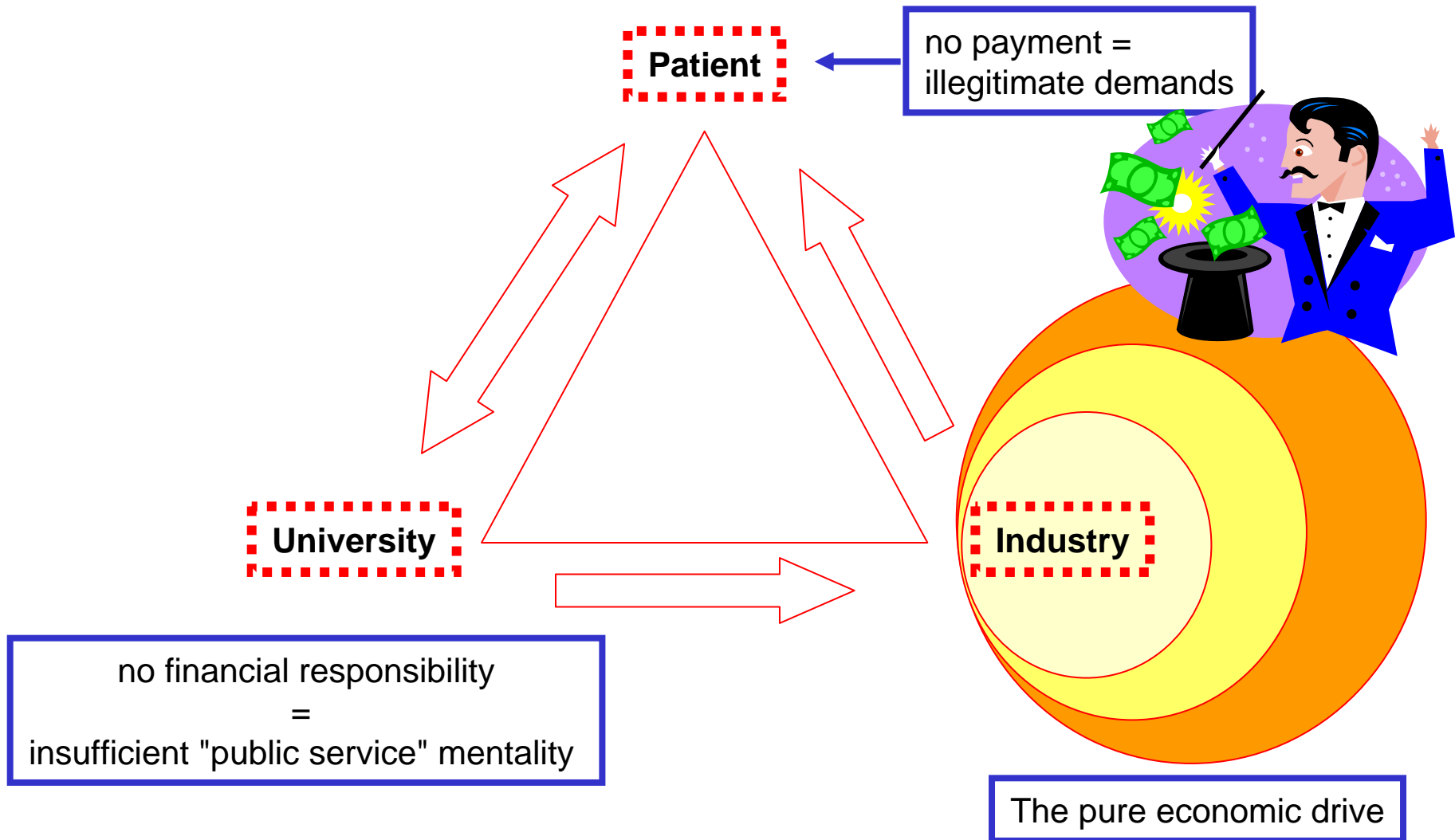


# Basic Science is essential but Medicine is about treating



Rosalind Franklin's Photograph 51\*

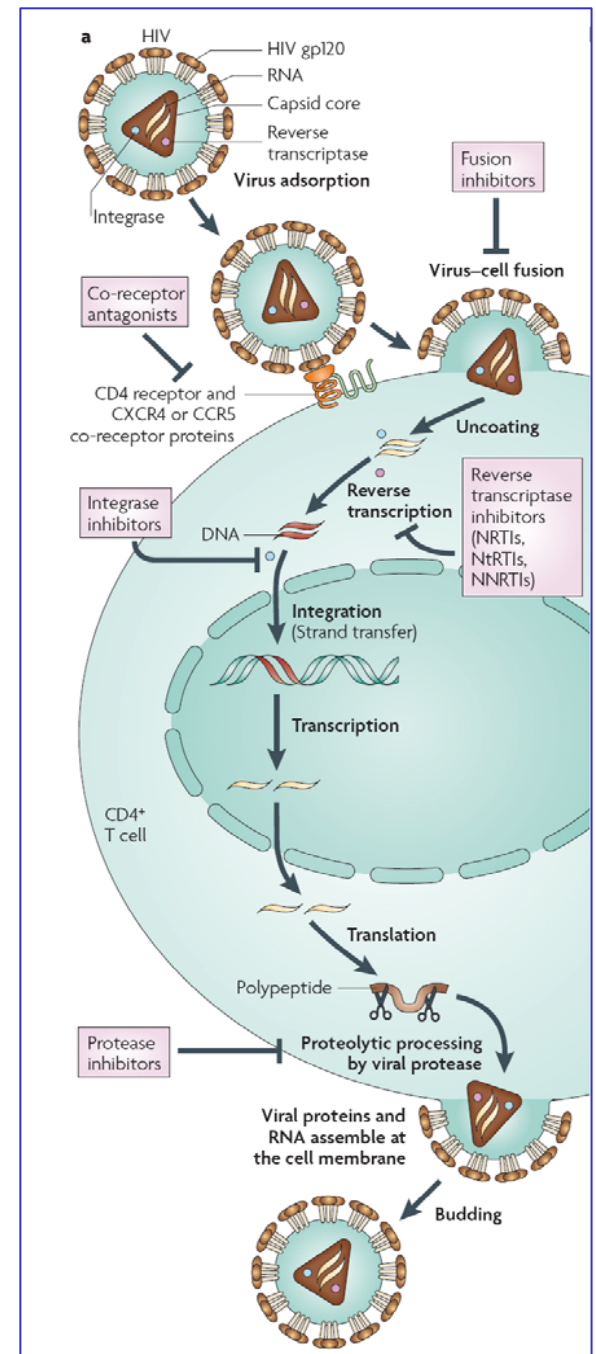
# What are the dangers in our current system ?





# Economic drive is not necessarily a problem...

The current multiples approaches to the treatment of HIV infection

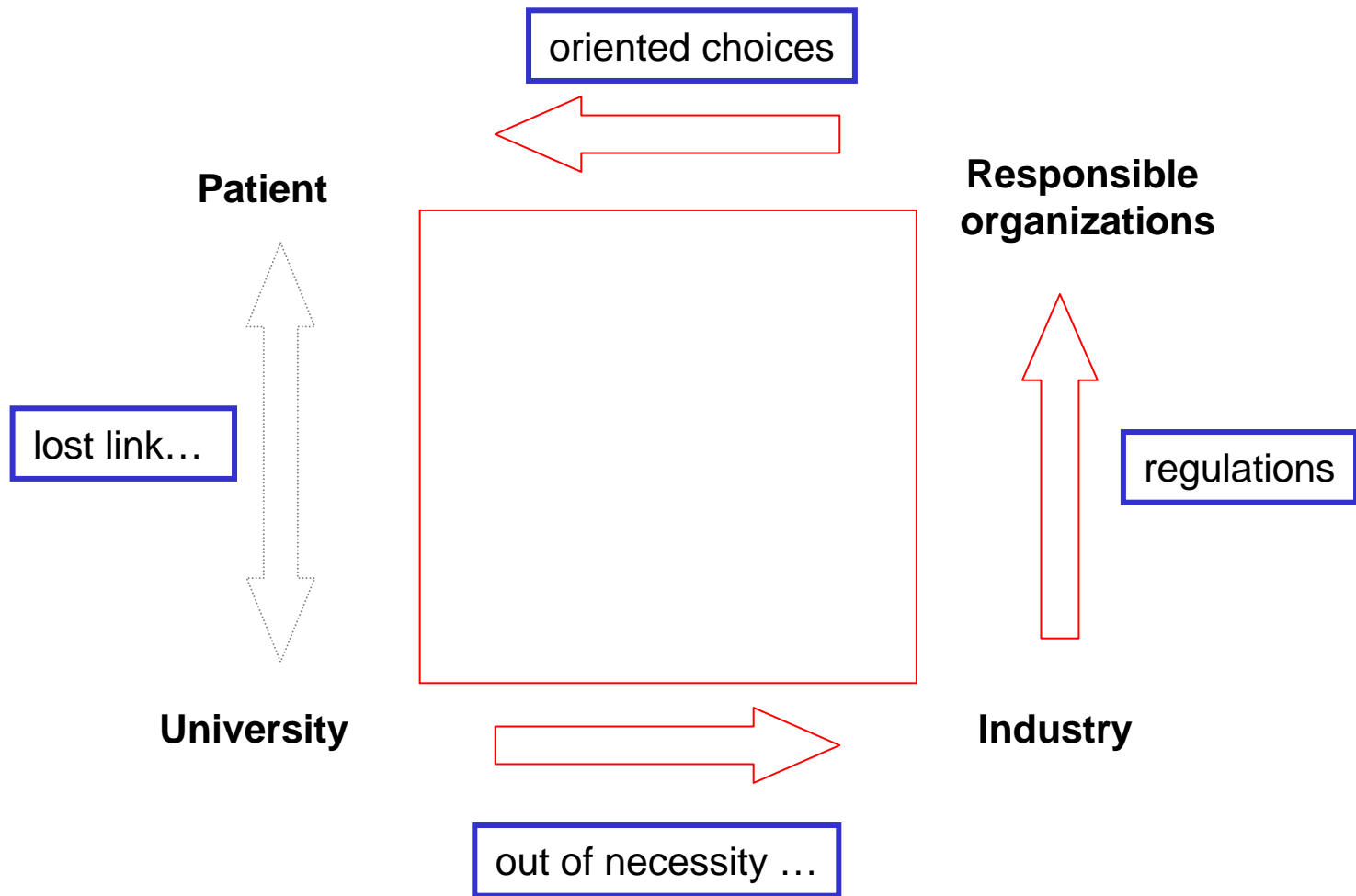


De Clercq, *Nature Rev. Drug Discov.*(2007) 6:1001-1018

# But "pure" economic drive may also lead us to failure ...

- loss of common sense in choice of therapeutic areas
  - cancer is a dreadful disease ... but anticancer agents are sold at > 30,000 €/QUALY ... (vs. 200 € to treat a pneumonia...)
  - obesity is a public health problem ... and represents a large market ... but most anti-obesity drugs have a poor pharmacological basis
- irrational (to scientists) choice of development processes
  - poor choice of comparators
  - clinical trials with non-really severe patients
- investments/promotion of promotion of "weak" scientific progresses
  - "pure" isomers
  - "mee too" compounds
- marketing deviations
  - trovafloxacin or the "lost quinolone"
  - cerivastatin or how you may kill the patient and your-self ...

# What are the risks for Academia and patients ?



# Why is this situation dangerous ?

- The real choices may no longer be those of the Medical Science

I will apply, for the benefit of the sick, all measures [that] are required, avoiding those twin traps of overtreatment and therapeutic nihilism \*

- We even may loose sight of the real patients, who are those who are sick, not those who are amongst an key market target
- Conversely, we may also ignore patients that are not in those "typical groups" in which therapy can be made according to guidelines

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\* Hippocrate's oath: 1964 translation by Louis Lasagna, Tufts University


# The risk of novel medicines...

BMJ

BMJ 2011;343:d6423 doi: 10.1136/bmj.d6423

Page 1 of 15

## Risk of venous thromboembolism from use of oral contraceptives containing different progestogens and oestrogen doses: Danish cohort study, 2001-9

 OPEN ACCESS

Øjvind Lidegaard *professor of obstetrics and gynaecology*<sup>1</sup>, Lars Hougaard Nielsen *statistician*<sup>1</sup>, Charlotte Wessel Skovlund *data manager and scientific assistant*<sup>1</sup>, Finn Egil Skjeldestad *professor of clinical medicine*<sup>2</sup>, Ellen Løkkegaard *senior registrar in obstetrics and gynaecology*<sup>3</sup>

<sup>1</sup>Gynaecological Clinic 4232, Rigshospitalet, University of Copenhagen, Denmark; <sup>2</sup>Department of Obstetrics and Gynaecology, Institute of Clinical Medicine, University of Tromsø, Norway; <sup>3</sup>Department of Obstetrics and Gynaecology, Hillerød Hospital, University of Copenhagen, Denmark

### What is already known on this topic

Studies have shown an increased risk of venous thrombosis (VTE) with use of combined oral contraceptives

The risk was higher with oral contraceptives containing the progestogens desogestrel and gestodene than those containing levonorgestrel

Results on the risk from oral contraceptives with drospirenone have been conflicting

### What this study adds

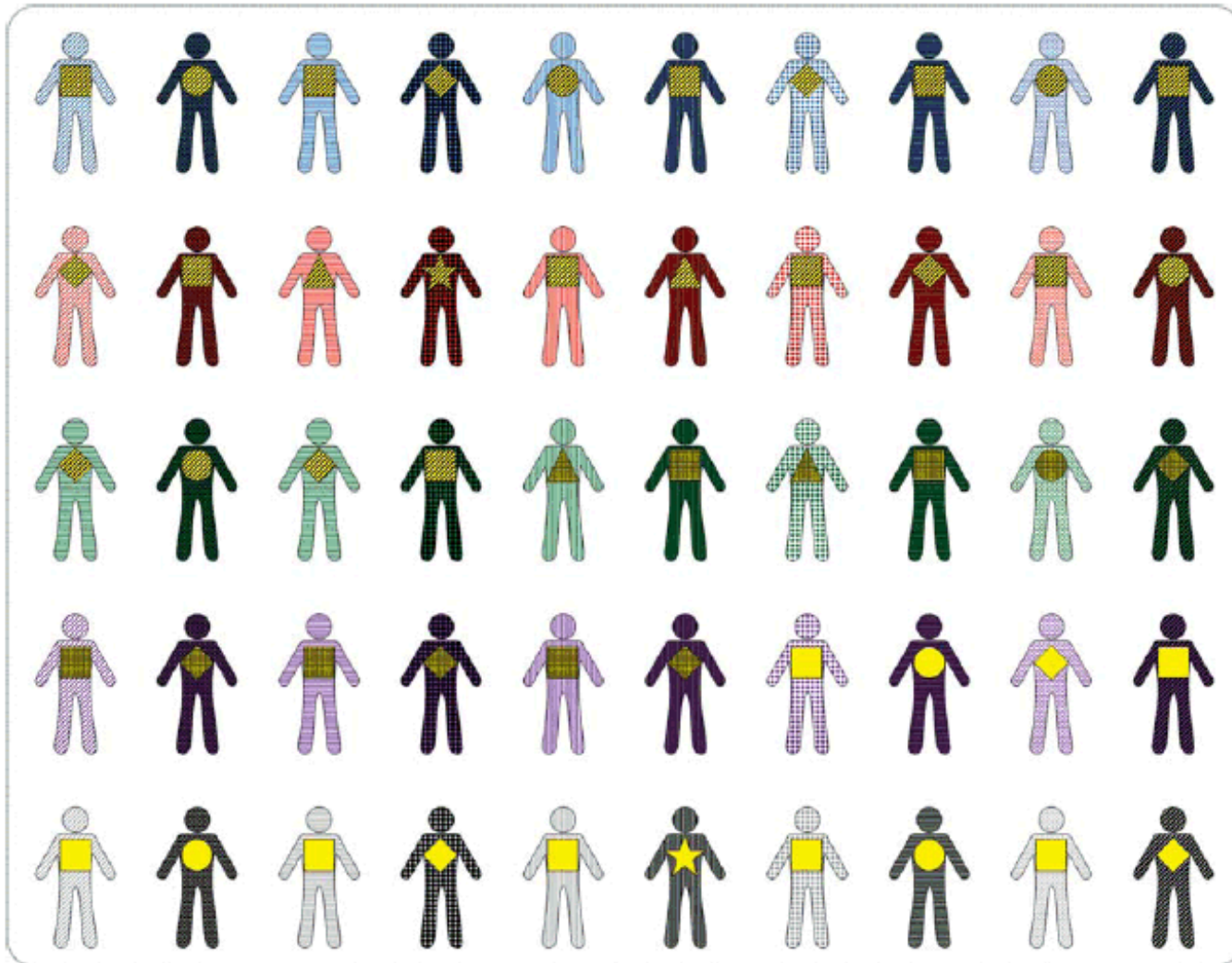
Women using oral contraceptives with drospirenone are at similar risk of VTE to those using oral contraceptives with desogestrel, gestodene, or cyproterone and higher than those using oral contraceptives with levonorgestrel

The risk of VTE was not reduced by using 20 µg oestrogen instead of 30 µg oestrogen in oral contraceptives with drospirenone

To prevent one event of VTE in one year about 2000 women should shift from using oral contraceptives with desogestrel, gestodene, or drospirenone to those with levonorgestrel



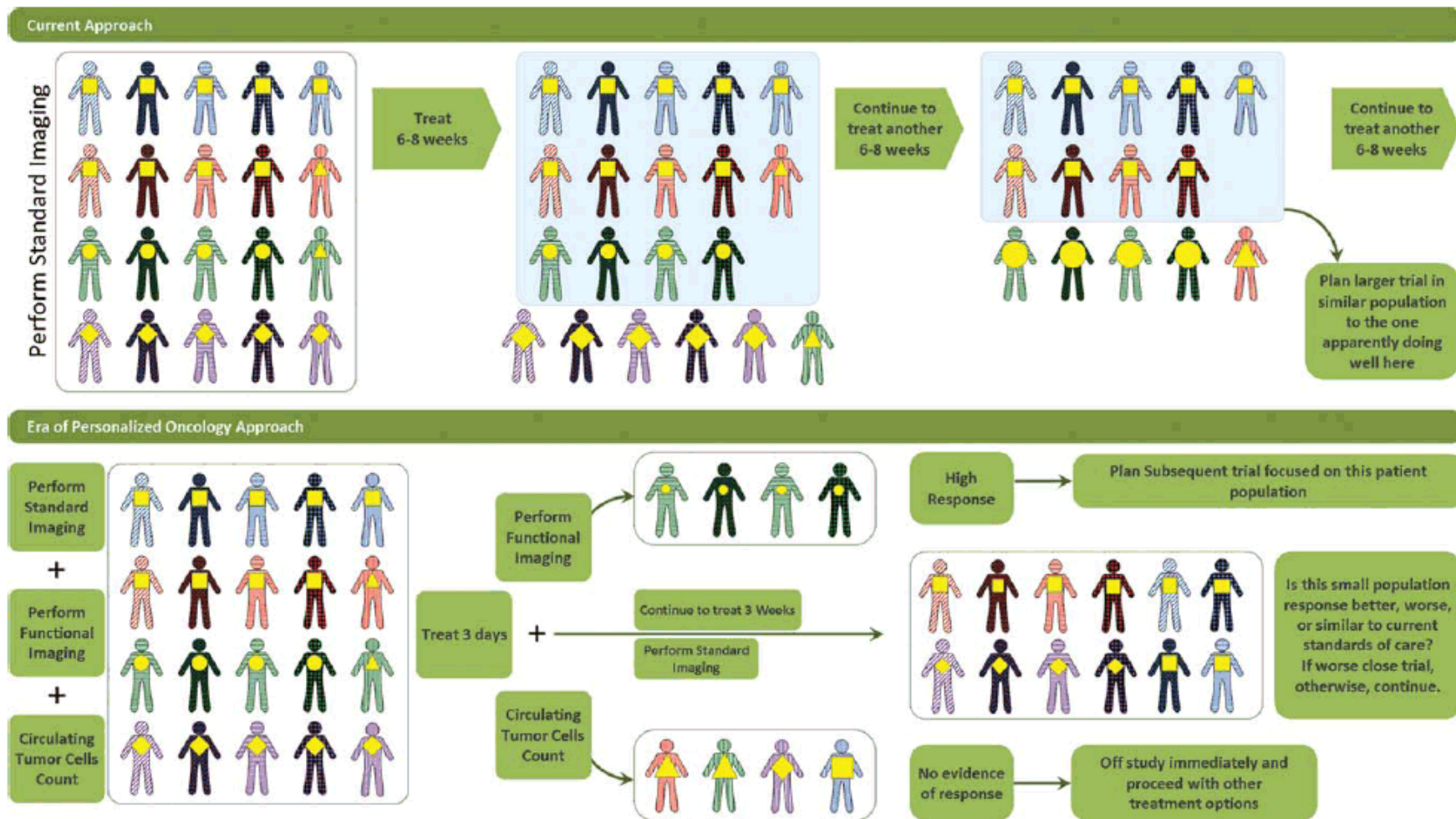
# But do not ignore the possibilities of Personalized Medicine



**FIGURE 4.** Viewing Patient and Disease Individually in the Era of Personalized Oncology.



# Personalized Medicine in Action



**FIGURE 5.** Potential Clinical Trial Strategies in the Era of Personalized Oncology/Quicker Assessment of Disease Response.



# An academic message for Industry:

- Industry efforts must be redirected towards real medical issues and challenges, and be more than ever based on mutual information exchange with academia
- Truly innovative medicines must have priority (e.g., personalized medicines)
- The financial framework in which Industry works (limited patent life causing aggressive marketing) must be changed (but avoiding any "*effet d'aubaine*")
- Marketing must make more use of the scientific knowledge shared by Industry and Academia and respect it
- Transparency with respect to costs and real investments would be very useful

# A message for Academia

- While basic research needs to be supported, and reinforced, Academy should explore all means of useful medical applications (to the point of proof-of-concept)
- Academy should support efforts of Industry to move from older economic frameworks to engage to more risky areas (e.g., by supporting the "provisional registration" approaches) and to restrict activities in medically useful areas (e.g. by providing scientific and clinical support when needed)
- Academy should refrain from considering Industry as a permanent source of funding for activities that are far away from true Science
- And last but not least, Academy should regain her position of providing health care professionals with best guidelines and recommendations for effective and safe therapy.

# Disclosures

Financial support from

- the Belgian *Fonds de la Recherche Scientifique* (and other federal and regional funding agencies) for basic research on pharmacology and toxicology of antibiotics and related topics
- the Public Federal Service "Public Health" for "Appropriate antibiotic use" studies in General Practice
- Pharmaceutical Industry for specific drug-related studies

Note:

- all scientific work and lectures, irrespective the source of funding, is published in peer-reviewed journals and/or is available from our web site
- P.M. Tulkens is member of the Committee organizing public campaigns for appropriate use of antibiotics in Belgium since 2000 \* and a past-member of the "*Commission de Transparence/Doorzichtigheids Commissie*" and of the "*Commission de Remboursement des Médicaments/Commissie Tegemoetkoming Geneesmiddelen*" (1998-2006).