

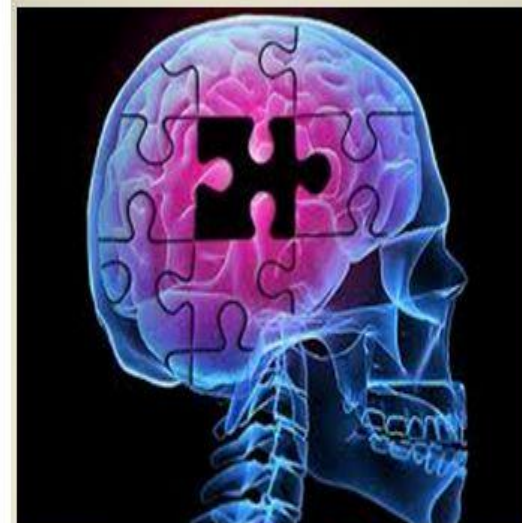
TOPICS FOR REGULATORY SCIENCE: AS SEEN FROM THE PATIENT'S JOURNEY

dr. h.c. Cees Smit, VSOP/EGAN, LUMC, dept Epidemiology

Lygature, Utrecht, October 12, 2017

THE CATCH-22 SITUATION

Unmet Medical Needs



HEMOPHILIA AS UNMET MEDICAL NEED (50'S)

*Heden werden wij verblijd met de geboorte van ons
zoontje en broertje*

CORNELIS

M. SMIT-KROON
J. SMIT
en WILLY

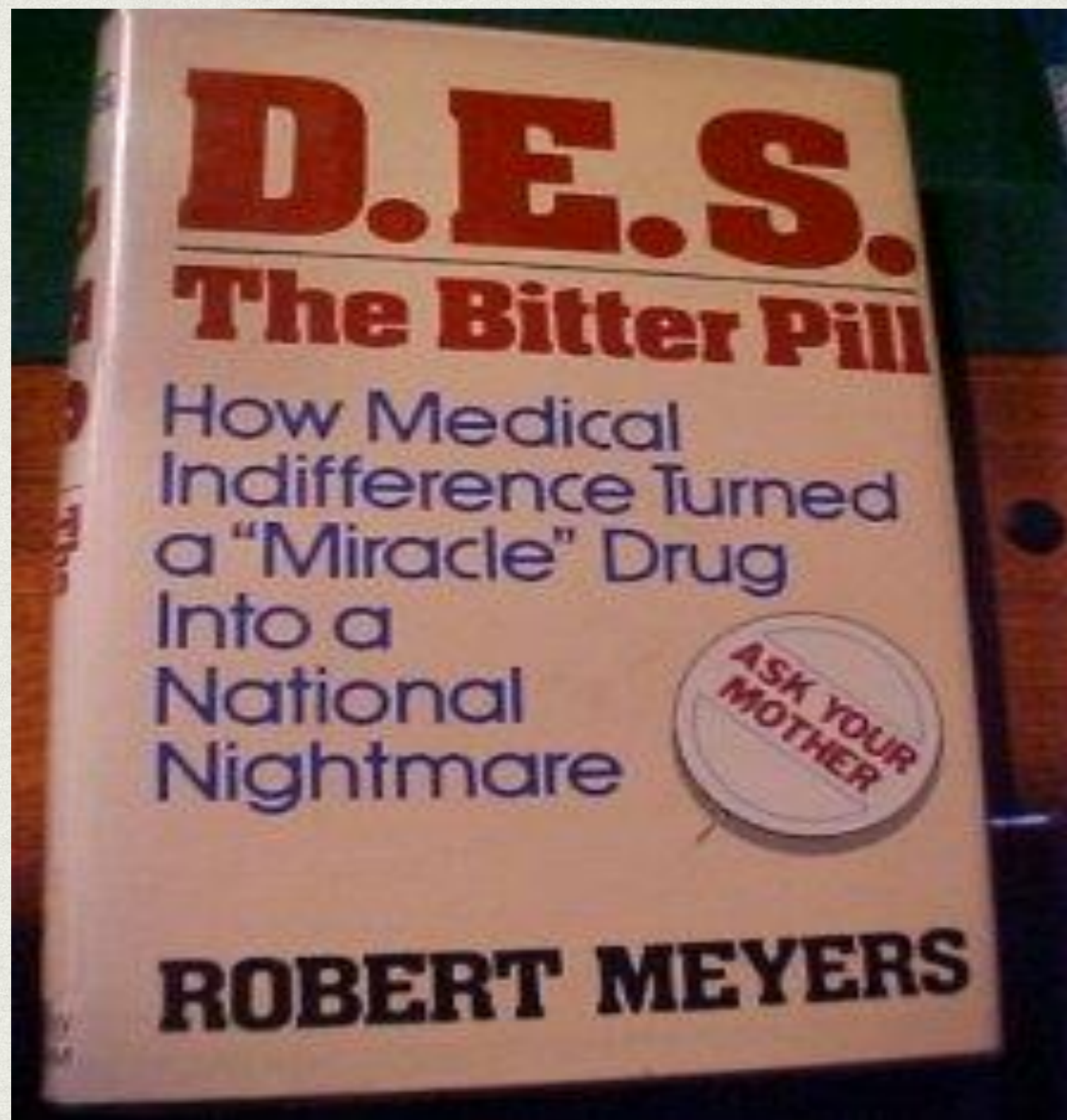


Wij noemen hem KEES

Nieuwe Niedorp,
1 Januari 1951
Laagzijde B 249



RISK IF THERE IS NO TREATMENT AT ALL



What is Declaration of Helsinki?

- Set of ethical principles
- Developed by WMA for medical community – human experimentation
- Followed Nuremberg Code (1947)
- Regarded as cornerstone document of human research ethics
- Included within clinical trial protocols



MEDICAL PROGRESS IN HEMOPHILIA

1965



2015



THE SAME PROGRESS IN

From 'unmet medical needs' → to 'effective treatments'

Hemophilia (70's)

HIV (90's)

HCV (2015)

Consequence: from paediatrics to care for the elderly/AOW

GESCHIEDENIS VAN HEMOFILIE (1971-2015/6)

1972 gestart als studentenproject in Leiden



Door een onzer redacteuren
LEIDEN, 20 sept. — In Nederland zijn ongeveer duizend patiënten die aan hemofilie lijden, de „bloederziekte”. Het is een erfelijke ziekte maar doordat de medische behandeling sedert 1965 sterk verbeterd is, is het sterftecijfer aanmerkelijk gedaald. Hierdoor valt een toeneming van het aantal patiënten te verwachten, althans indien men niet probeert om overbrenging via nakomelingschap in te perken.



Leids Dagblad 1972

Hemophilia in The Netherlands: results of a survey on the medical, genetic and social situation of Dutch hemophiliacs. Acta Medica Scandinavica, 1974

COST-EFFECTIVE STUDIES IN HEMOPHILIA

Reprinted from the **BRITISH MEDICAL JOURNAL**, 28th January 1989, 298, 235-238

MIDDLES

Physical condition, longevity, and social performance of Dutch haemophiliacs, 1972-85

C Smit, F R Rosendaal, I Varekamp, A Bröcker-Vriends, H Van Dijck, Th P B M Suurmeijer, E Briët

Abstract

A study was carried out among haemophiliacs in The Netherlands to evaluate the effect of modern substitution treatment (replacing the missing clotting factors) on medical and social performance. Three questionnaires were sent between 1972 and 1985. The use of prophylactic treatment in the group of patients with severe and moderately severe haemophilia increased from 21% (n=242) in 1972 to 36% (n=559) in 1985. Home treatment programmes increased from 4% to 53%. Overall mortality was 2.1 times higher than in the general male population, which leads to a calculated life expectancy of 66 years compared with 74 years in the general male population. Severe joint impairment was prominent in the older age groups, reflecting insufficient treatment in the past. A sharp decrease in the use of inpatient and outpatient hospital facilities was observed as well as much less absence from school and work.

It is concluded that the high costs of modern substitution treatment are fully justified.

employment. Moreover, these studies concerned single treatment networks so that the conclusions may not be generalised.¹⁻⁶

The aim of our study was to evaluate modern haemophilia treatment in The Netherlands. Therefore, we reviewed the medical and social performance of Dutch haemophiliacs by means of questionnaires sent out in 1972, 1978, and 1985.

Methods

We carried out three postal surveys among Dutch haemophiliacs in 1972, 1978, and 1985. The first was based on a haemophilia questionnaire used by the Children's Orthopedic Hospital in Los Angeles, California.⁷ The questionnaire was prestructured (multiple choice) and had some open questions. The standardised questionnaires covered a broad range of aspects of haemophilia—for example, type and severity, number of bleedings, transfusion treatment, treatment regimens, orthopaedic state, hospital admissions, education, disability and employment, insurance, social relations, genetic counselling, and so on. Many items were repeated in the second and third

HTA & HEMOPHILIA

- *‘Prospective well conducted studies on economic issues in hemophilia care are scarce’*

(ref. Swedish Council on Health Technology Assessment. 2011. SBU-

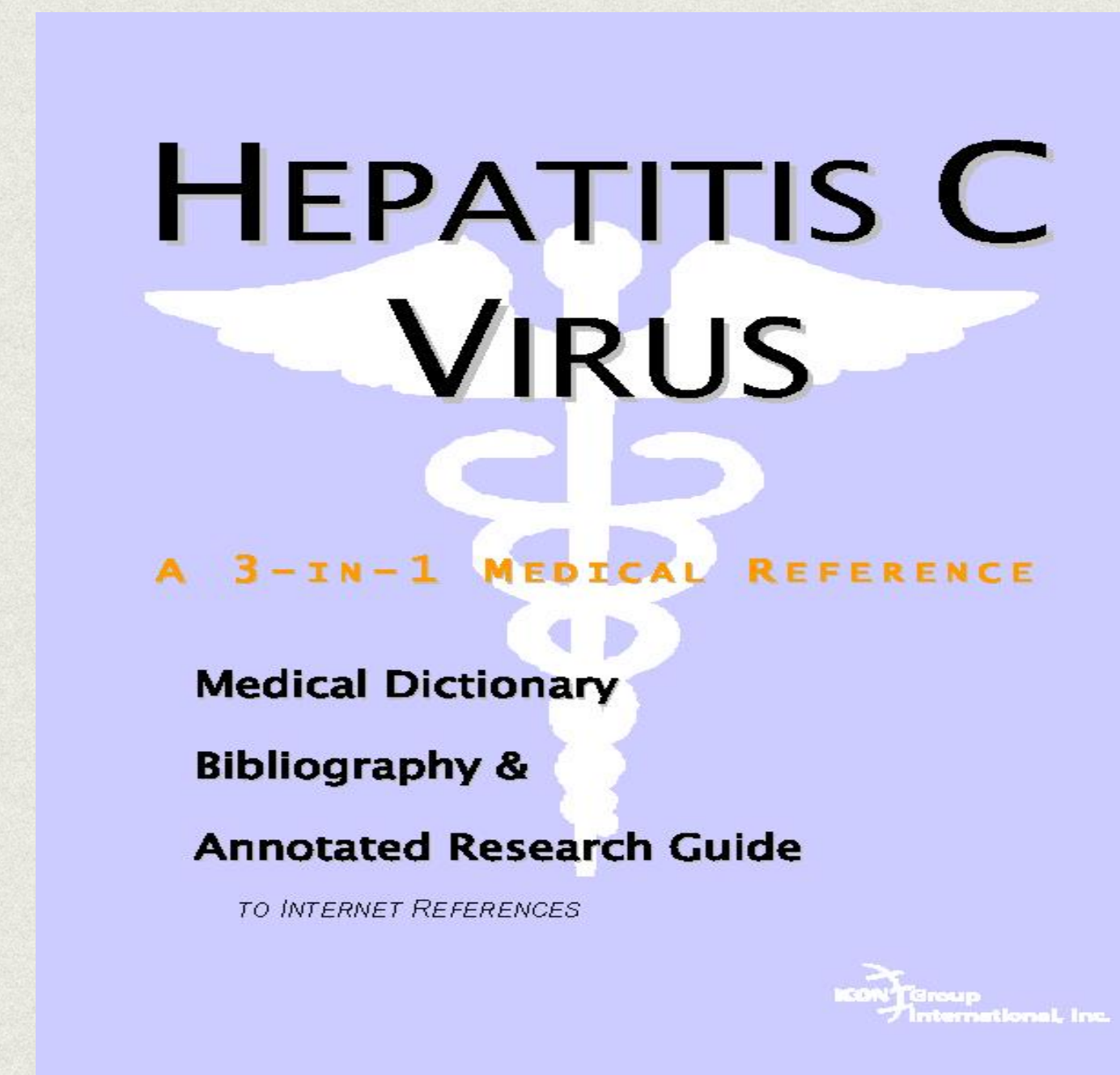
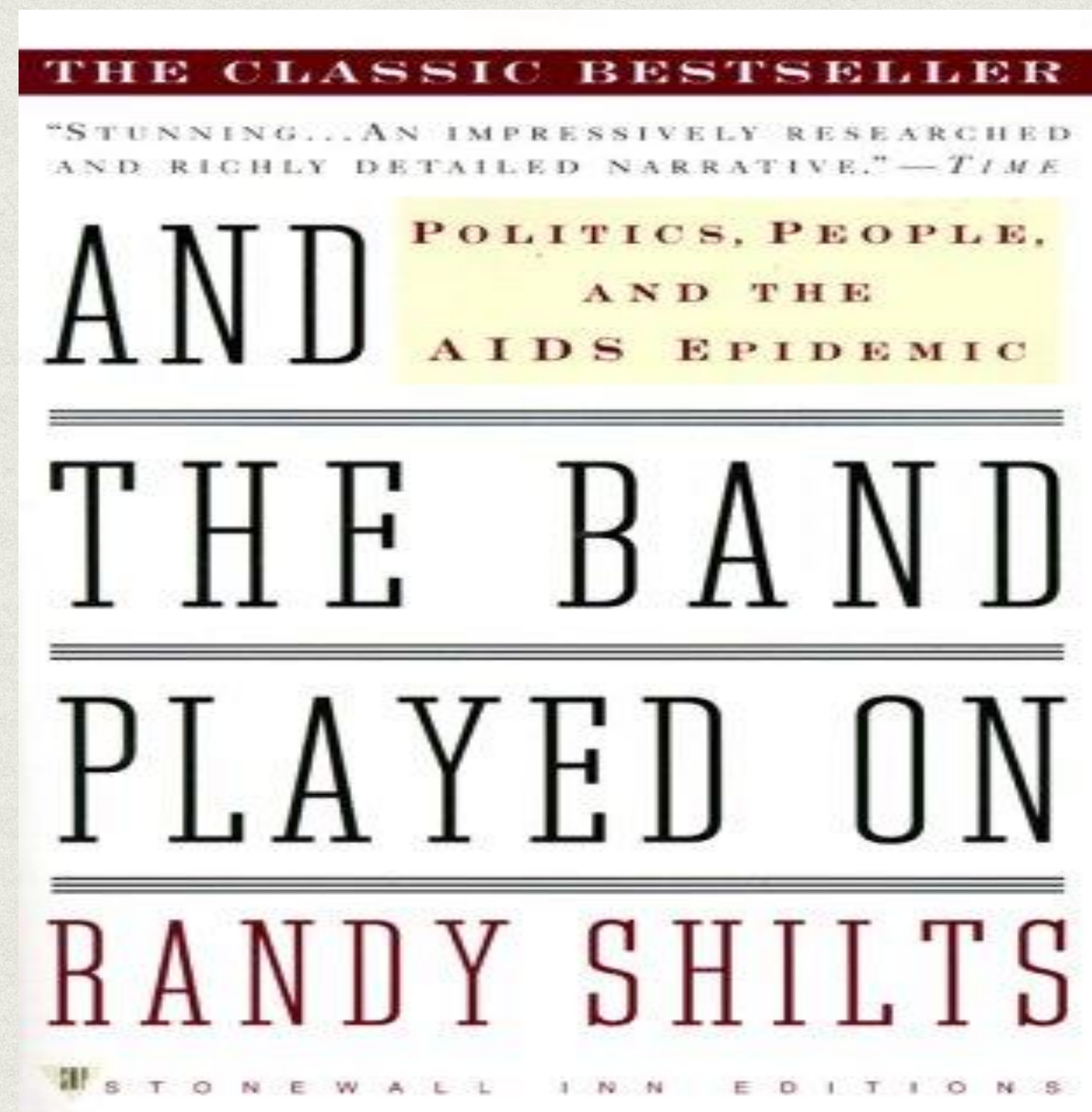
Rapports; Band 208E)

- *‘RCT’s of hemophilia patients is difficult not only because of low patient numbers’.*

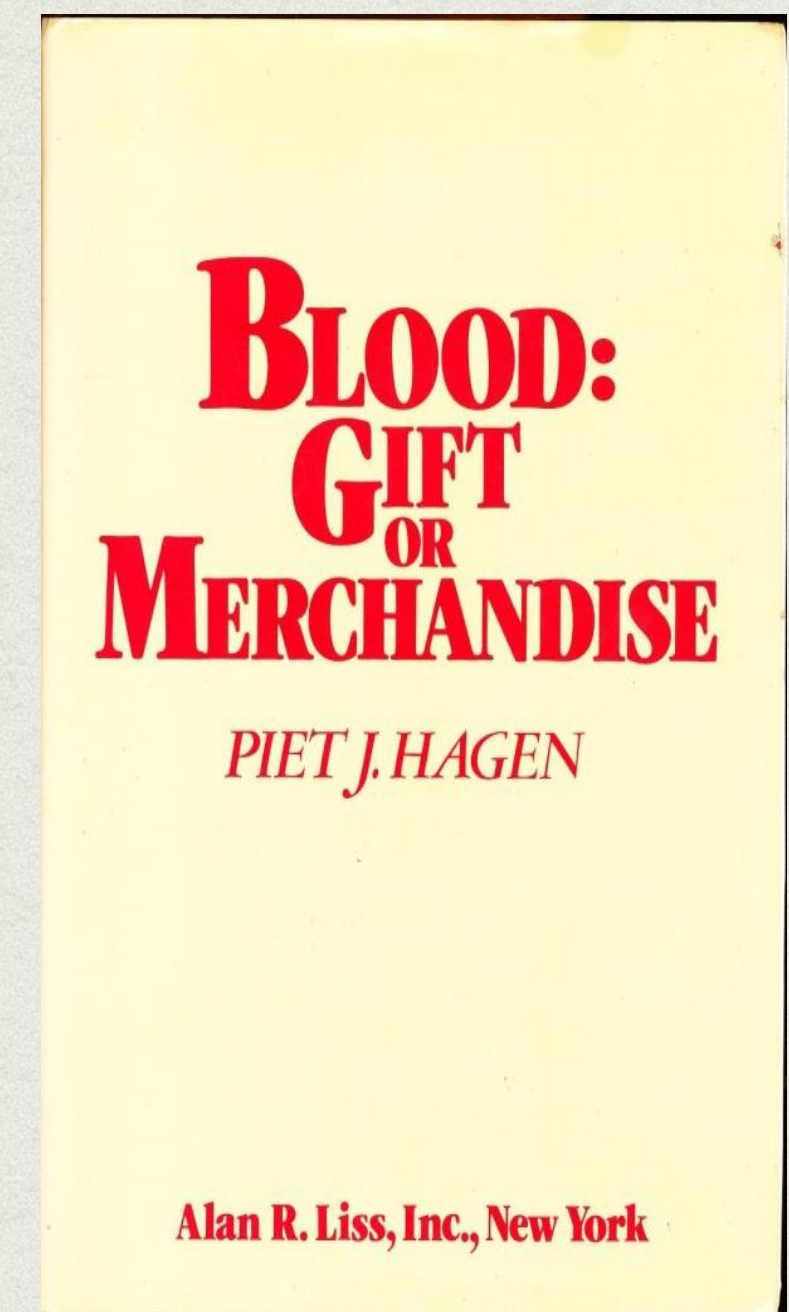
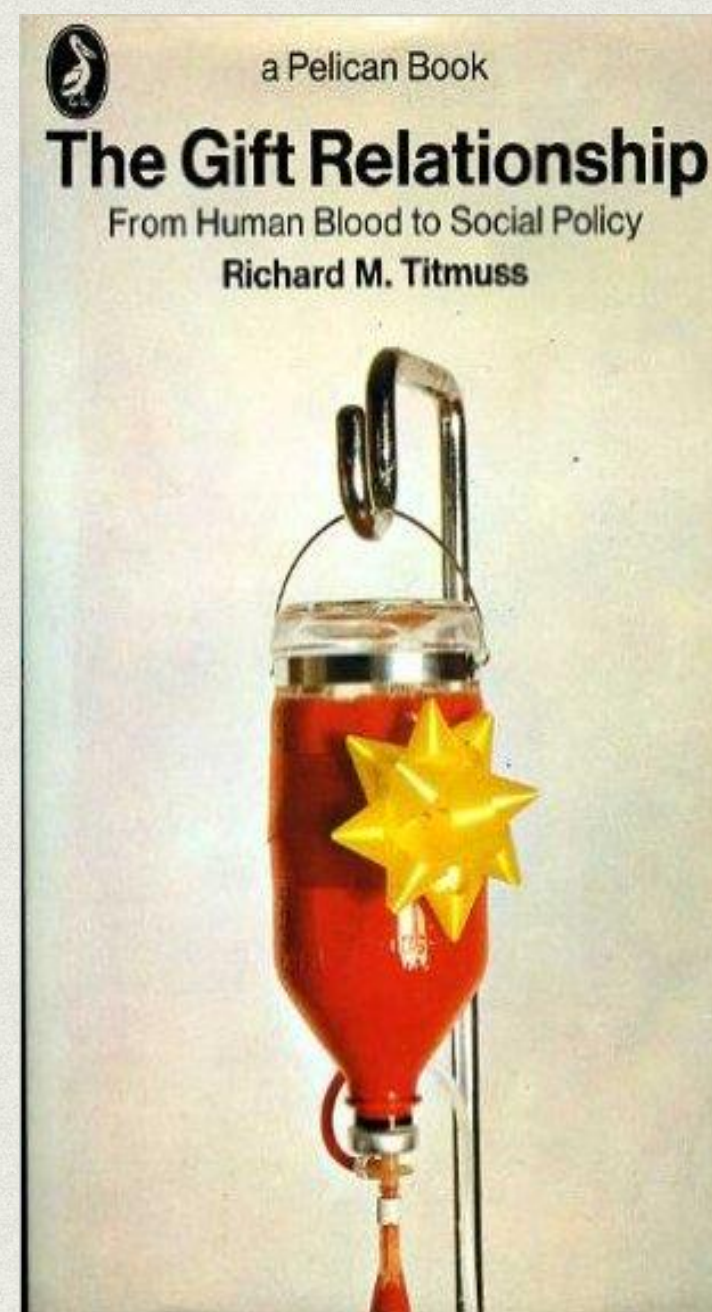
(ref. IQWiG-Berichte – Nr. 305; 2015)



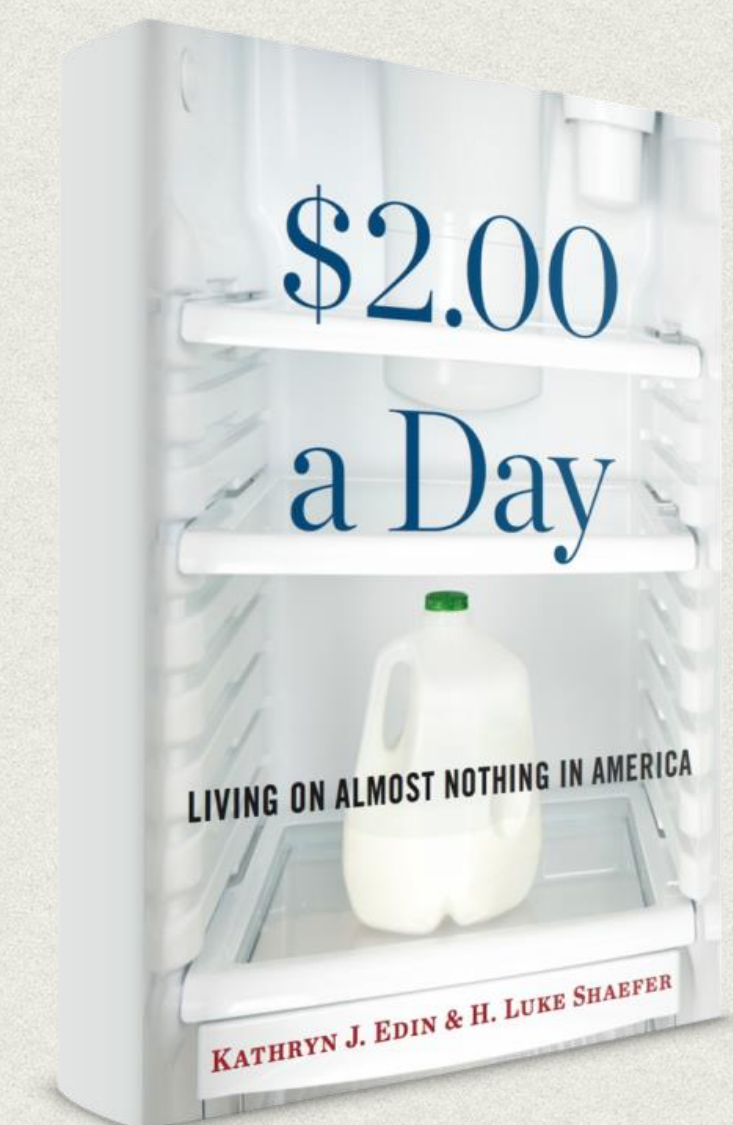
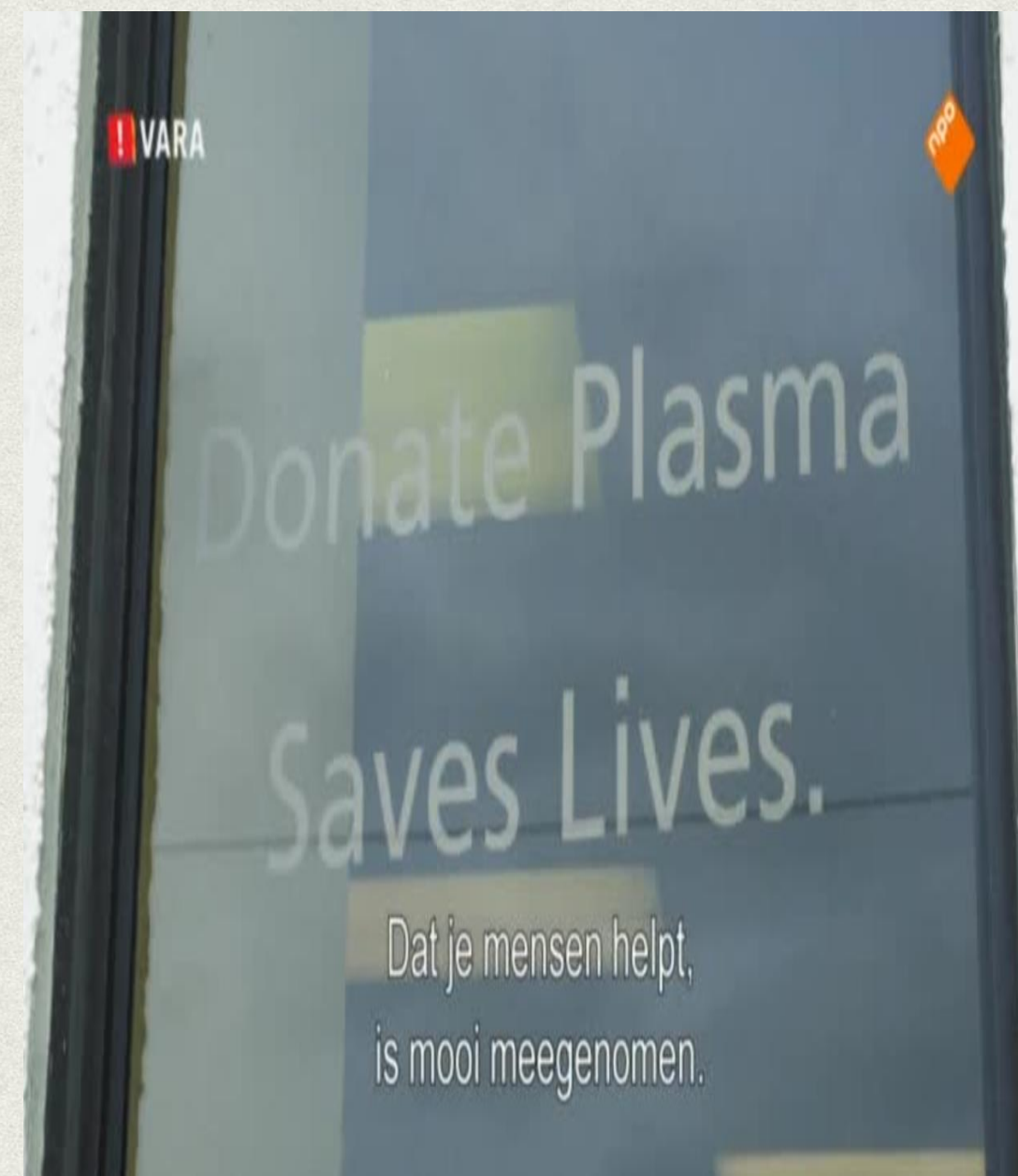
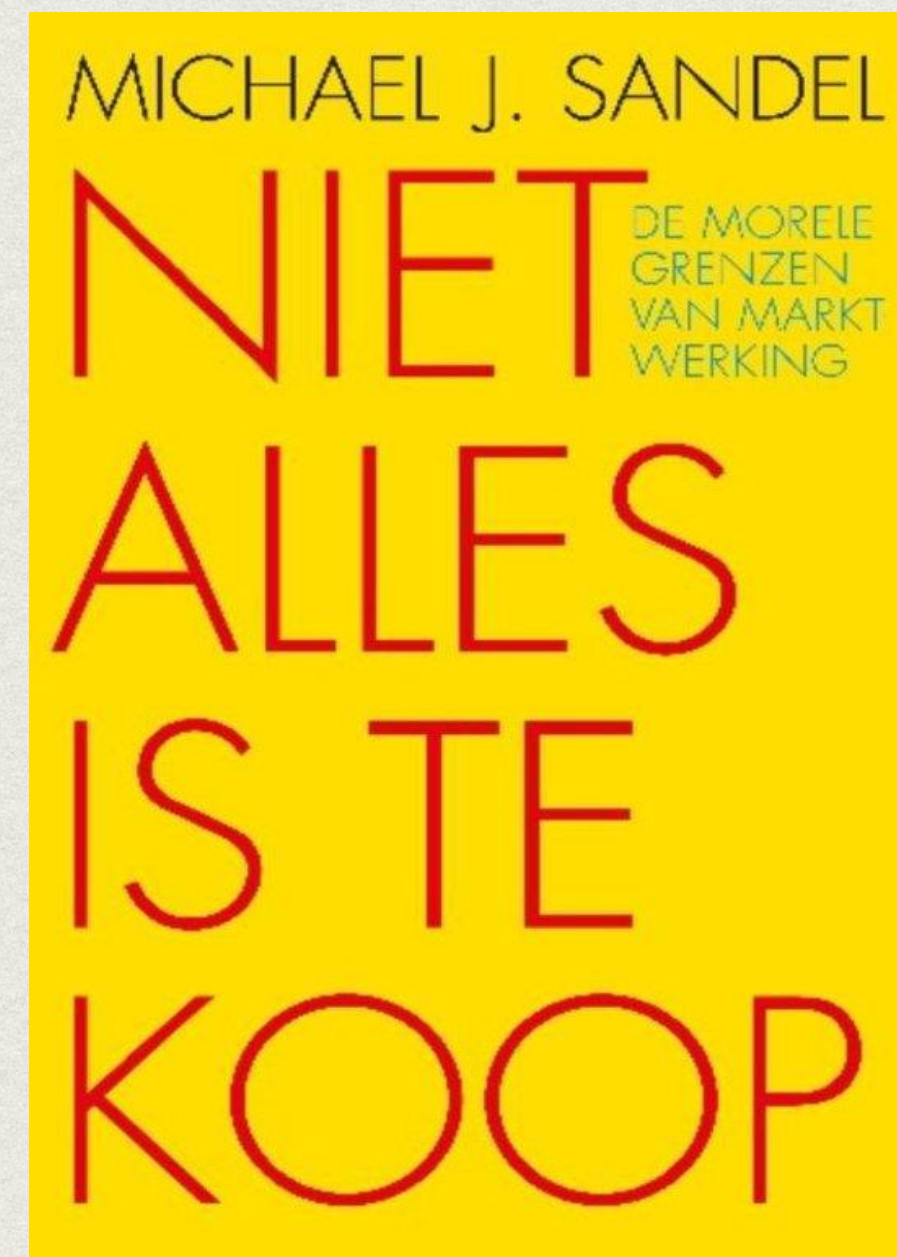
DRAWBACKS IN HEMOPHILIA



SAFETY WARNINGS BEFORE



SAFETY WARNINGS AFTER



BLOOD AS STRATEGIC GOOD

Nederland steeds afhankelijker van buitenlands bloedplasma

Cees Smit en Annemarie de Knecht-van Eekelen

(Pharmaceutisch Weekblad, to be published)

CHICAGO, 1987

- Safer plasmaproducts for hemophiliacs
- Recombinant DNA (biologicals)
- Transgenic animals (Bull 'Herman', rabbits)
- Gene therapy



SIDE-EFFECTS BIOLOGICALS

- Original Article
- **A Randomized Trial of Factor VIII and Neutralizing Antibodies in Hemophilia A**
- Flora Peyvandi, M.D., Ph.D., Pier M. Mannucci, M.D., Isabella Garagiola, Ph.D., Amal El-Beshlawy, M.D., Mohsen Elalfy, M.D., Vijay Ramanan, M.D., Peyman Eshghi, M.D., Suresh Hanagavadi, M.D., Ramabadran Varadarajan, M.D., Mehran Karimi, M.D., Mamta V. Manglani, M.D., Cecil Ross, M.D., Guy Young, M.D., Tulika Seth, M.D., Shashikant Apte, M.D., Dinesh M. Nayak, D.N.B., Elena Santagostino, M.D., Maria Elisa Mancuso, M.D., Adriana C. Sandoval Gonzalez, M.D., Johnny N. Mahlangu, M.Med., Santiago Bonanad Boix, M.D., Monica Cerqueira, M.D., Nadia P. Ewing, M.D., Christoph Male, M.D., Tarek Owaidah, F.R.C.P.A., Veronica Soto Arellano, M.D., Nathan L. Kobrinsky, M.D., Suvankar Majumdar, M.B., Ch.B., Rosario Perez Garrido, M.D., Anupam Sachdeva, M.D., Mindy Simpson, M.D., Mathew Thomas, M.D., Ezio Zanon, M.D., Bulent Antmen, M.D., Kaan Kavakli, M.D., Marilyn J. Manco-Johnson, M.D., Monica Martinez, M.D., Esperanza Marzouka, M.D., Maria G. Mazzucconi, A.P., Daniela Neme, M.D., Angeles Palomo Bravo, M.D., Rogelio Paredes Aguilera, M.D., Alessandra Prezotti, M.D., Klaus Schmitt, M.D., Brian M. Wicklund, M.D., Bulent Zulfikar, M.D., and Frits R. Rosendaal, M.D., Ph.D.
- N Engl J Med 2016; 374:2054-2064 [May 26, 2016](#) DOI: 10.1056/NEJMoa1516437

DISEASE-EXCEEDING ANTIBODIES GROUP

Nog veel vragen over vorming antistoffen bij biologicals

Antistofvorming kan medicijn hinderen in werkzaamheid

Een belangrijke complicatie van de behandeling met biologicals en biosimilars is de vorming van antistoffen die de werking tegengaan. Dit artikel behandelt de belangrijkste uitdagingen. "Voor alle ziekten (uitgezonderd factor VIII) bestaat een gebrek aan goede *assays* die inhibitie van het gebruikte middel in vitro kunnen aantonen."

Auteurs **Anouk Donners, Shermarke Hassan, Karin Rademaker** en **Cees Smit**

In de effecten van antistoffen

Ref: Pharmaceutisch Weekblad 37, 2017

PRICE OF BLOOD/PLASMA

Barrel oil (188 liter) Barrel blood

1988 13 \$

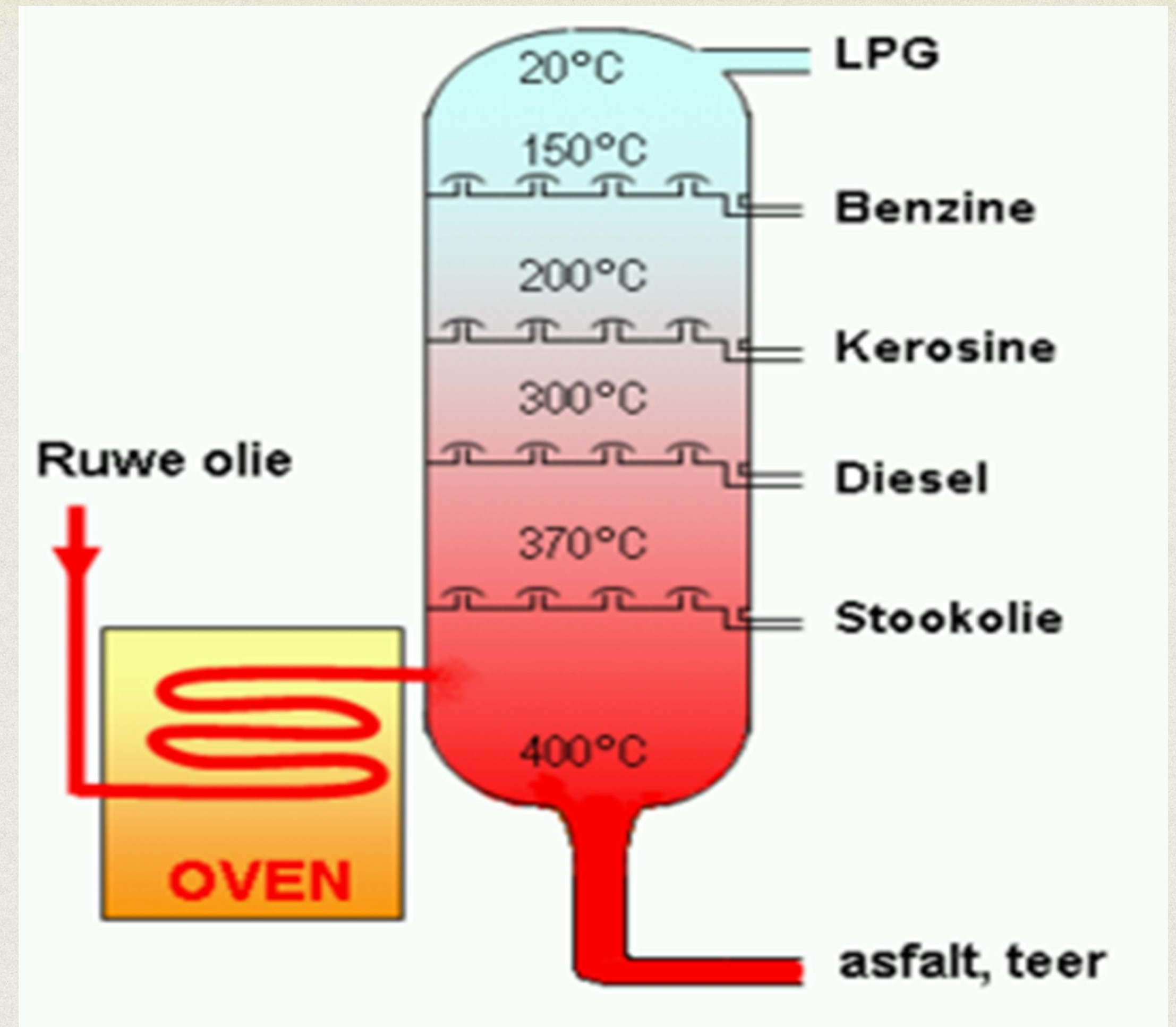
20.000

After refining

42 \$

67.000 \$

(ref.: Chase S, 2012)



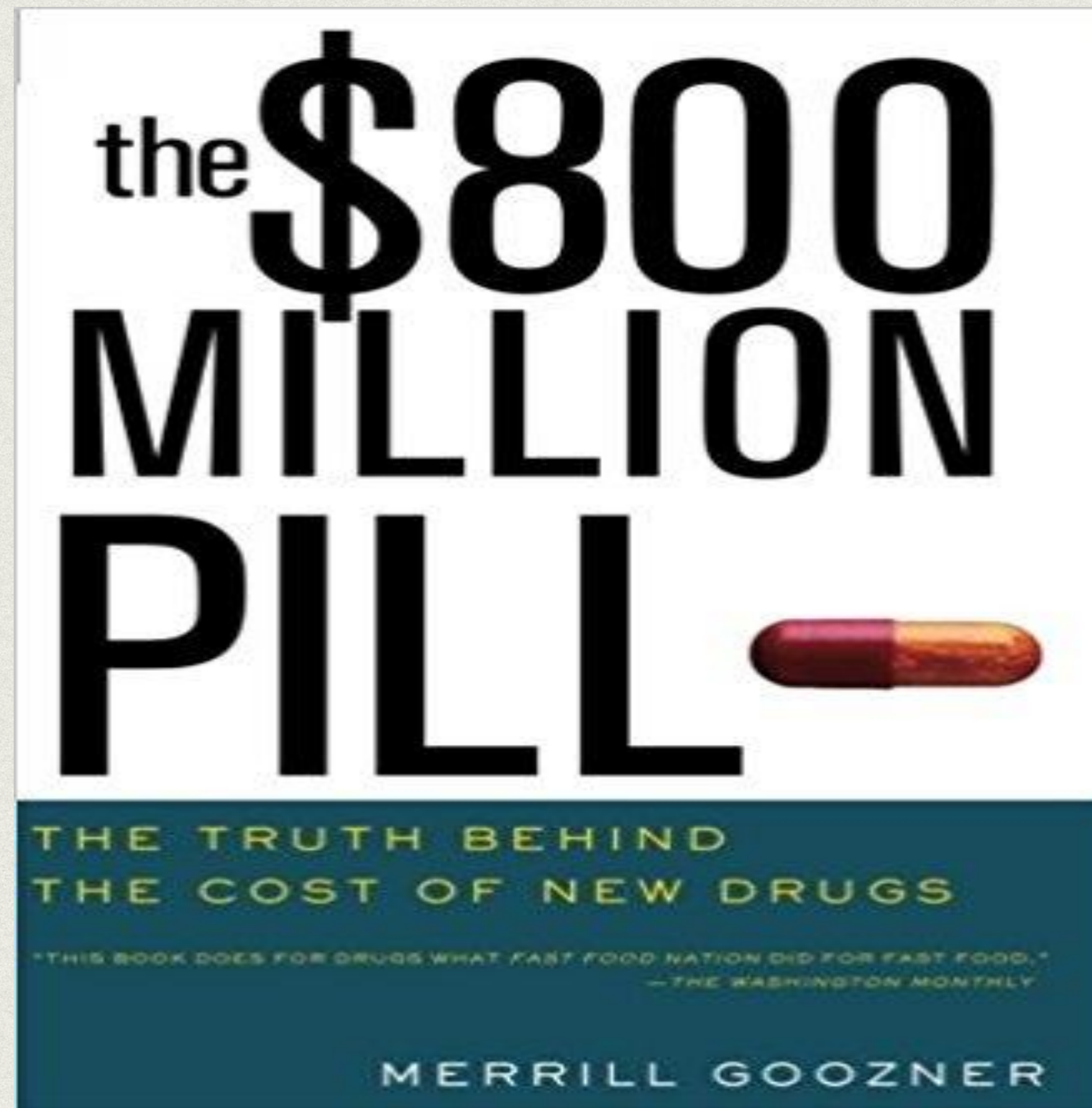
COULD IT BE CHEAPER?

- It did not happen in the past 40 years ('profit'/'not for profit')
- Continued product innovation necessary (viral safety: hiv, hcv, BSE, ebola, Q-fever, hev)
- Replacement of plasmaproducts by rDNA (biologicals, biosimilars: Iran)
- Cheaper technology (who is going to pay for it? Gene therapy)

TENDER HEMOPHILIA PRODUCTS

- 2017: Three Academic Hospitals
- Substantial price reductions for Factor VIII/IX
- Radical swift of the market shares and product choice
- Patients society dissatisfied, free choice of product under pressure
- Questions: Legal procedure? Who is responsible for side-effects?

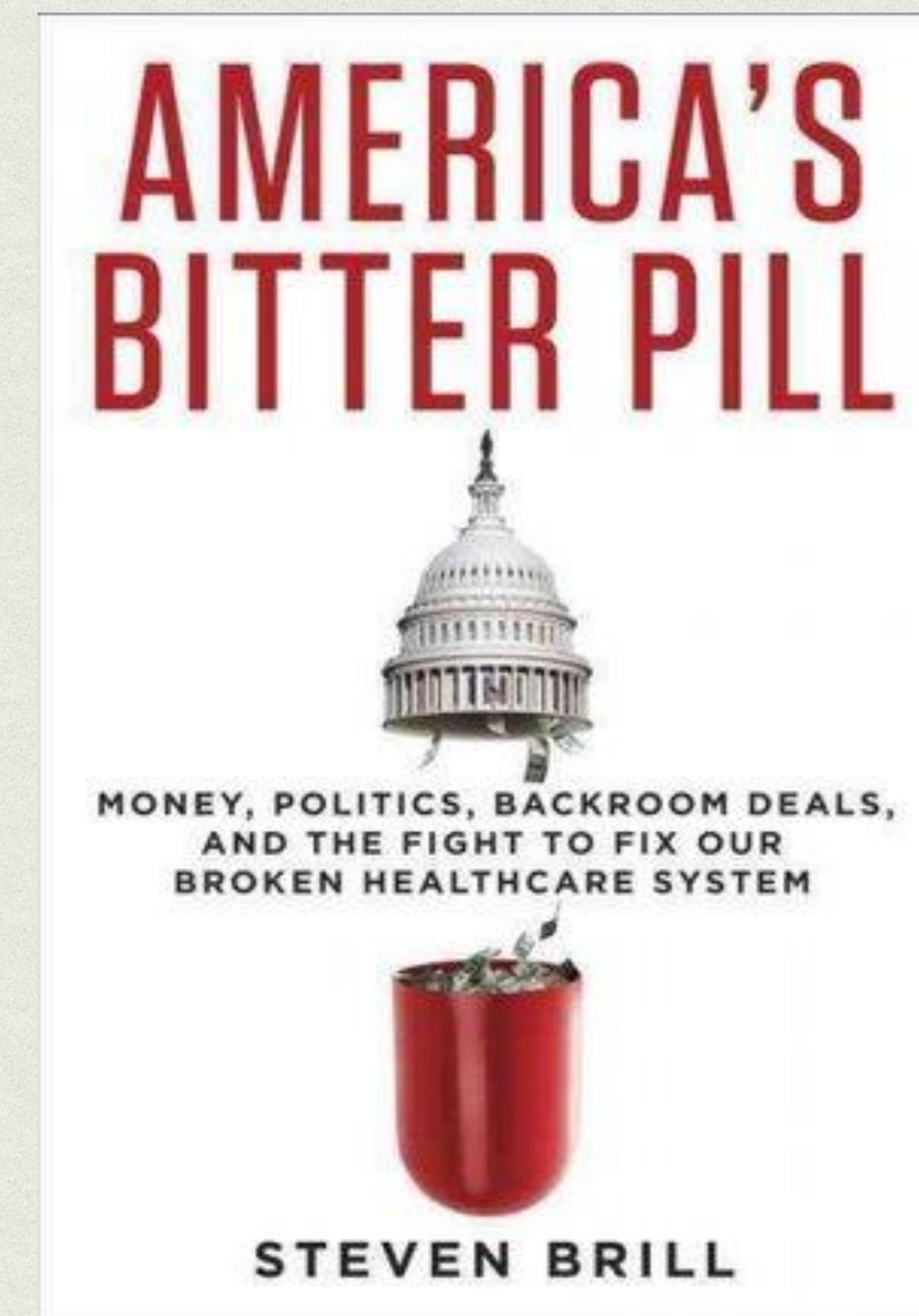
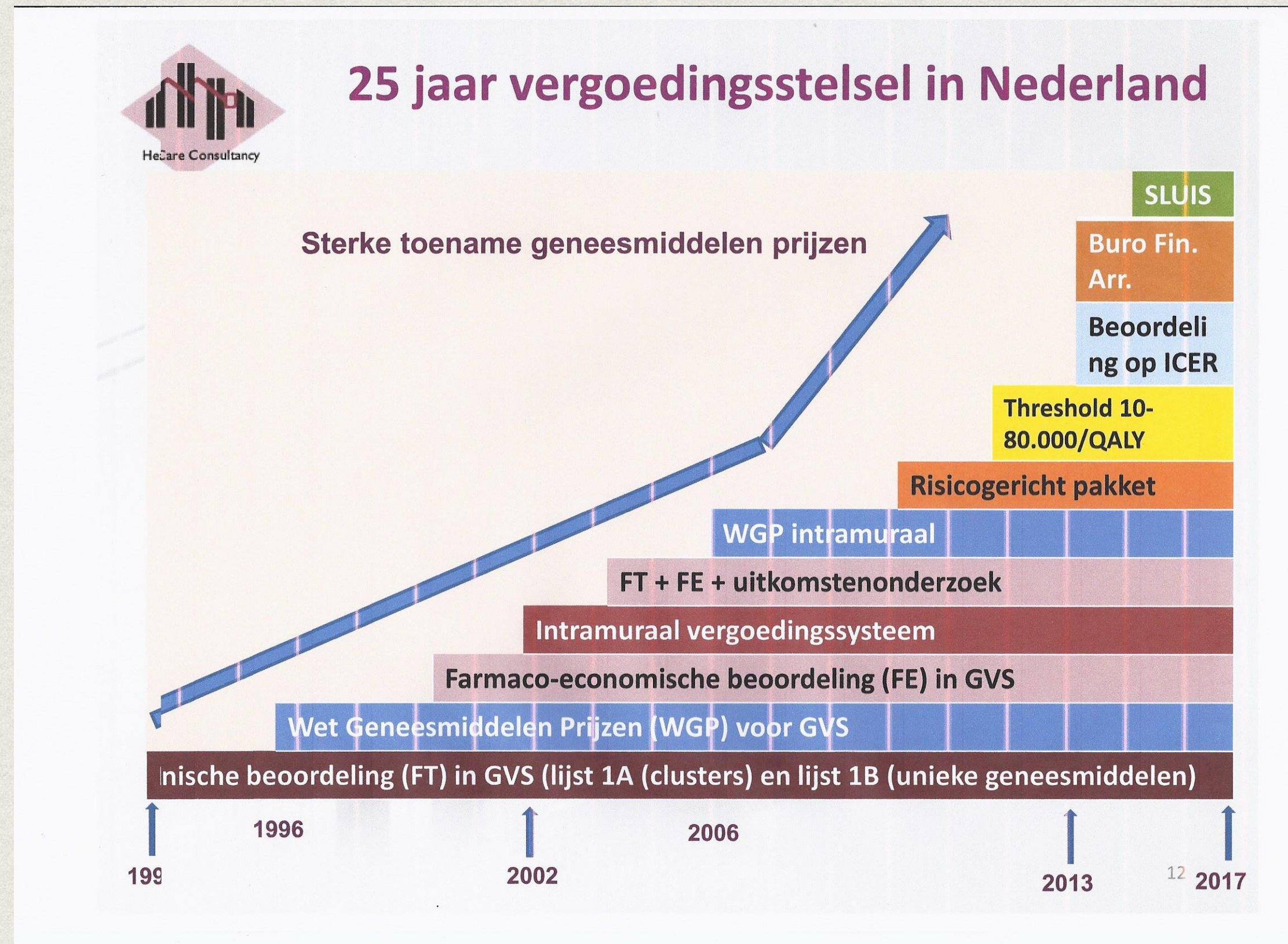
PRICE OF A DRUG ?



PRICE OF A DRUG

- 1/5 Production costs
- 1/5 Capital costs / shareholder value
- 1/5 Clinical Research
- 1/5 Registration procedures
- 1/5 Reimbursement/HTA procedures
- $\approx 3/5$ Can be influenced by EU & Member States ↓

MARJA PRONK (RUG) & STEPHEN BRILL (USA)



MORE INFORMATION

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