Metrology as a driver of economic innovation in Europe

Professor Matt Reed

25th June 2008

Metrology

- The desire to develop methods and apparatus to measure fundamental physical constants
  - A purely scientific endeavour
  - Governmental investment required
  - Requires ingenuity and determination

- How to derive economic benefit for Europe from this source of deep knowledge?
- How to build “wealth & welfare” from the activity?

The march of resolution 1609-2008

The history of science over the centuries can be written in terms of improvements in resolution. From the beginning and all the way up to 1609, when Galileo's telescope first assisted human vision, scientific knowledge consisted of making descriptions and comparisons for events taking place at measurement scales accessible to the human eye, from about 10^{-3} (a tiny speck) and up to 10^{+7} meters (the Milky Way), some 11 orders of magnitude.

Now, 400 years later, scientific descriptions and comparisons take place at scales from 10^{-18} and up to 10^{+25} meters, some 44 orders of magnitude.

That is, from 1609 to 2003, scientific resolution improved an average of about 8 orders of magnitude per century (or 100 million-fold per century) in each of the 4 centuries since Galileo.

Edward Tufte, June 16, 2003 (http://www.edwardtufte.com/)

The same “march of resolution” continues to drive progress in science

Fundamentals of Measurement
***Science* November 2004**

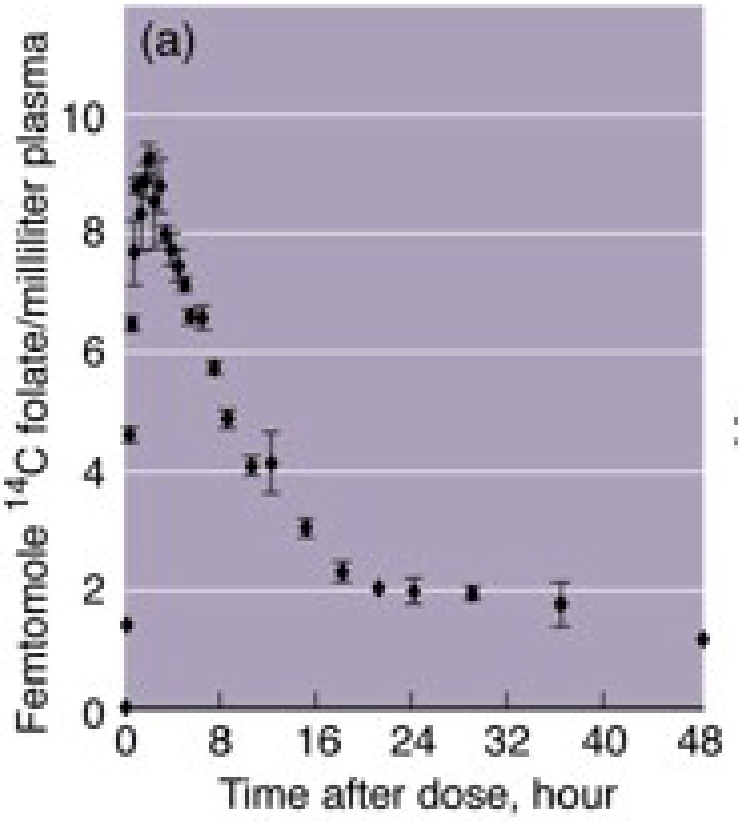
Nature Methods
Launched September 2004

An example of pure metrology coming to market

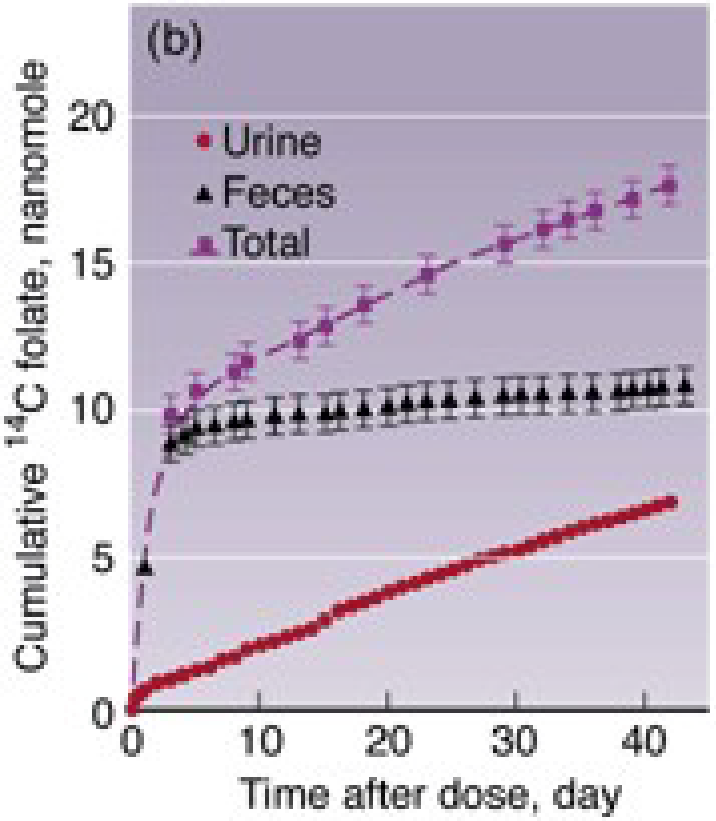
- Accelerator Mass Spectrometry is an exquisitely sensitive measurement method and is close to theoretical limits of how mass spectrometry can be used
  - Can detect zepto- to attomoles of the isotopically labeled compounds in micro- to milligram samples
  - Can also separate isobars (e.g. ^{14}N from ^{14}C)

- Fundamentally measures mass!
- A result of government investments in metrology
  - e.g. Lawrence Livermore (US), CSL (UK)
- Already used for geological aging of rocks
- But…

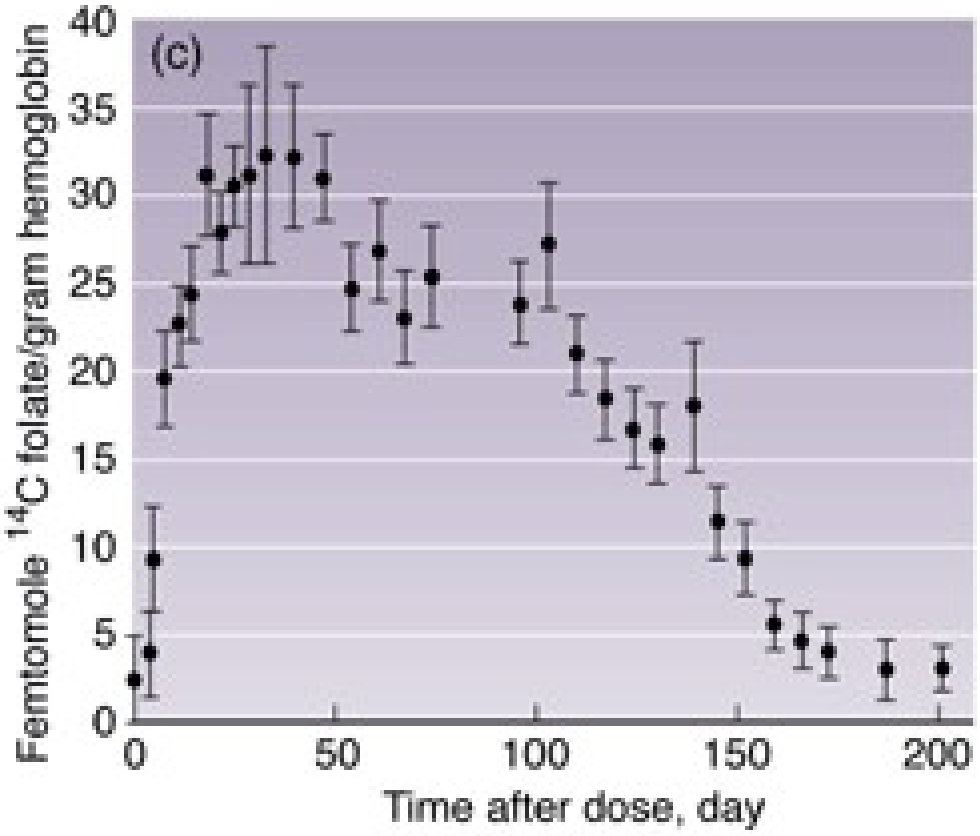
A single 35 microgram dose of C^{14} labeled Folic acid is given to a human.



(a) The tagged folic acid appears very quickly in plasma and tapers off in about 2 days



(b) The eliminated folate was followed for 40 days in urine and feces.



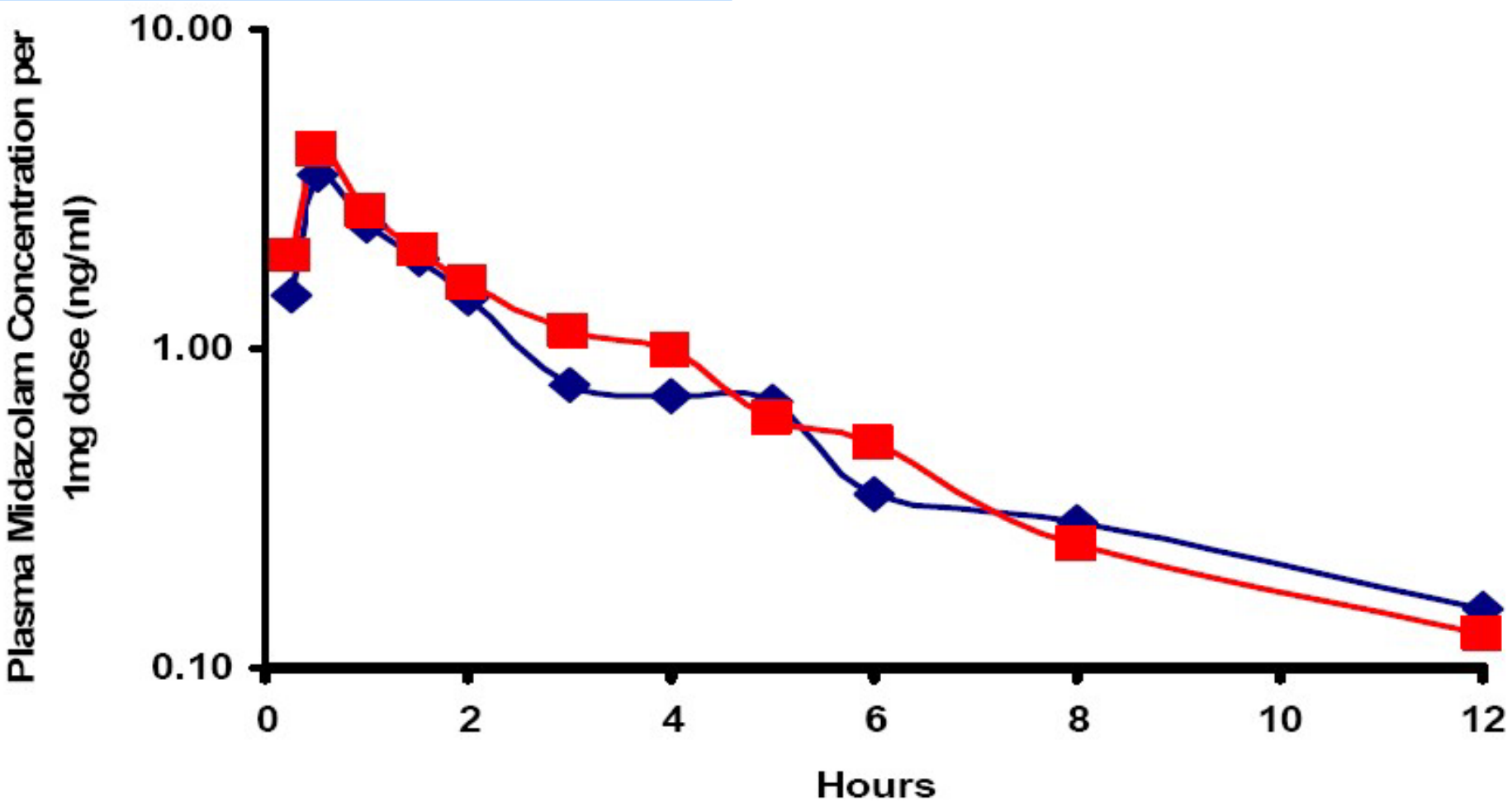
(c) Folate is incorporated into haemoglobin at day 5. The level of folate in haemoglobin peaks at day 30 and disappears after 200 days.

https://www.llnl.gov/str/Knezovich.html

Human micro-dosing (Phase 0 Clinical)

- Avoids using allometric scaling on animal data
- Directly doses a human being at one hundredth of the proposed pharmacological dose [never to exceed 100 micrograms].
- Assume that many of processes controlling human pharmacokinetics are independent of dose level
  - At these doses, the studies are classified as research and do not require GMP manufacture of the drug.

- LC-AMS is one of the best ways to measure these sub-pharmacological doses in plasma, urine, CSF and biopsy.



Semi-log plot of plasma concentration versus time of midazolam following a microdose (■) and a therapeutic dose (◆) both normalised to a 1-milligram dose to allow comparison.

CREAM (Consortium for Resourcing and Evaluating AMS Microdosing) 2005 trial

How could AMS impact bio-medicine?

- November 23rd 1998
  - "The first Accelerator Mass Spectrometer (AMS) in the world to be dedicated to biomedical research is launched officially today by Lord Sainsbury, the Minister for Science at UK Government, Central Science Laboratory at Sand Hutton, York"
  - Operated by a York University spin-out,CBAMS Ltd, CBAMS became Xceleron
- Its big
  - 20-tonne AMS, two years and £2.75 million to build, five million volts to operate.
- To date
  - Xceleron have analysed >200 compounds for 100 clients
  - Worked with GSK, Pfizer, Bristol Myers Squibb, Novartis, Janssen, Corcept, Sanofi-Avantis, Organon, Speedel.
- Set up US subsidiary in 2006
- Xceleron led an EU project EUMAPP 2006-2008

Potential Economic Impact

- Costs of drug development > $800M per registered drug
- Up to 40% of candidate drugs fail to get past Phase 1 due to inappropriate PK parameters

"Currently, preclinical studies can take up to 18 months at a cost of €2.3-3.8M. Microdosing techniques could reduce the time to four to six months and the costs to € 0.26 M per molecule."

Prof Colin Garner, CEO, Xceleron. May 2005

Corcept Therapeutics (Menlo Park, California) announces Promising Results of Human Microdosing Study of selective GR-II Antagonist

May 2008

How to make it happen more often?

- Not easy to force the situation
- Requires metrologists to keep doing great metrology!
- And governments to support that
- Requires other people, those more adept at building economically sustainable businesses, to work with metrologists and spot opportunities
  - In the case of AMS micro-dosing; serial scientific entrepreneurs, York University, UK Government lab working together

- Not every metrology investment will have an immediate economic benefit
- But the “march of resolution” provided by metrology has high potential for numerous innovations in the knowledge economy

Thank You