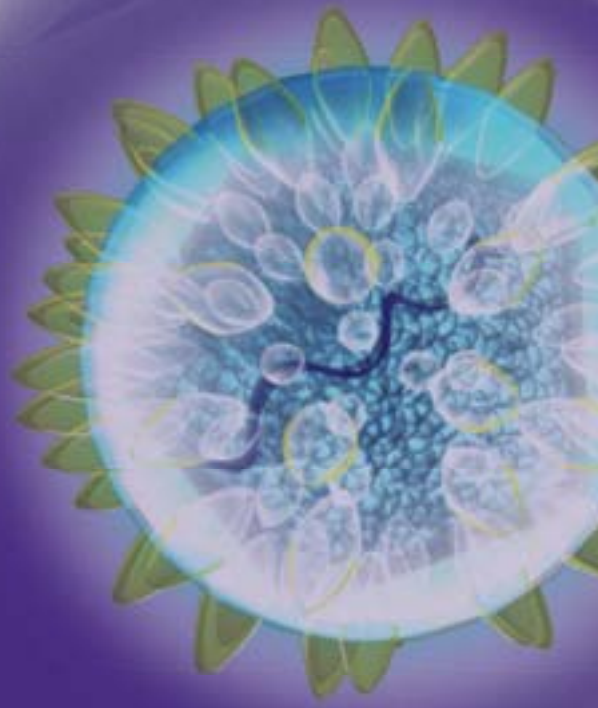
Now What?
The State of Drug Discovery



Derek Lowe

16th SCI/RSC Medicinal Chemistry Symposium

VERTEX

Drug R&D These Days

A festival of fun, right?

You all know the drill: more money going in, and not enough approvals coming out.

Thus the plunge into cost-cutting and into headless-poultry mode in general. . .

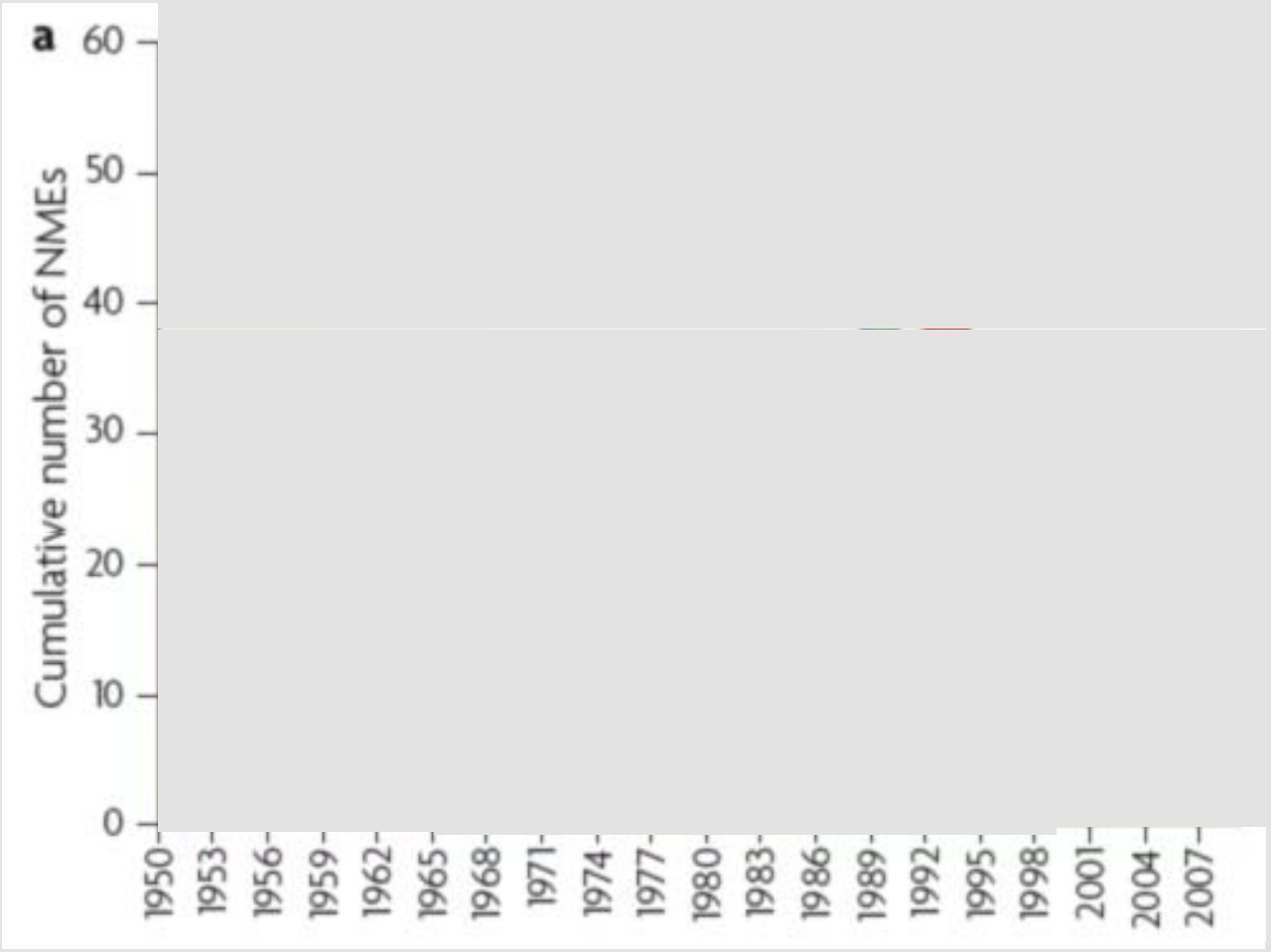
“If something can’t go on, it won’t”: Herbert Stein

The Rate of Drug Discovery

Weirdly linear, actually

Note that the 1970s and 80s are plausible candidates for being the “good old days”.

Of course, the problem is the amount of money needed to keep those lines up. . .



Munos, *Nat. Rev. Drug Disc.* **8**, 959 (2009)

Analogies to Pharma

Good ones and bad ones

The Hollywood analogy - closest one? Spend money up front to try for a hit, then spend more to advertise and distribute it.

But Hollywood has no FDA. And no one will sue if a movie isn't entertaining enough, or gives them a headache.

Wildcat oil exploration - pretty close, considering how rare it is to find a really worthwhile oil field. And it gets harder over time, too. . .

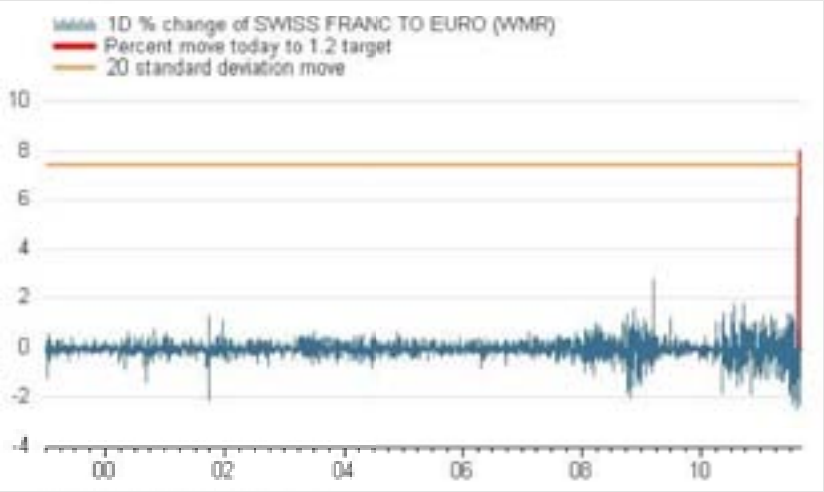
But oil is fungible, and it has no patent expirations.

Drug Discovery vs. High Finance

Lessons from economics

The usual financial practice: going short on volatility and risk.

This works well most of the time, but every so often it blows up spectacularly (*circumspice*)



A 20-standard-deviation event - which in a world of Gaussian risks would be impossible. . .

Cowen, *The American Interest,* **Jan-Feb 2001**

We Are Wall Street's Opposite

Compare and contrast

R&D is forced to do the opposite: we go long on risk
(which is why we argue with the business/financial folks)

And this works the opposite way: it fails most of the time, but every so often it works spectacularly

Note also: Wall St. tries to unload its catastrophic losses onto the public ("Heads I win, tails you lose"

But we have to eat our failures (or pass the costs on to the paying customers as best we can)

The Great Stagnation

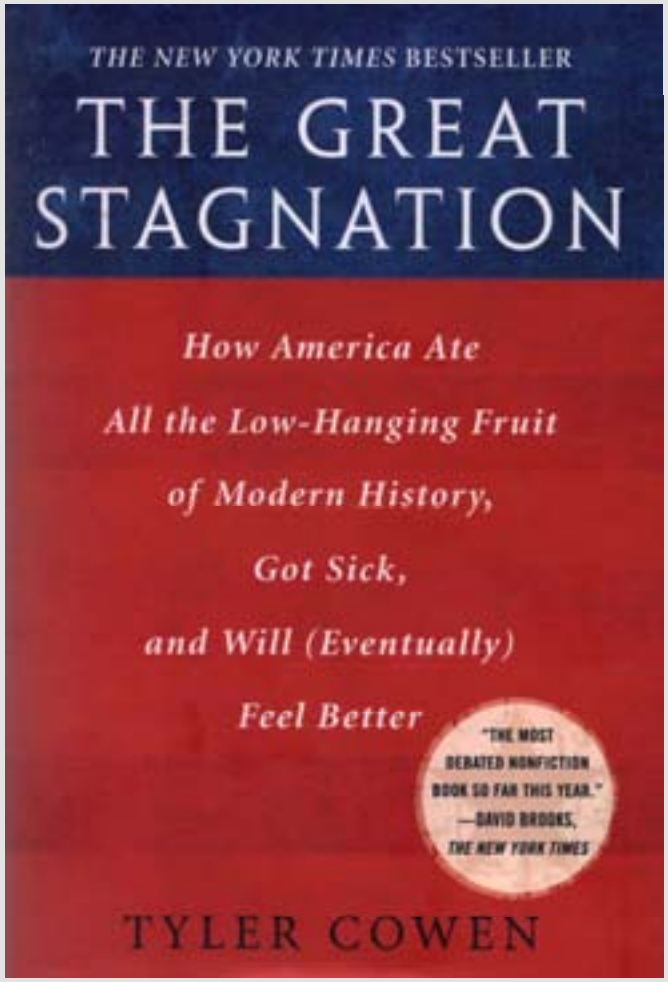
Economist Tyler Cowen's take on recent history

Cowen's low-hanging US fruit:

Free land to expand in

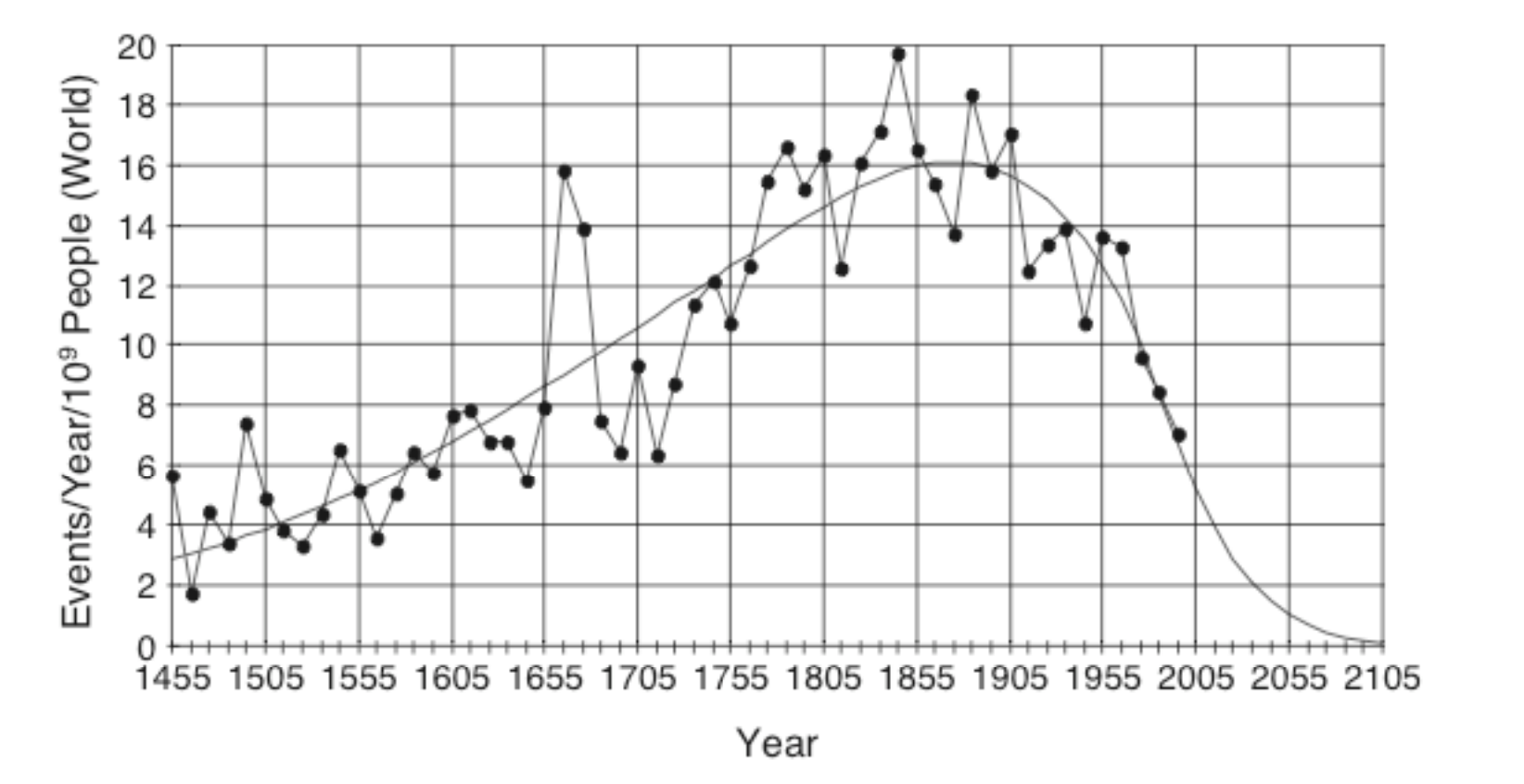
Big gains from educating a population for the first time

More big gains from first use of electricity, fossil fuels, and other key technologies



Innovation Over the Centuries

Did we peak in the *1800s*?



Huebner, *Tech. Forecasting Soc. Change* **72**, 980 (2005)

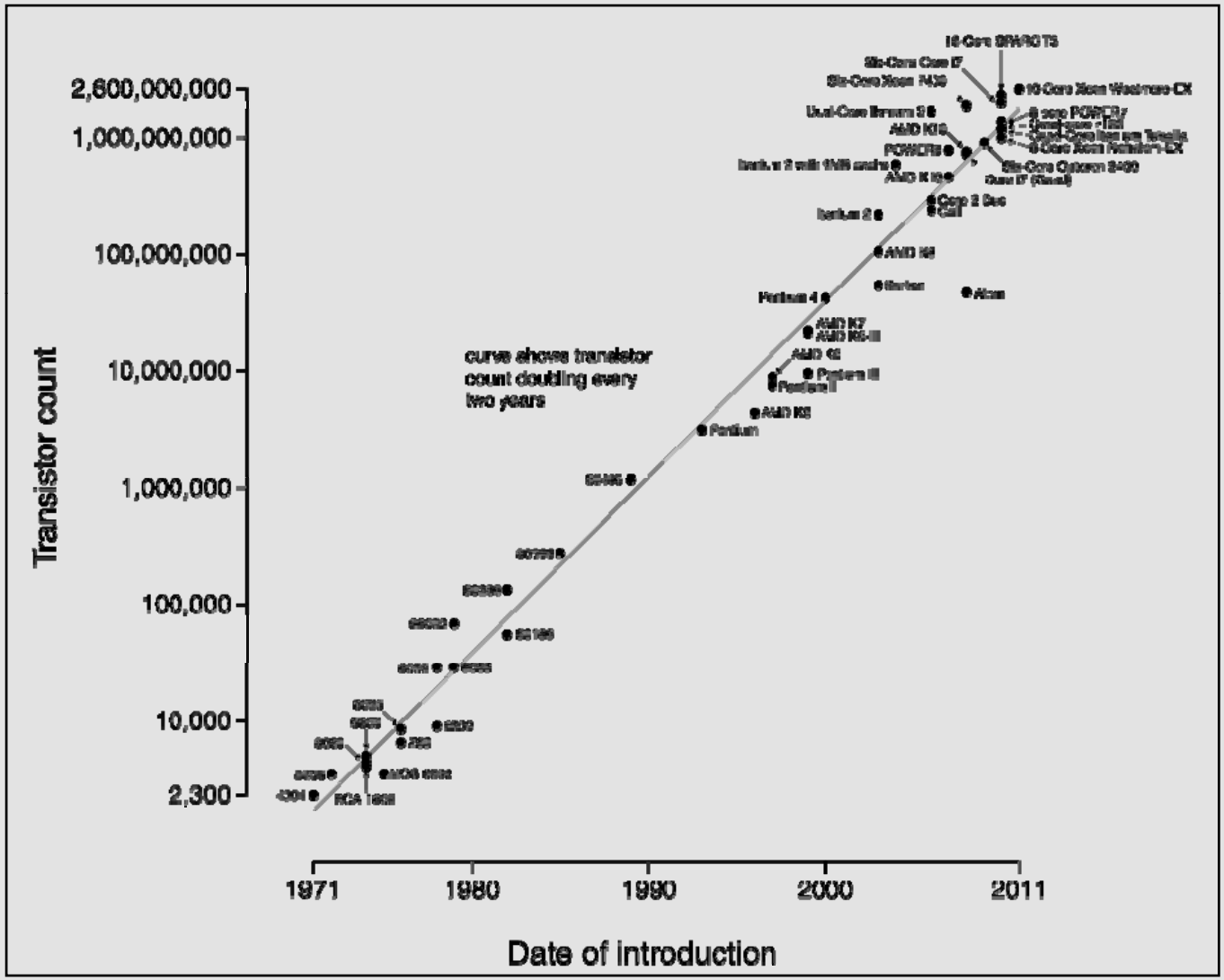
But What About Moore's Law?

Won't it save us?

Now here's some low-hanging fruit for you!

Moore's Law helps you the most if your rate-limiting step is the number-crunching.

Ours is *understanding* what the numbers are telling us. . .



The Great Stagnation in Pharma?

What was our low-hanging fruit, then?

Accumulated natural product wisdom, for one thing

Fundamental discoveries in **PK and tox**

The easier drug targets and mechanisms

Nonresistant infectious disease organisms

Stagnant Parallels

Between drugs and the economy

Cowen: “We thought we were richer than we were”

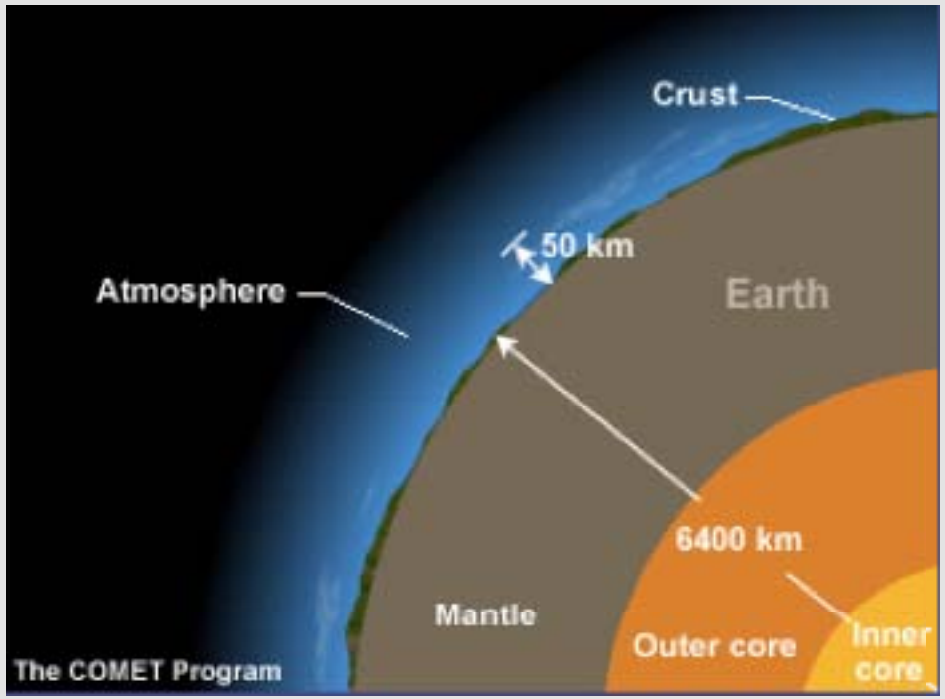
Modified for Pharma: “We thought we were *smarter* than we were”

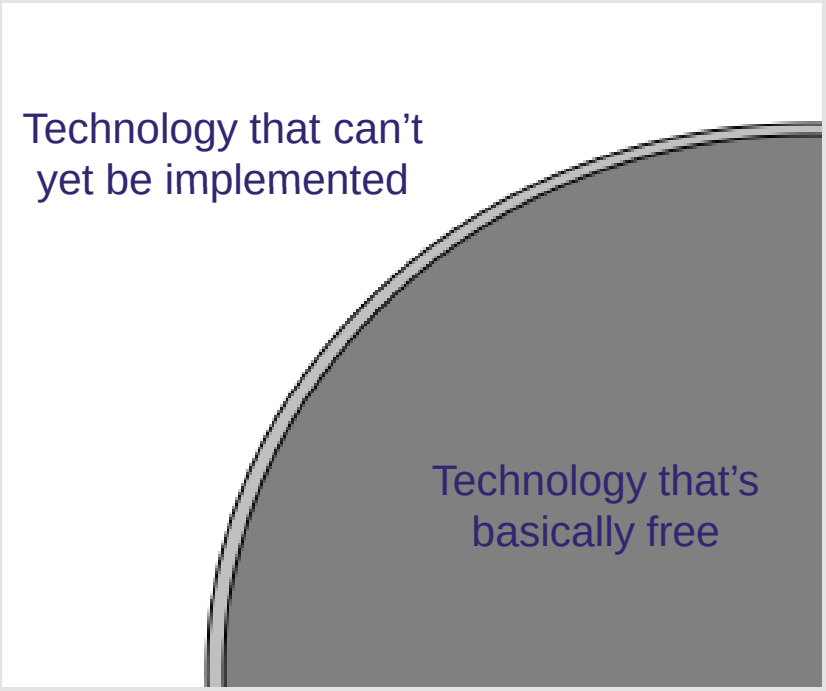
Cowen: “We’ve been making plans. . .as if we would have ongoing productivity growth of 3% or more. . .”

For Pharma: We’ve been making plans as if we would be able to keep discovering drugs at our peak rate.

Another Way to Look at Our Business

Neal Stephenson's "Technosphere"



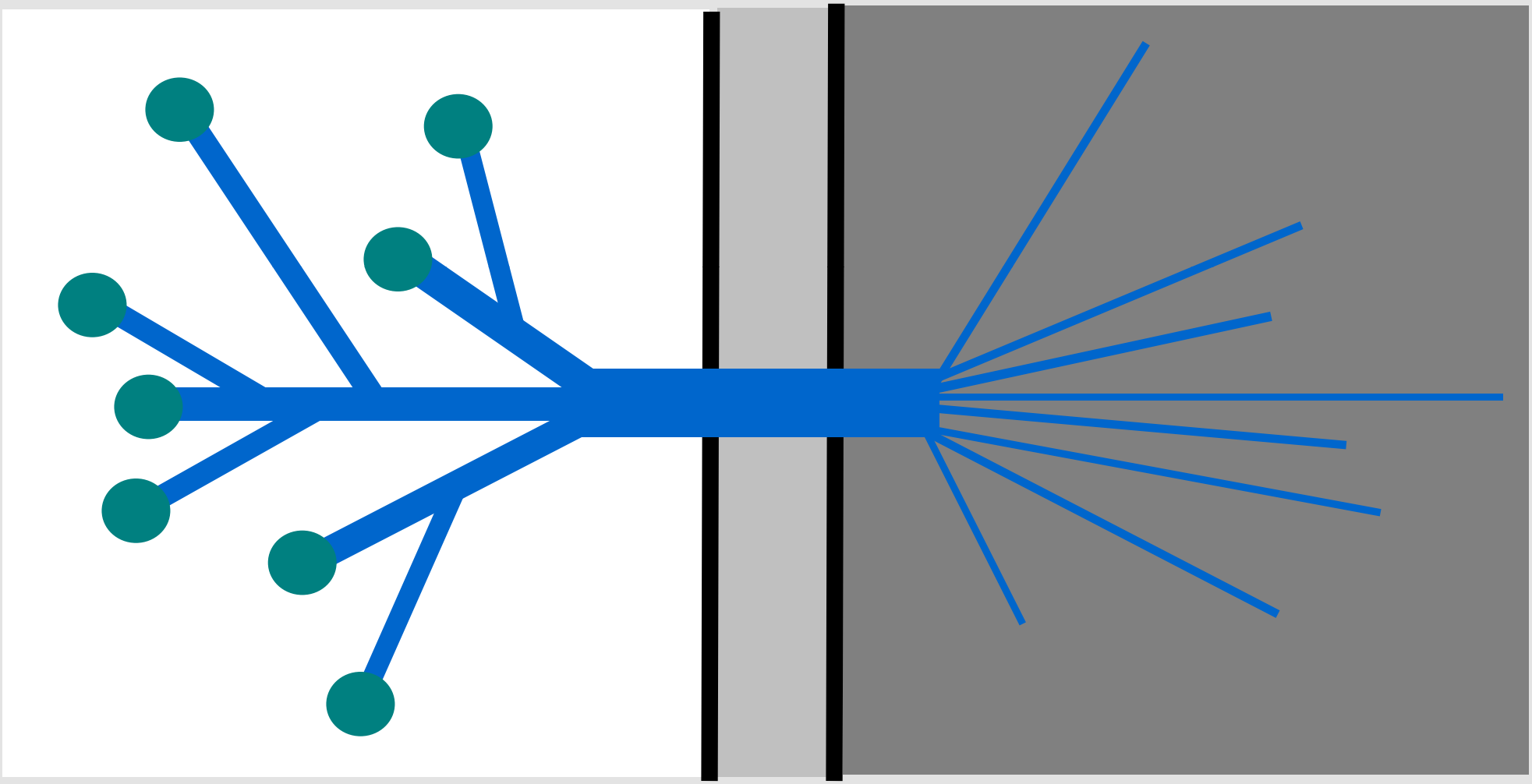


Technology that can be sold for a profit

Stephenson, *"In the Beginning Was the Command Line", 1999*

Surviving in the Middle

Gradients are your friends



What Kind of Creature?

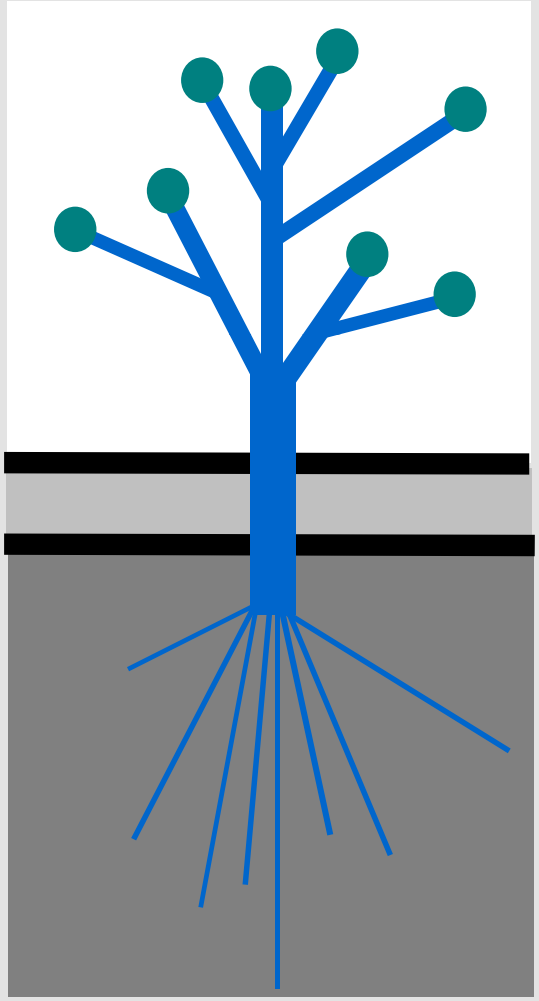
Or what kind of organization?

It's a tree.

In the biosphere: oxygen, sunlight, CO_2 on one side - water, nitrogen, and phosphorus on the other.

In the technosphere: speculative (expensive) possibilities on one side - and established (cheap) technologies on the other.

Living creatures survive by moving goods across spatial gradients. R&D survives by moving them across time.



Temporal Arbitrage

A common technology business model

Financial arbitrage is often **spatial**: prices for the same goods vary slightly in different markets (and can be exploited)

Patent lifetimes mean that we have to take advantage of **temporal** arbitrage: the prices will always vary with time.

"*Temporal arbitrage. . . hinges on the arbitrageur knowing what technologies people will pay money for next year, and how soon afterwards those same technologies will become free.*"

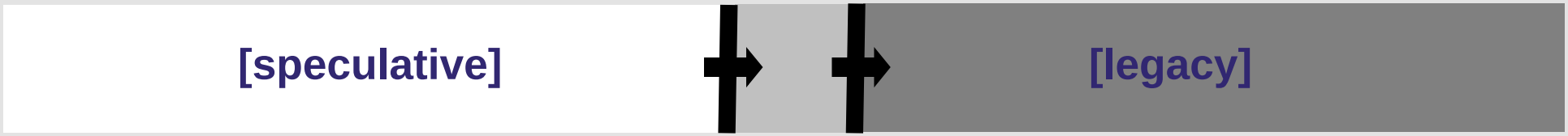
Neal Stephenson, *"In the Beginning Was the Command Line",* 1999

What Does This Tell Us?

The Great Stagnation, via physical chemistry

Not enough out here that's ready to become real?

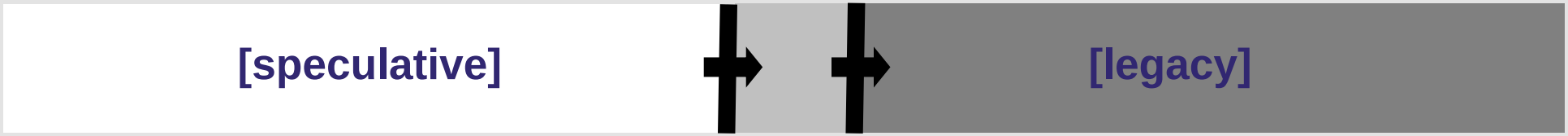
Too much piled up here to move against the gradient?



Keep in mind, our legacy technologies don't go away very easily (from aspirin all the way to Lipitor)

Now Look at the Kinetics

Two important rate constants



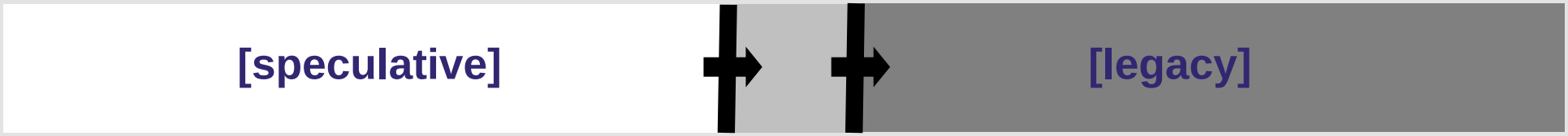
$k_{inventive}$ $k_{generic}$

Has the rate decreased at which we can realize new technology?

Or has the rate increased at which technology moves into the low-priced regime?

All Our Strategies in Terms of Kinetics

Speeding up or slowing down



$k_{inventive}$ $k_{generic}$

Things that are (or were) supposed to **increase $k_{inventive}$**:

Genomics (and other -omics). Combichem. Modeling. Fragments. Biomarkers.

Rearranging R&D departments, mergers and acquisitions

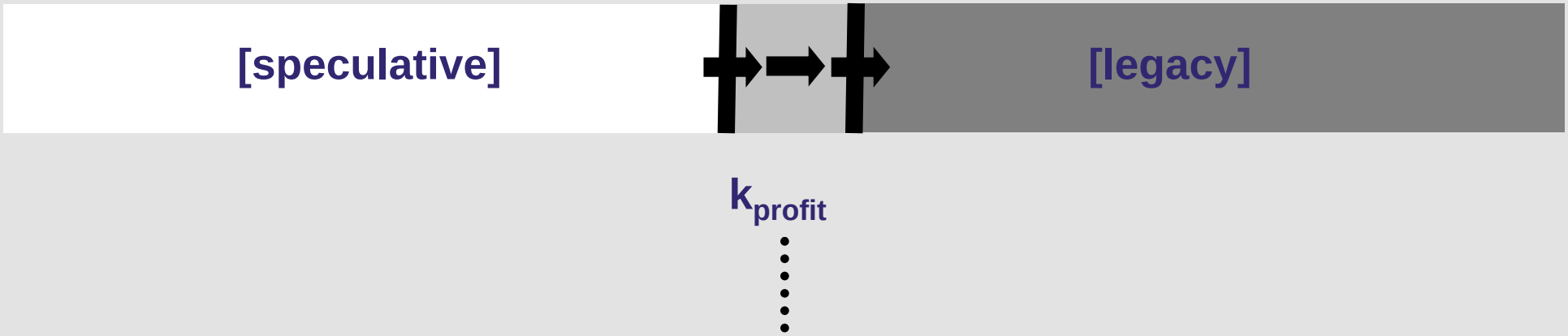
Things that are supposed to **decrease $k_{generic}$**:

Follow-on drugs. Biologics. Patent extensions.

Paying generic firms to go away

One More Rate Constant

For one whole side of the business



While things are in the profitable zone, all of Sales and Marketing is trying to increase the $ / unit time rate.

So, What About These $k_{inventive}$ Strategies?

The business-focused ones aren't new

Flat organizations, competing internal units, mergers (and spinoffs), centralization (and decentralization). . .

See Ecclesiastes 1:9

"The thing that hath been, it is that which shall be; and that which is done is that which shall be done: and there is no new thing under the sun."

An Example From Pfizer

(Not that they're alone)

"Drug designers" as opposed to those who just synthesize the molecules. . .hmmm. . .

Frederick W. Taylor, originator of "Taylorism", the first major scientific management fad.

"One of Taylor's most controversial proposals was that labor and analysis should be strictly divided. The boss plans, and the hired man executes. Workers who don't need to think ahead can go faster, while observant managers benefit from unfettered clarity. . ."

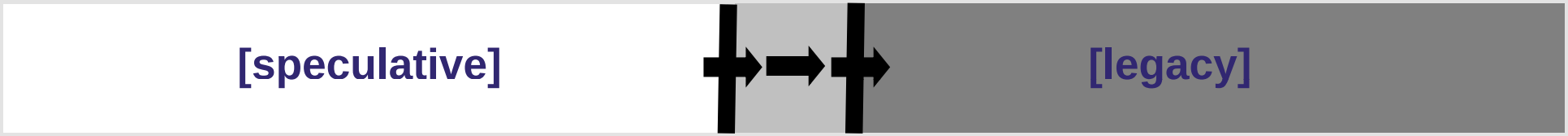
Gary Wolf, *Wired,* September 2007

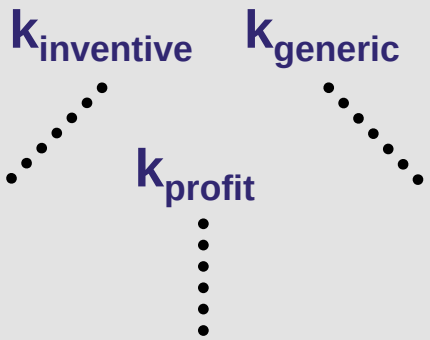
So, What to Do?

Five interventions

Plenty of neat ideas out there; doesn't seem to be a shortage of dreams and wish lists.

We're not going to be able to make this go away: old drugs are here to stay.





Probably still our best shot. But how do we do that?

A rear-guard action at best. Patent terms are not going to get longer

And these strategies are why everyone hates us.

. .

Reasons for Optimism

Take ‘em where you can find ‘em

Remember that Moore’s law slide? Turn it around: it means that we’re probably *not* running up against the laws of physics

Our problems are intellectual, and should admit of intellectual solutions

Perversely, it’s because our tools lack so much that we can improve

If we move from 9/10 failures to 8/10, we will double the number of drugs that make it through

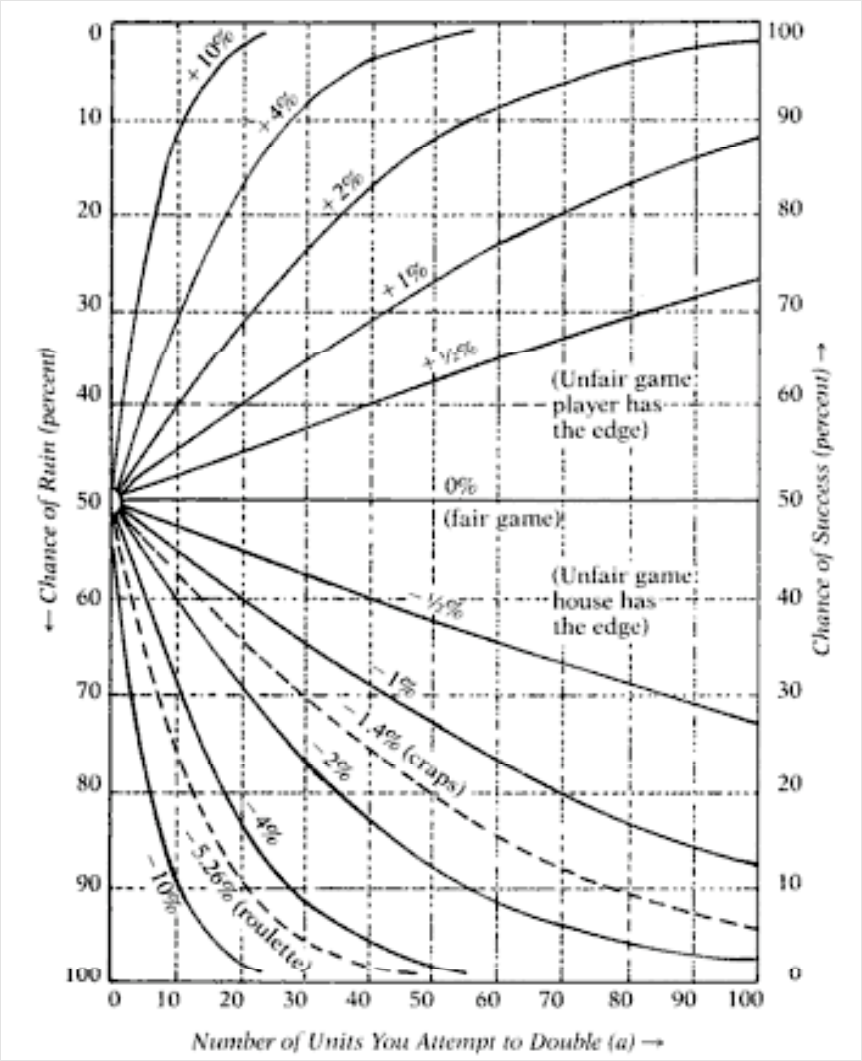
Running out of the low-hanging stuff is going to force us to act differently - nothing else could.

What To Do? Part One

Look at the assays?

Our false negative and false positive rates may be too high in too many assays.

And it doesn't take much: the longer and more comprehensive your cascade, the worse the problem is.



Thomas Bass, *"The Eudaemonic Pie"*, 1985

What To Do, Part Two

Fix a fundamental mistake?

Has target-based drug discovery been a huge detour?

Complexity has bred complexity, and there have been a lot more knots to untie than we would have thought.

“Gene to protein to drug” is not a corollary of the Central Dogma

When It Changed

Insights from 50 years of J. Med. Chem. molecules

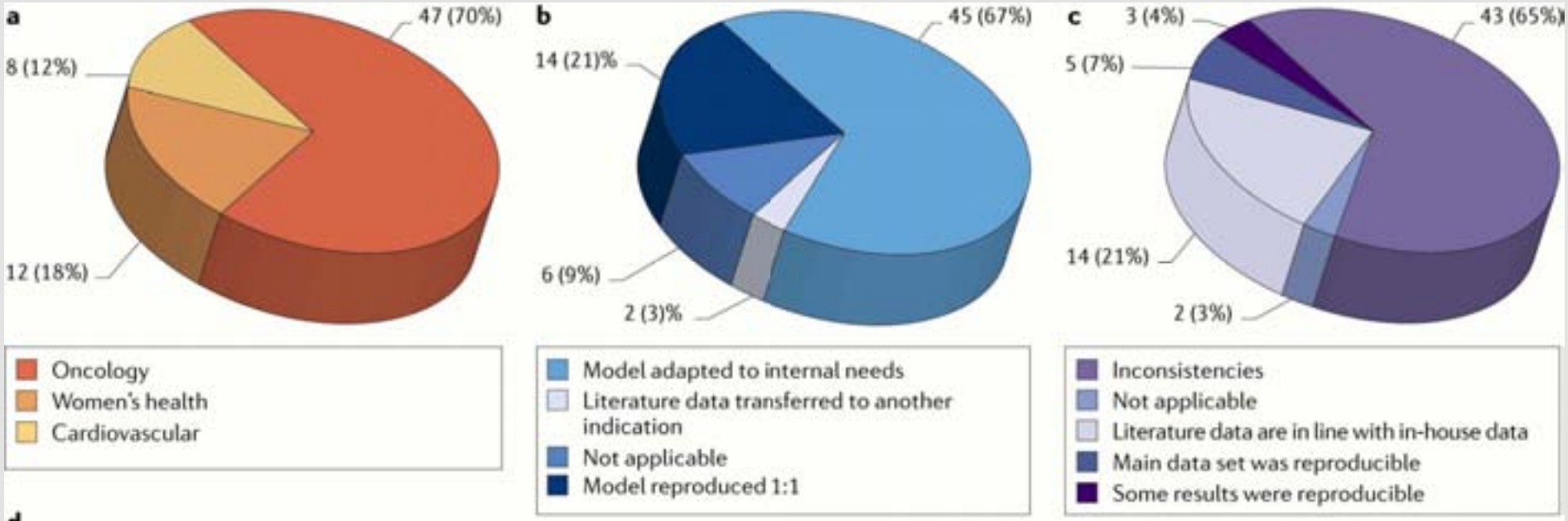
*"It is worth noting that these trends seemed to accelerate in the mid-1980s, indicating that **some change took place in the early 1980s**."*

*"The most likely explanations . . .seem to be **advances in molecular biology**, i.e., understanding of receptor subtypes leading to concerns about specificity; target-focused drug design and its corresponding one-property-at-a-time optimization paradigm (possibly exacerbated by structural biology); and improvements in technologies which enabled the synthesis and characterization of more complex molecules"*

Walters et al., *J. Med. Chem.* **ASAP** (July 2011) DOI: 10.1021/jm200504p

And It's Not Like They're All Real

Bayer's experience



d

	Model reproduced 1:1	Model adapted to internal needs (cell line, assays)	Literature data transferred to another indication	Not applicable
In-house data in line with published results	1 (7%)	12 (86%)	0	1 (7%)
Inconsistencies that led to project termination	11 (26%)	26 (60%)	2 (5%)	4 (9%)

Nature Reviews | Drug Discovery

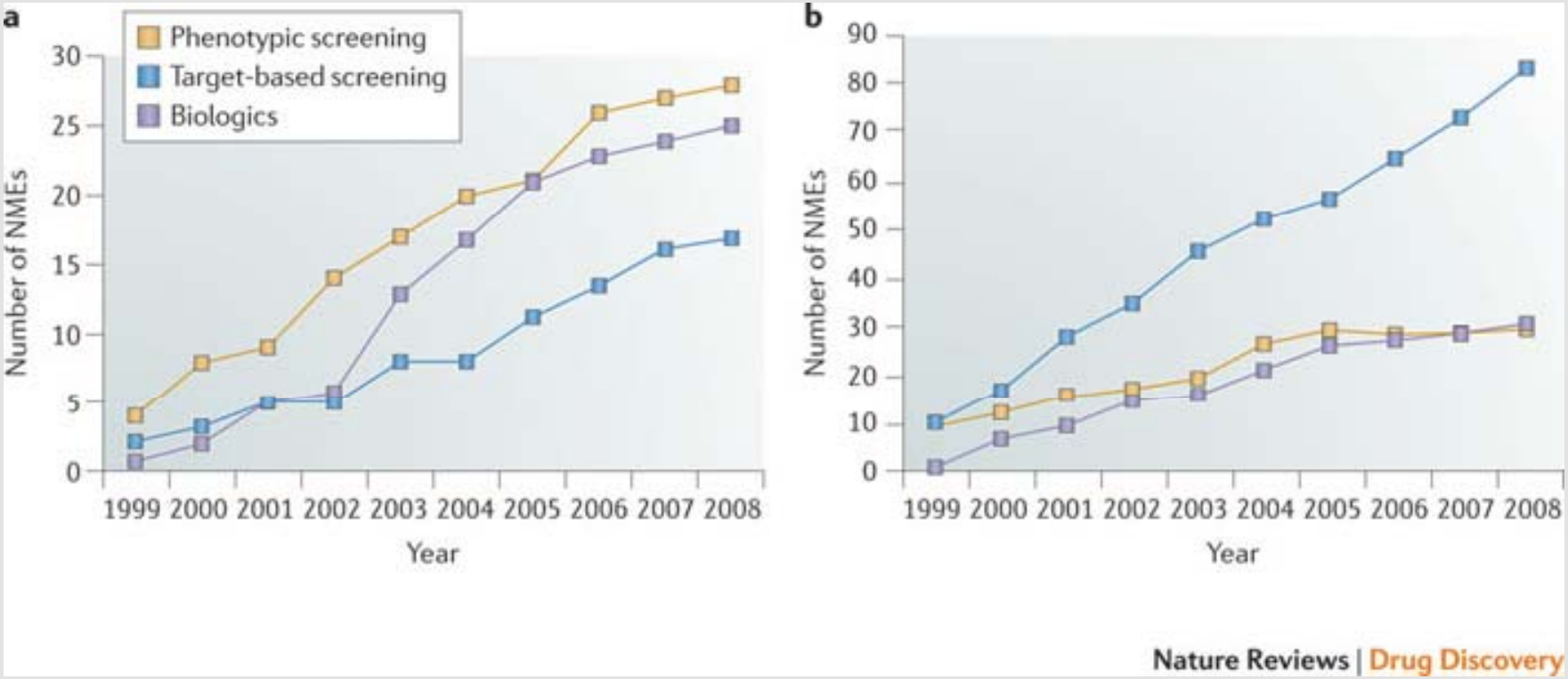
Prinz et al., *Nat. Rev. Drug Disc.* **10**, 712 (2011)

Phenotypic Screening's Track Record

Not too shabby

First-in-class

Followers



And when you consider that most screens aren't phenotypic. . .

Swinney and Anthony, *Nat. Rev. Drug Disc.* **10**, 507 (2011)

What To Do, Part Three

Revitalize Med Chem?

Mix organic/med-chem in with biological techniques;
it can only improve them

For example: Chemical genetics, small molecule/biologic hybrids, stapled peptides, new probes and tools

It’s our job to keep small molecules relevant;
there’s no law that says biologics are better.

Last Slide Full of Wisdom

(Take it where you can find it)

Get back to basics with phenotypic screens

Tighten up your assays

Pick programs with a fast clinical POC

Never think you know more than you really do