How to do a DPhil in the WIMM

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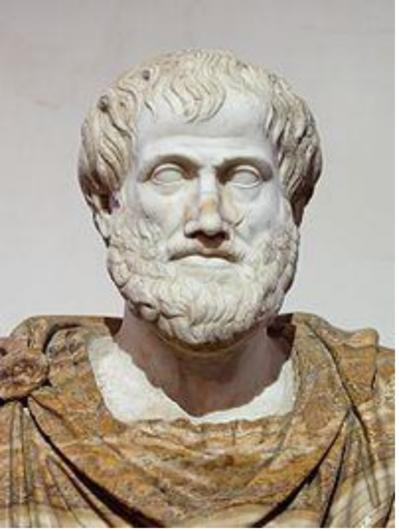
The MRC Weatherall Institute of Molecular Medicine is a strategic alliance between the Medical Research Council and the University of Oxford

Background:

development of the scientific method



Aristotle (384-322 BC)

Natural Philosophy

Aristotle's method of investigation varied from one natural science to another and on the problems encountered, usually included:

1: defining the subject matter
2: considering the difficulties involved by reviewing the generally accepted views on the subject, and suggestions of earlier writers
3: presenting his own arguments and solutions.

There is no experiment to test the hypothesis!

Aristotle himself did occasionally perform ‘experiments’
eg examining the contents of fertilized eggs over time, dissections of animals.

But he was the arch-observer of nature, rather than a practical tester of ideas.

He said experiments were “an interference in the natural course of Nature”.

His scientific work became irrefutable truth and axiomatic throughout post-Roman Europe and into medieval times, because of its incorporation into Doctrine (St Thomas Aquinas ‘baptized’ Aristotle)

Eventually Aristotelian science was questioned, in the Renaissance. (which would probably have been a relief to Aristotle)

Sir Francis Bacon -
"The Father of Experimental Philosophy" 1561-1626
Not a scientist! But was unhappy with Aristotelian methods:

"If men … apply themselves to philosophy and contemplations of a universal nature, they wrest and corrupt them by their preconceived fancies of which Aristotle affords us a signal instance, who made his natural philosophy completely subservient to his logic, and thus rendered it little more than useless and disputatious"

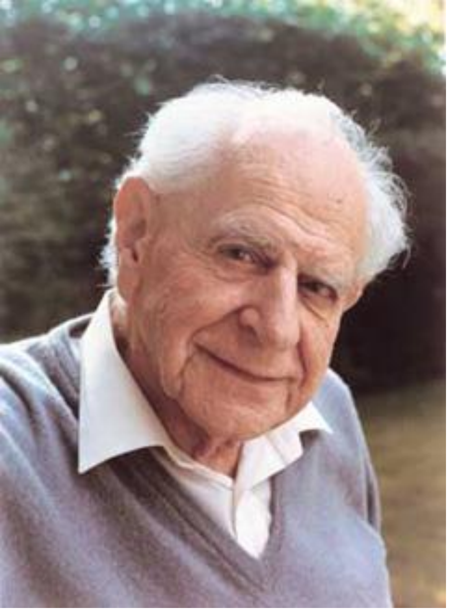
Instead, Bacon proposed the use of **Empiricism:** Emphasized experiment and ‘disinterested gathering of facts’ - using an Immaculate Perception of nature.

Out of the aggregation of data, patterns would become self-evident, and a hypothesis could be based on these observations of behaviour, and then tested experimentally, leading to a refinement of the theory.

“All depends on keeping the eye steadily fixed upon the facts of nature and so receiving their images simply as they are”

Letting the piled up data speak for itself?
Not really what happens.
Ignores the unspoken prejudices
inherent in any experimental system,
and inherent in human perception.

Also ignores the likely human response to data -
results that seem to confirm your or your supervisor's ideas
are likely to be better received than those that don't.



Karl Popper The Logic of Scientific Discovery 1959
Admits the generation of a testable hypothesis as key.
Admits the use of experimentation in refining hypotheses.
Admits also the ever-pervasive presence of prejudice.

But emphasizes the *power of falsification*:

Asymmetry of hypothesis testing
ie can't ever prove a hypothesis, can only disprove one
Science advances by refinement, built on disproving ever more sophisticated ideas and replacing them with better ones

"No amount of experimentation can ever prove me right; a single experiment can prove me wrong." ***Albert Einstein***

But this is idealistic, unrealistic and human nature doesn't really go this way:

"The great tragedy of Science — the slaying of a beautiful hypothesis by an ugly fact."
T.H. Huxley

In fact, a scientist very very rarely attacks his own hypothesis.
He/she seeks to verify it first.
When a bright new theory comes along, other scientists often try to confirm it too.

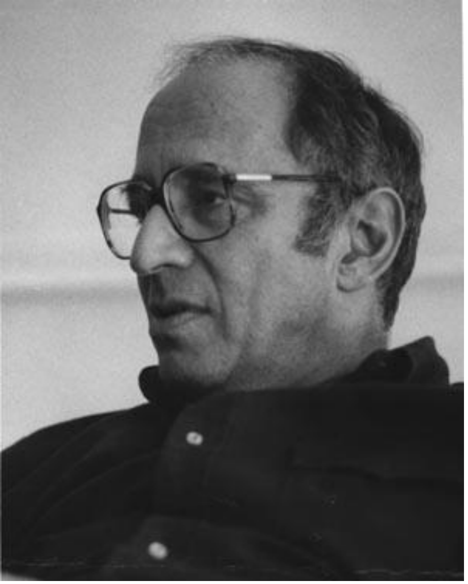
Credit is given for a right hypothesis, not as much for falsifying them!

However, disproving an old established hypothesis
is crucially important

Popper is also inaccurate, because a fact does *not* necessarily slay a hypothesis. Either the fact is not in fact a fact, or the experiment that yielded the fact had inbuilt assumptions that are wrong.
It is often very hard indeed to conclusively falsify a hypothesis -
there usually turns out to be both supporting and conflicting data, which have to be weighed against each other.

"No theory … can possibly explain all the experimental observations because so many of them are mutually contradictory."
McCance and Widdowson, The Lancet, 1937

The asymmetry of the impossibility of confirmation versus the relative ease of falsification, on which Popper bases his ideas, frequently does not really exist, particularly in biology.



Thomas Kuhn The Structure of Scientific Revolutions (1962)

Science does not proceed by gradual refinements of hypotheses, but rather by an accumulation of knowledge that eventually does not fit the old dogma. The old rules are eventually overturned and replaced with the new, and everything has to start again.

This is the **"paradigm shift"**

The scientific viewpoint before the shift is said to be *'incommensurate'* with the viewpoint afterwards.
Example in cosmology: It was held from Aristotelian times, and ingrained into the Church's dogma for centuries, that the Earth was the centre of the universe.
More and more knowledge of planets' and moons' orbits accumulated that could not be fitted easily with this model.

Eventually Copernicus published De Revolutionibus Orbium Caelestium in 1543, with the idea that the sun was the centre, and the Earth, Mars etc went round it.
These two views are truly incommensurate - either the Earth and planets go round the sun, or the sun and planets go round the Earth.

This paradigm shift view correlates in some ways with a scientist’s experience – there are rare moments of breakthrough or sea-change,
after which everything does look different.

But Kuhn is inaccurate too:
It is exceedingly rare for a paradigm shift to involve a change from one view to another that is *incommensurate*.

Relativity and quantum mechanics, a huge epoch-making advance, did not make Newtonian Laws actually wrong or useless, it just explained things at a deeper level.

Although the progression of science is not gradual, it is not the all-or nothing that Kuhn implies.
Some changes are bigger than others, that is all…

Towards a synthesis?

From Aristotle:	Think about the problem before doing experiments
From Bacon:	Treat the evidence with respect, do your own experiments, gather your own evidence - report it 'immaculately'
From Popper:	Design clear-cut experiments, think about what the experimental system can and cannot tell you
From Kuhn:	Be prepared to change your point of view and re-interpret your own experimental evidence

Which sort of science is deemed "reliable" in a court of law? (US Supreme Court decision, 1993 *Daubert*)

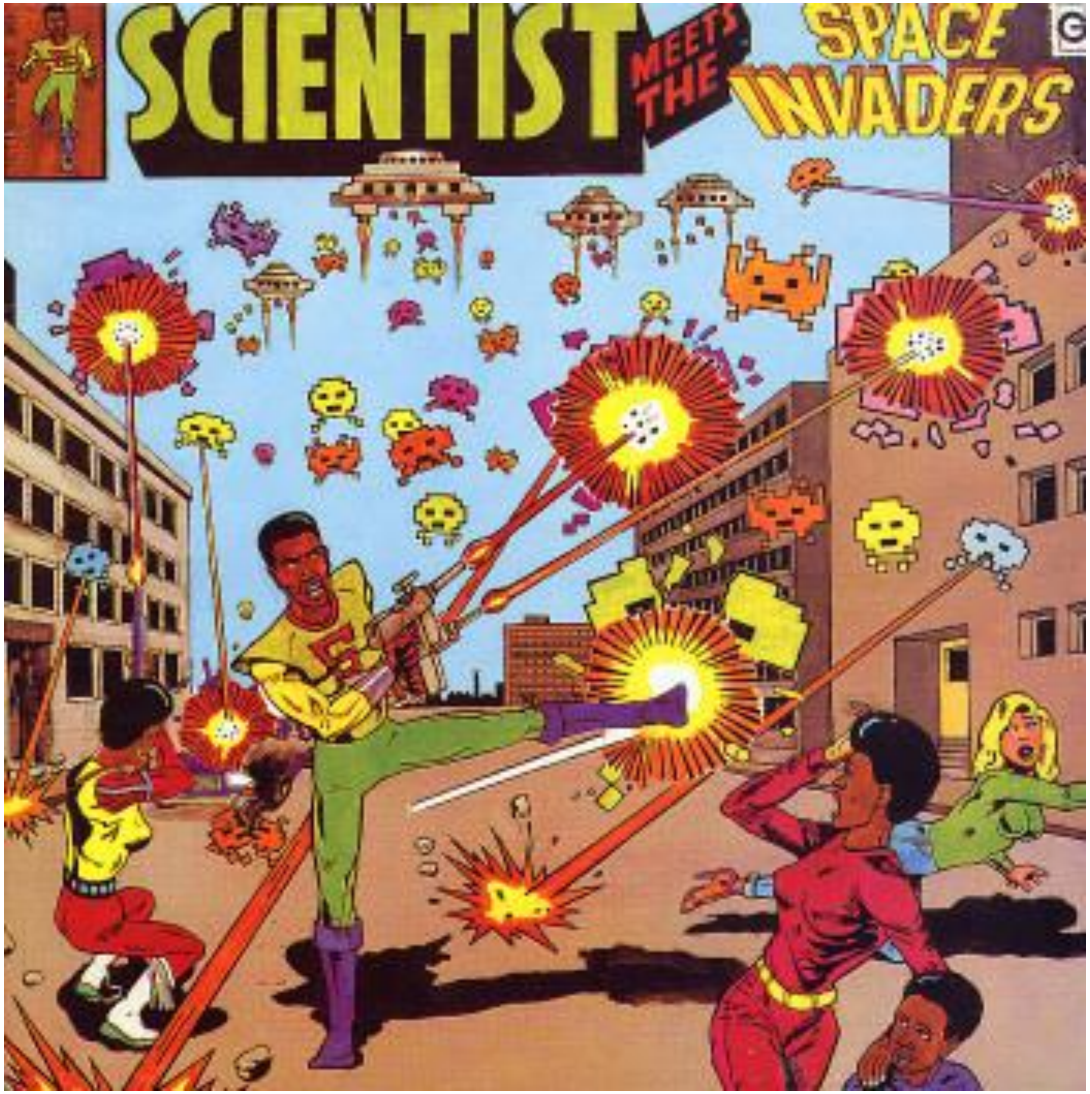
1. The theoretical underpinnings of the methods must yield testable predictions by means of which the theory could be falsified.

2. The methods should preferably be published in a peer-reviewed journal.

3. There should be a known rate of error that can be used in evaluating the results.

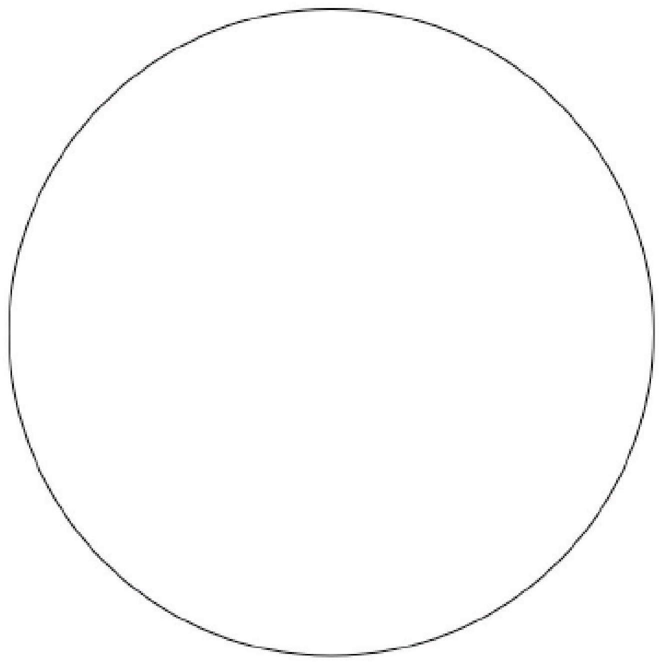
4. The methods should be generally accepted within the relevant scientific community.

What' s this got to do with me?

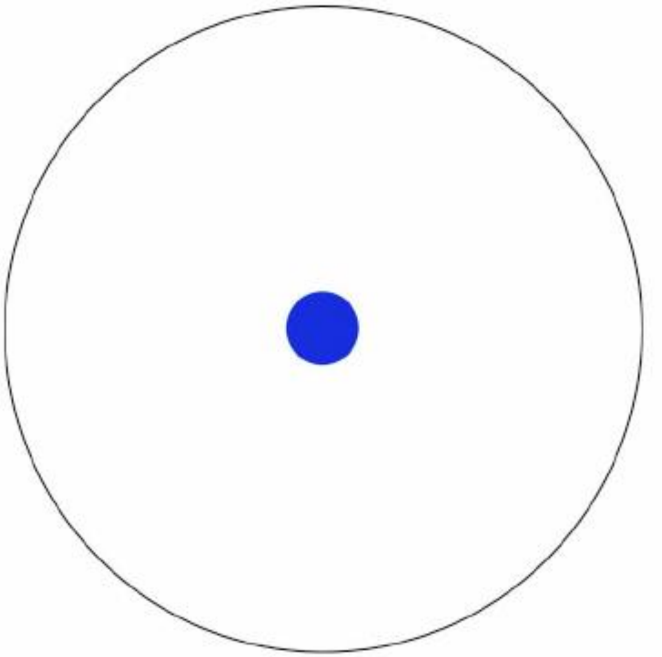


Context: What is a PhD?

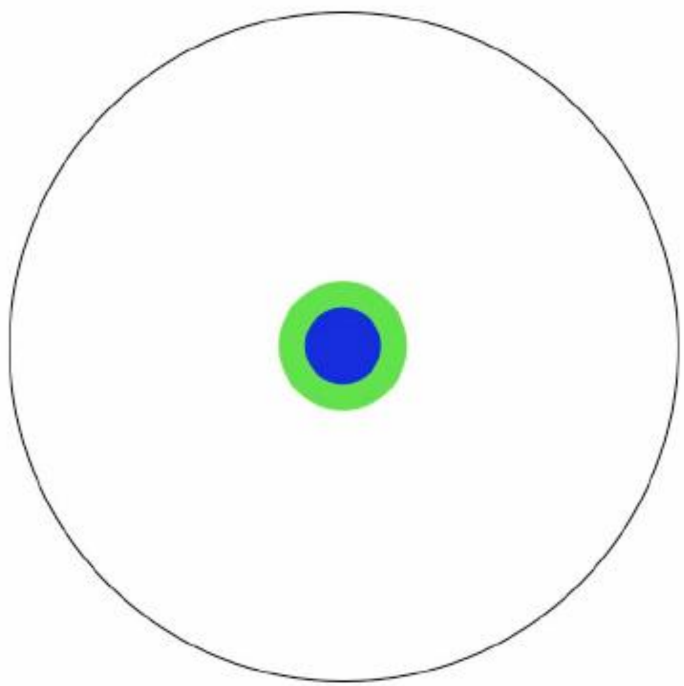
Imagine a circle that contains all of human knowledge:



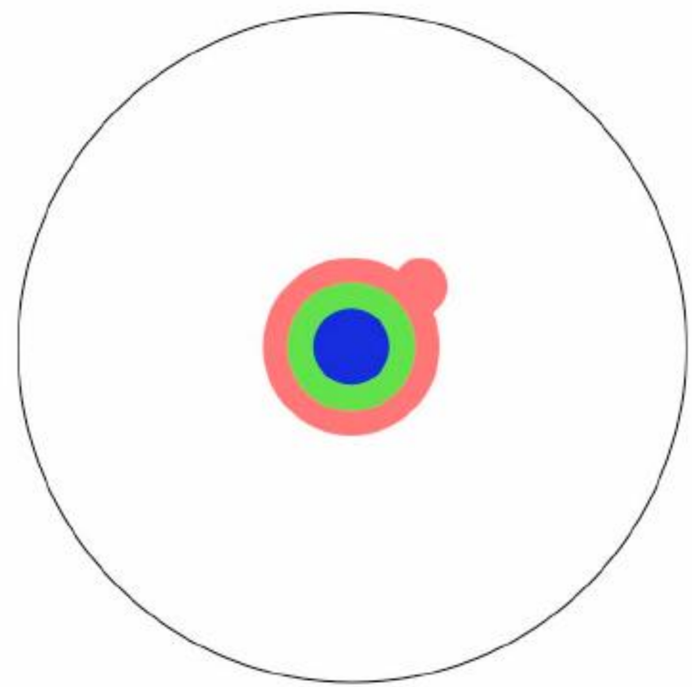
By the time you finish elementary school, you know a little:



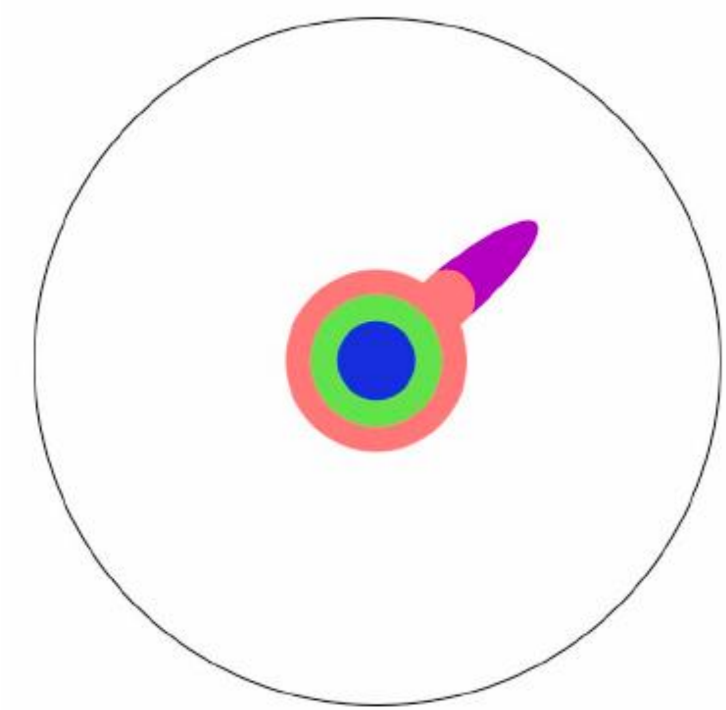
By the time you finish high school, you know a bit more:



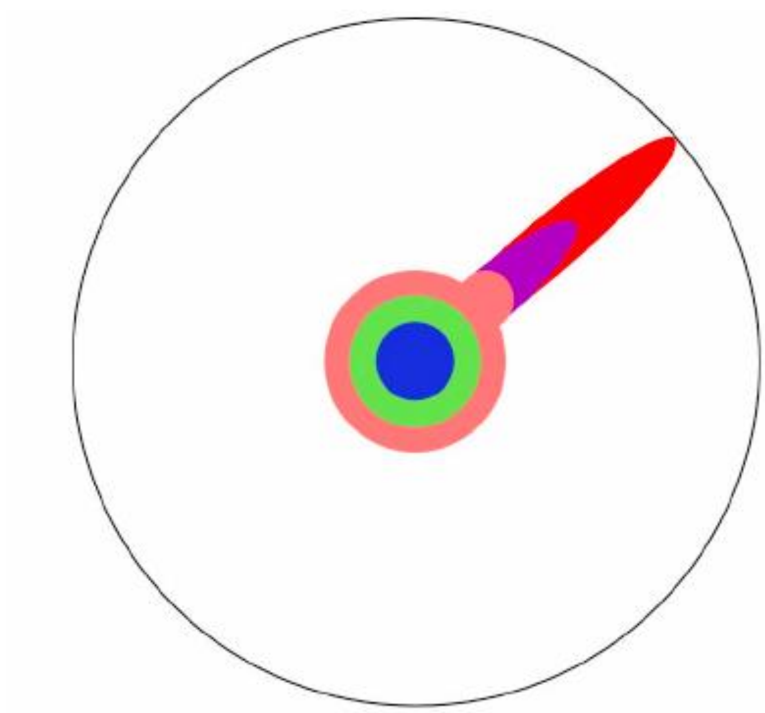
With a bachelor's degree, you gain a specialty:



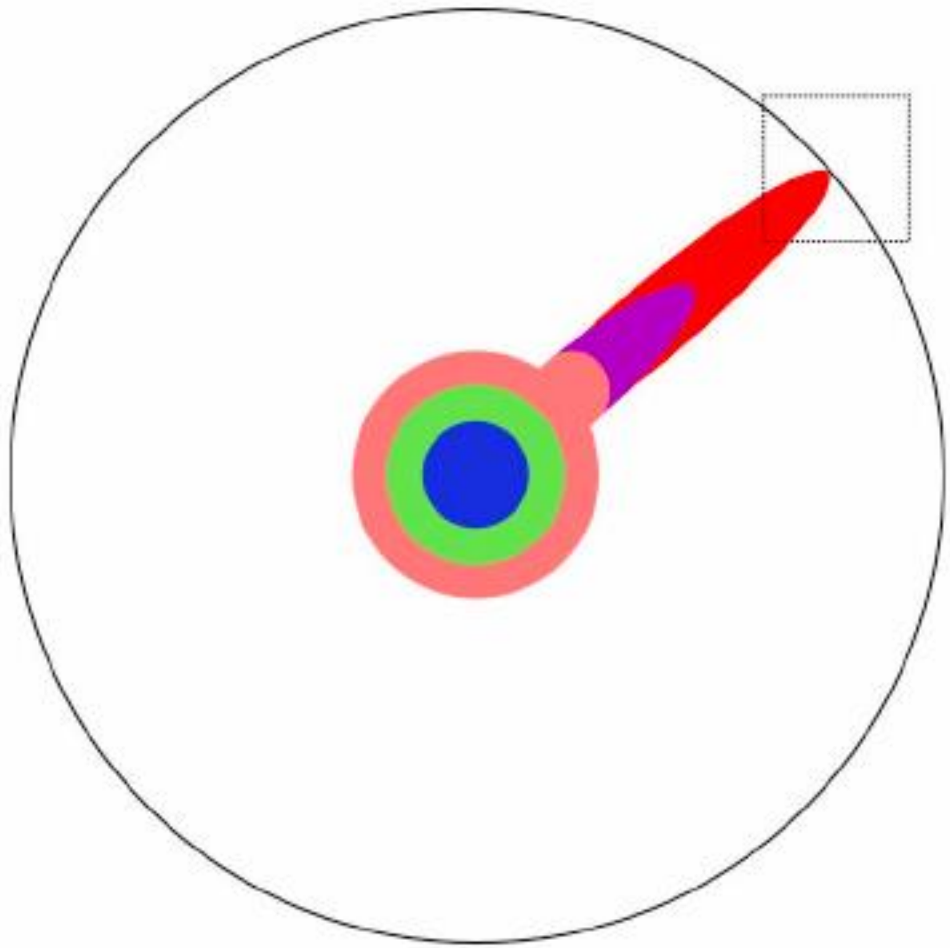
A master's degree deepens that specialty:



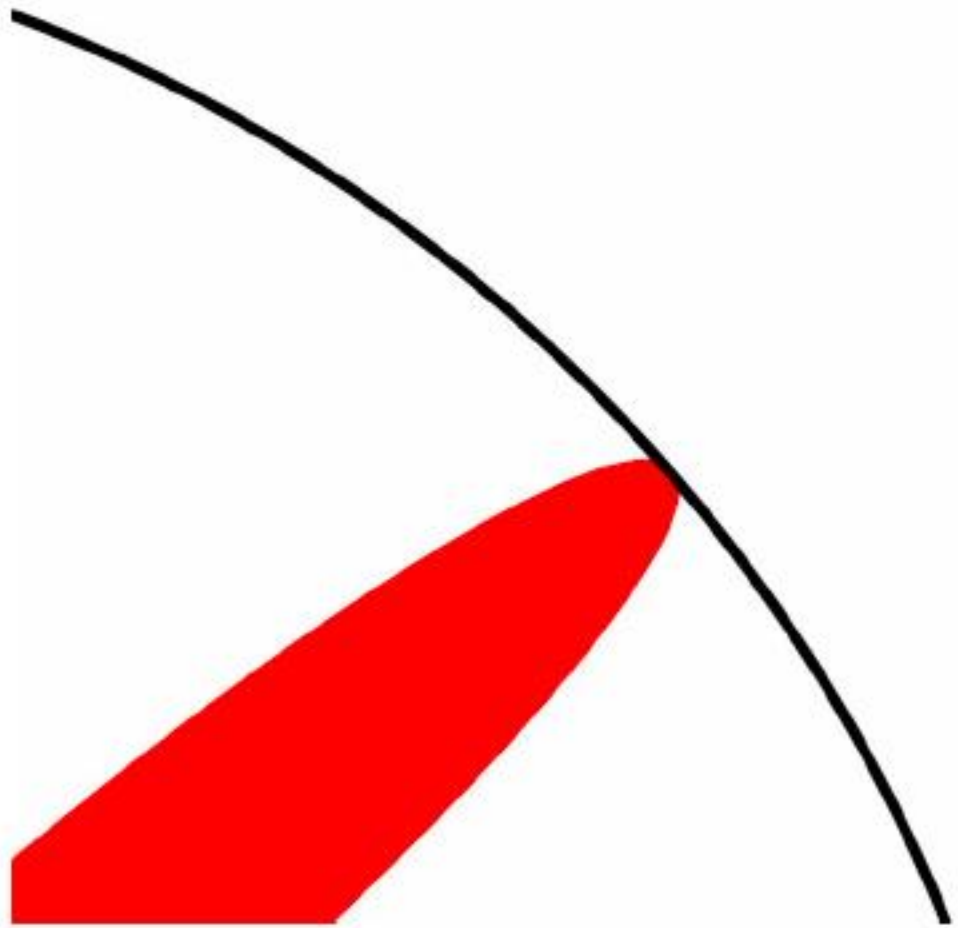
Reading research papers takes you to the edge of human knowledge:



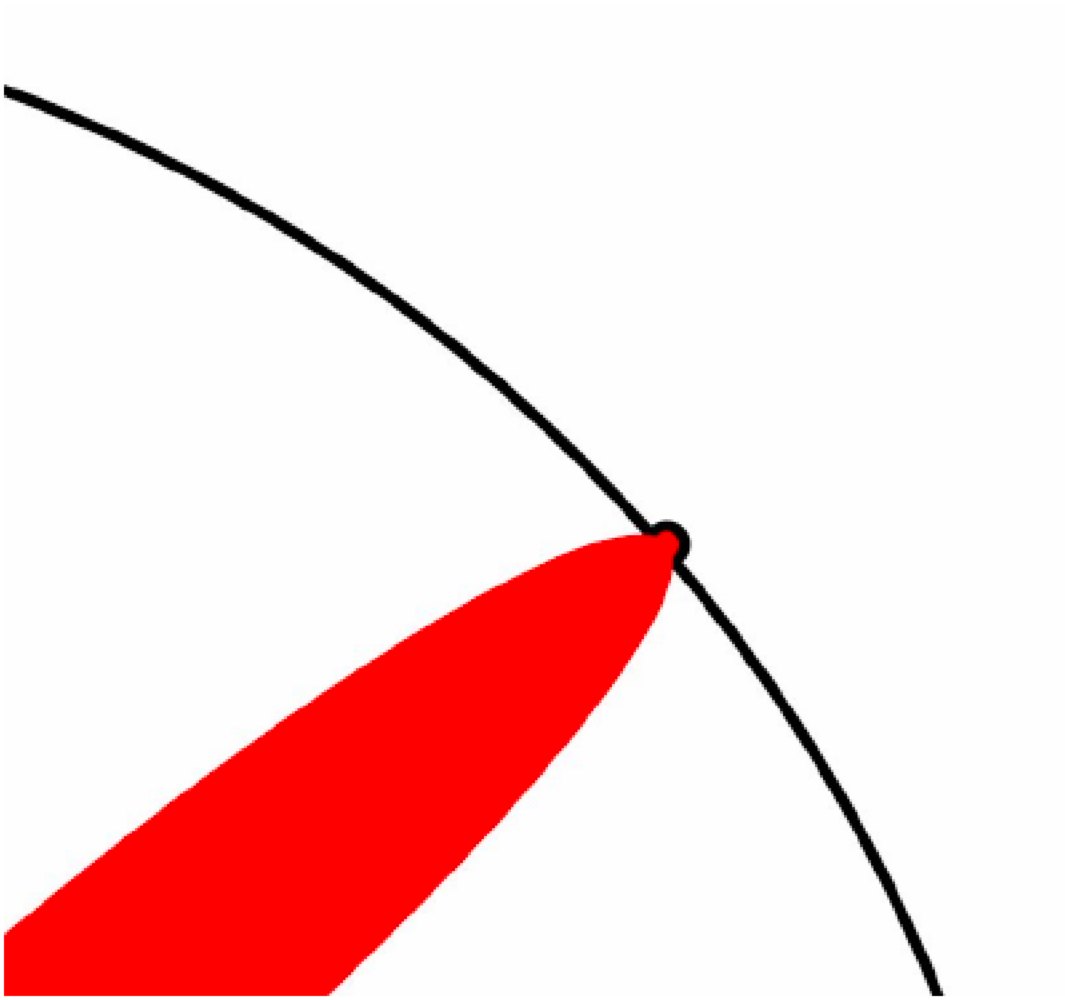
Once you're at the boundary, you focus:



You push at the boundary for a few years:

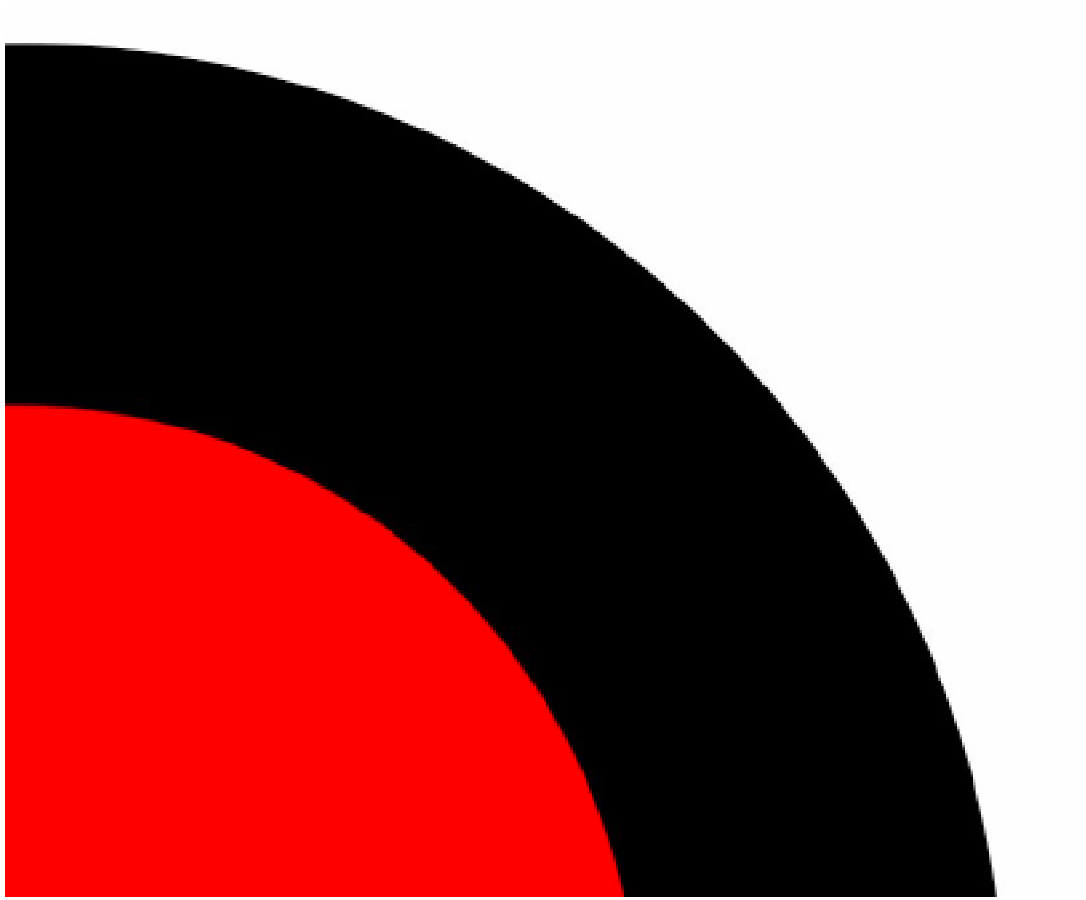


Until one day, the boundary gives way:

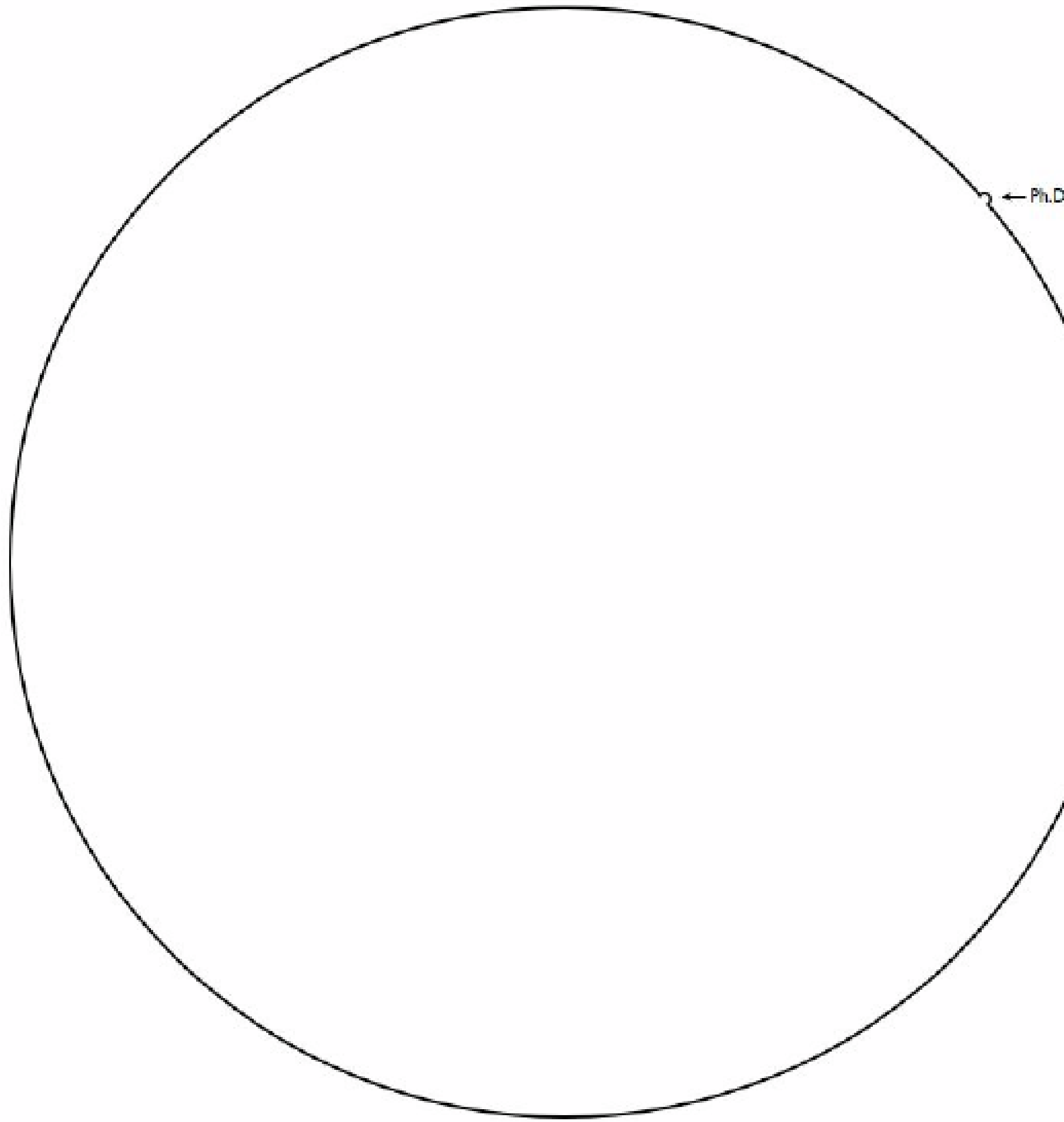


And, that dent you've made is called a Ph.D.:

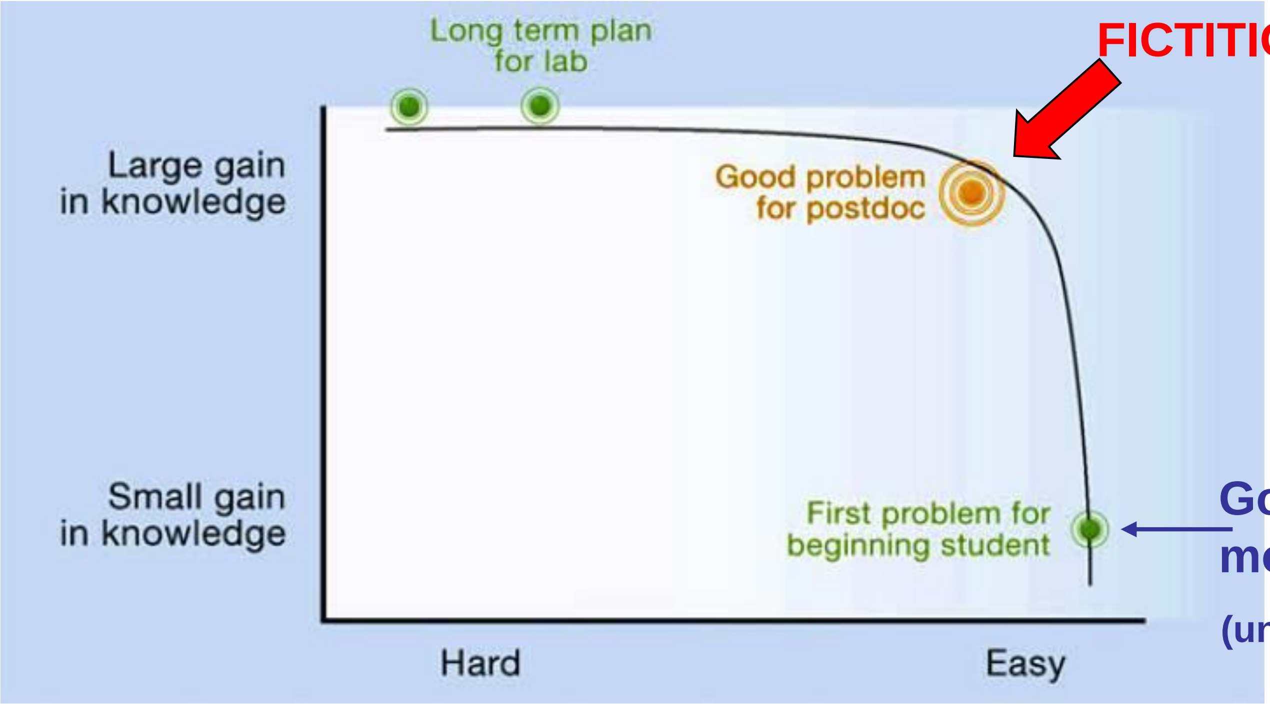
Of course, the world looks different to you now:



So, don't forget the bigger picture:



Preparing the way:
Choosing the right problem

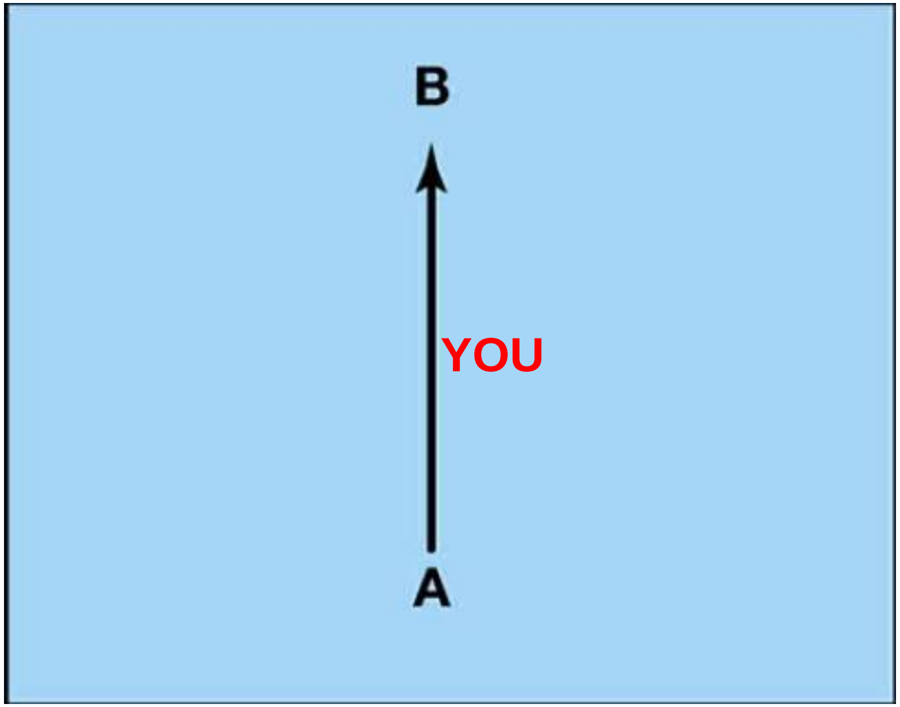


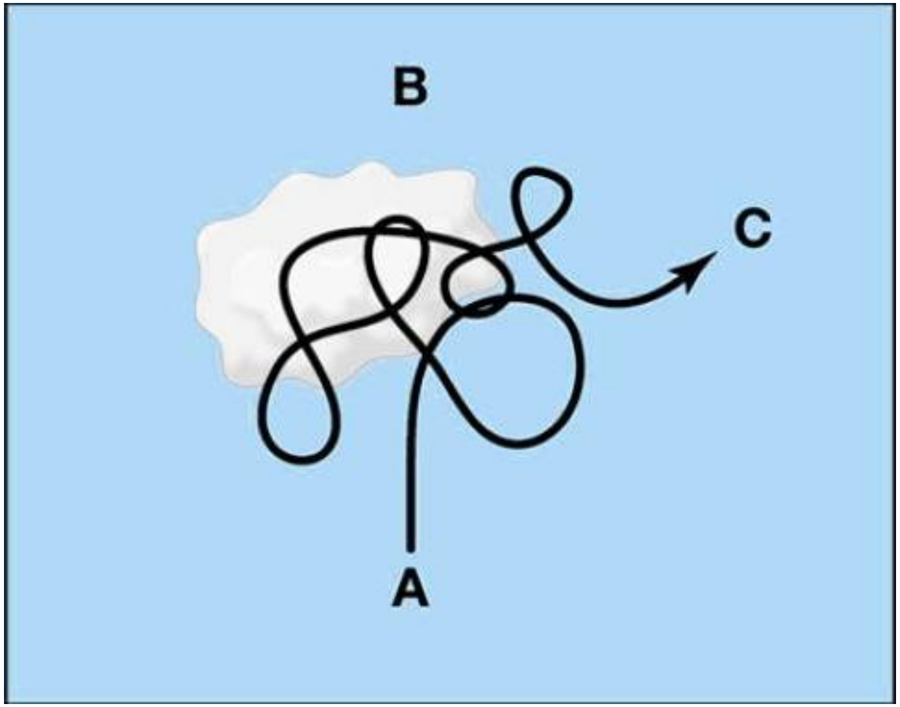
FICTITIOUS

Good for morale!

(unless you mess it up)

Preparing the way:
Managing your expectations (and your supervisor's)





What happens in the 'cloud' is what really matters

Inventing hypotheses: incubation and rumination

“Hypothesis is the most important mental technique of the investigator, and its main function is to **suggest new experiments** or new observations” *W.I.B. Beveridge*

A project for study presents itself (either after reading, or by your supervisor)

To begin with, the experimental approach is usually suggested by others

With time, you will inevitably find yourself incubated by the cloud…

Rumination: an idea comes along! First consider:

Is it a big or small hypothesis?
Is it a useful hypothesis?
Is it one that is justifiable/affordable to actually test?

“I cannot remember a single first-formed hypothesis which had not after a time to be given up or be greatly modified” *Charles Darwin*

Inventing hypotheses: importance of discussion

1: Another person may actually have something useful to say

2: Pooling information - two people alone unable to progress, but together they may crack a problem

3: Uncover errors, false assumptions, unjustified enthusiasms

4: Provides reassurance and encouragement

5: Escape from a pattern or conditioned habit of thinking

Discuss with labmates, peers in other labs, friends in other subjects, parents, dog…

Inventing hypotheses: intuition and illumination

Some problems are just very hard and even first ideas do not come easily

"Inspiration comes during the slow ascent of wooded hills on a sunny day"
Von Helmholtz

Also bear in mind:

The dreams of Kekulé
The illness of A R Wallace
Kary Mullis's girlfriend

Verification: experimentation and observation

Geber / Jabir c.721 - c.815

"The first essential in chemistry is that you should perform practical work and conduct experiments, for he who performs not practical work nor makes experiments will never attain the least degree of mastery."

Geber invented the **controlled** experiment

"The experiment serves two purposes… it allows the observation of new facts, hitherto either unsuspected, or not yet well defined; and it determines whether a working hypothesis fits the world of observable facts" *René Dubos*

What do you need to do a decent experiment?

While performing an experiment, try to forget intuition, hypothesis etc

Know your Method: repeat and repeat again

Know enough statistics: can you actually get a clear result with your numbers?

Large-scale experiments: what are the limitations of your chip / mass spec / flow cytometer, and does your question go beyond the limits of the system?

Have you included the right controls??

"It is the care we bestow on apparently trifling, unattractive and very troubling minutiae which determines the result" *Theobald Smith*

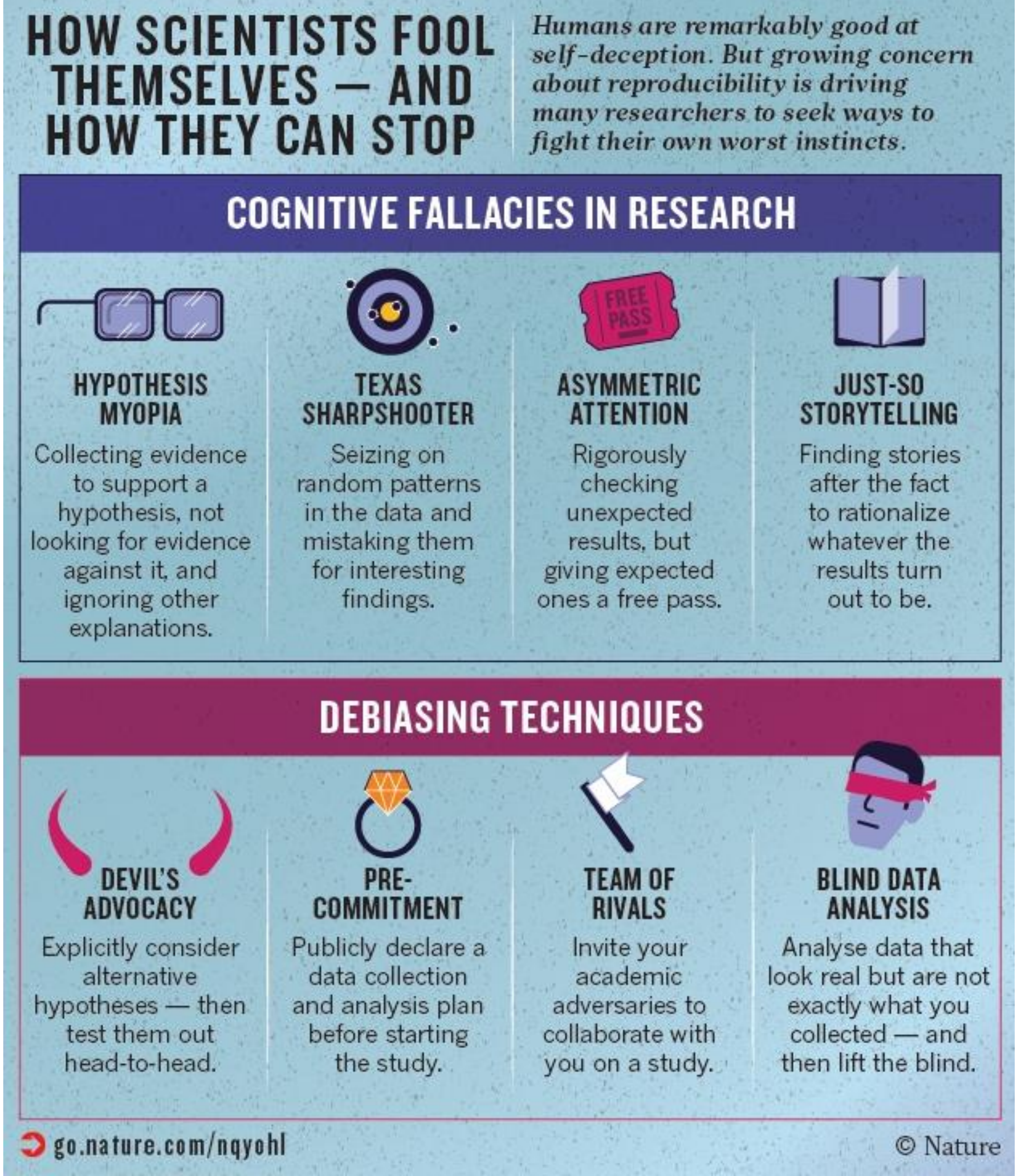
Sources of error

"We see only what we know"

Johann Wolfgang von Goethe

"People forget that when we talk about the scientific method, we don't mean a finished product…Science is an ongoing race between our inventing ways to fool ourselves, and our inventing ways to avoid fooling ourselves."
Saul Perlmutter, University of California, Berkeley.

"I'm not trying to produce misleading results — but I do have a stake in the outcome."
Brian Nosek, Center for Open Science in Charlottesville, Virginia



http://www.nature.com/news/how-scientists-fool-themselves-and-how-they-can-stop-1.18517

Problems with observation

Sources of error:

Incompetence (very common)

Materials not what they are believed to be (John Hunter)

Unconscious bias not accounted for

Errors of interpretation (lack of phenotype of knock-out mice)

The card players of Caravaggio, Cézanne and Mark Twain: tips for getting lucky in high-stakes research

Joseph L Goldstein

NATURE MEDICINE VOLUME 17 | NUMBER 10 | OCTOBER 2011

"The harder I work, the luckier I get."

You may need to **collaborate**!

Science & Society

CellPress

Putting together a scientific team: collaborative science

L. Garry Adams

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Trends in Microbiology, September 2014, Vol. 22, No. 9 483

One of the most enjoyable parts of a science career is collaborative team experiences and developing life-long social networks. When the hypothesis being tested requires innovative efforts greater than any single laboratory, collaboration becomes an essential component for success – everyone is a stakeholder and trust is the driving force.

Box 1. Trust

The basic assumption is that as scientific collaboration increases so will the advancement of knowledge for the betterment of society and environment, yet successful outcomes ultimately hinge largely on the most basic of human relationships – trust.

How to form and use a hypothesis in the WIMM

Preparation:
Read a lot
Go to relevant seminars

Incubation:
Think a lot
Talk a lot - use the coffee room, WIMM day, Unit days
Don't think or talk at all but ruminate
Go to irrelevant seminars

Illumination:
Have long baths
Go to the pub
Go on holiday

Verification:
Don't take yes or no as immediate answers
Try many different complementary approaches
Get good independent advice
Test and re-test

Some further things to bear in mind

Analyze your data and make thesis-ready figures **as you go along**

Figure out what sort of science **you like doing**

Self-express, satisfy **your own curiosity**
(Friday and Birthday experiments…)

You won't get fed, **you have to feed yourself**

“Experiment escorts us last --
His pungent company
Will not allow an Axiom
An Opportunity”

Emily Dickinson

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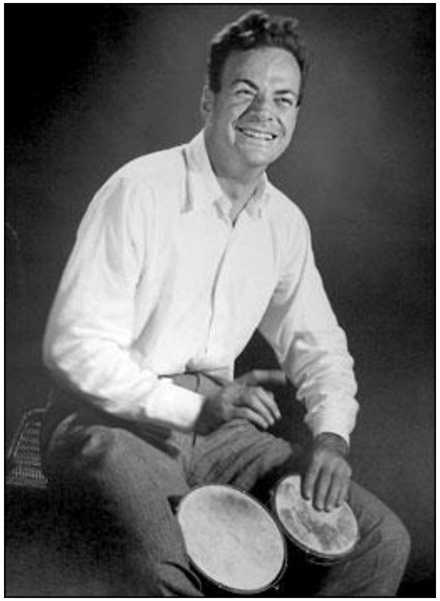
Reward: The pleasure of (sometimes) finding things out

“Research is like sex

sometimes there’s a very important product

but that’s not why we do it”



Richard
Feynman