Animal testing: A Historical Perspective

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Pathfinder

What I will tell you in the next 20 minutes:

- I will tell you the **History Thalidomide and its 2 back-stories** ...

- Why **History is a very good tool in Science Education**, i.e., the role of history in two perspective: **evolutionary** (cognitive biases) and **contemporary** (recent papers)

- Immediately, I will show you **what I will not tell you**
- There would be no knowledge of the functioning of tissues, organs, physiological systems etc., without animal testing.
- No experimental medicine and therefore no cures for most diseases. Since it is very well known history, I will show a **quick look at a list of advancements** in medicine permitted by animal testing.
- With a premise: who claims that this is not true must demonstrate that historical documents are fake and that it possible to develop a drug with “alternative” methods.

![Scientific discoveries](image)

**Discoveries relating to blood circulation**
(experiments on different species, **warm/cold blooded animals**)

**Discoveries about the physiology of digestion**
(birds and small mammals)

**Discoveries concerning chemical and physiological bases of respiration**
(birds and small mammals)

**Discoveries concerning the functions of the peripheral nerve fibers and anatomy of the brain**
(birds and mammals)

**Discoveries about the biochemical basis, genetic and anatomical and functional immune responses**
(mammals)

**Discoveries concerning the function of hormones and the endocrine physiology** (mammals)
Timeline of Medical Advances made possible by Animal Experiments

Pre twentieth century

Discovery of the cause of tuberculosis and other infectious diseases (guinea pigs, rabbits, cattle, birds)
Smallpox vaccine (cattle)
Vaccination against anthrax (sheep)
Use of the first anesthetic (cats, rabbits and dogs)
Rabies vaccine (rabbits and dogs)
Vaccines for typhoid fever, cholera and plague (mice and rats)

Cure for beriberi (chickens)

1900-1910:

Cure for rickets (dogs)
Corneal transplantation (rabbit)
Discovery of local anesthetics (rabbits and dogs)
Discovered vitamin C (guinea pigs)

1910-1920:

Blood transfusions (dogs, guinea pigs and pigs)

### Timeline of Medical Advances made possible by Animal Experiments

<table>
<thead>
<tr>
<th>Period</th>
<th>Advancements</th>
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<tr>
<td>1920-1930</td>
<td>Discovery and use of insulin (dogs, rabbits and mice)</td>
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<tr>
<td></td>
<td>Vaccine against canine distemper (dogs)</td>
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<td>Discovery of sulfonamides (guinea pigs)</td>
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<tr>
<td>1930-1940</td>
<td>Development of modern anesthetics (rats, rabbits, guinea pigs, cats, dogs, monkeys)</td>
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<td>Tetanus vaccine (horses and guinea pigs)</td>
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<td>Diphtheria (horses, monkeys, rabbits and guinea pigs)</td>
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<td></td>
<td>Discovery and development anticoagulants (rabbits, guinea pigs, mice and cats)</td>
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<td>1940-1950</td>
<td>Discovery of penicillin and streptomycin (mice)</td>
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<td>Discovery rhesus (monkey)</td>
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<td></td>
<td>Renal dialysis (guinea pigs, rabbits, dogs and monkeys)</td>
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<td>Pertussis vaccine (mice and rabbits)</td>
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<td>Heart-lung machine for cardiac surgery (dogs)</td>
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<td></td>
<td>Polio vaccine (mice and monkeys)</td>
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<td></td>
<td>Surgery for hip replacement (dogs, sheep and goats)</td>
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<td>Kidney transplant (dogs)</td>
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<td></td>
<td>Cardiac pacemaker (dogs)</td>
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<td>Medications for hypertension (rats, mice and dogs)</td>
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<td></td>
<td>Replacement heart valves (dogs, calves, rabbits, guinea pigs, and rats)</td>
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<tr>
<td></td>
<td>Chlorpromazine and other psychiatric drugs (rats, rabbits and monkeys)</td>
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<tr>
<td>1960-1970</td>
<td>Heart transplantation (dogs)</td>
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<td></td>
<td>Coronary artery bypass graft (dogs)</td>
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<td>Measles vaccine (monkeys)</td>
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<td>Trivalent MMR vaccine (monkeys)</td>
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<td></td>
<td>Antidepressants and antipsychotics (rats, guinea pigs and rabbits)</td>
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<td></td>
<td>Levo dopa to treat Parkinson's disease (mice)</td>
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</tbody>
</table>

### Timeline of Medical Advances made possible by Animal Experiments

#### 1990-2000:
- Combination therapy for HIV (rats and monkeys)
- Antimeningite vaccine (mice)
- Antidepressant medications (rats)
- Drugs for cancro breast and prostate (mice, rats and dogs)
- Medicines for type 2 diabetes (mice)
- New drugs for asthma (guinea pigs and monkeys)
- Statins to lower cholesterol (mice)

#### 2000-2010:
- Deep brain stimulation for Parkinson's disease (monkeys)
- Monoclonal antibodies for leukemias and lymphomas (mice)
- Vaccine against cervical cancer (rabbits and cattle)
- Oral or inhaled insulin for type 1 diabetes (mice)
- Ongoing development of gene therapy for muscular dystrophy, cystic fibrosis and sickle cell anemia (rats and dogs)

#### 2010-2013:
- Stem cells for the treatment of neurodegenerative disorders (mice, rats and monkeys)
- Ongoing development of the vaccine for Alzheimer's disease (mice)
- Ongoing development of the malaria vaccine (mice and monkeys).
Thalidomide (alpha-phthalimido-glutarimide) became an over-the-counter drug in West Germany on October 1st 1957 under the trade-name **CONTERGAN** (by drug company Chemie **Grünenthal**), and was first marketed in the UK in April 1958 as Distaval.

As early as November 1956 thalidomide was primarily prescribed for the treatment of **respiratory infections** under the trade name **Grippex** (combination of thalidomide with quinine, vitamin C, aspirin). Since overdoses of thalidomide caused **prolonged sleep**, it started to be used to cure **insomnia**.

It was hailed as a **"wonder drug"** that provided a **"safe, sound sleep"**.

It was marketed in 46 countries, under different names (e.g. Isomin in Japan, Softenon in Europe, etc..)
Thalidomide

Nausea Vomiting in Pregnancy NVP is top around 10 week (during 1st trimester), a very delicate phase for the baby's development.

Physicians started to prescribe thalidomide to pregnant women for a variety of symptoms, especially morning sickness. Many of these women gave birth to children with serious, rare birth abnormalities, including shortened limbs and mental retardation.
At the time of the drug's development, scientists did not believe any drug taken by a pregnant woman could pass across the placental barrier and harm the developing foetus (excepted alcohol).

But thalidomide was able to cross the placenta and disrupt the growth patterns of the growing foetus (within the 10th week).
In the late 1950s and early 1960s, more than 10,000 children in 46 countries were born with deformities such as phocomelia.

It is not known exactly how many worldwide victims of the drug there have been, although estimates range from 10,000 to 20,000 to 100,000.
Thalidomide

It took almost 4 years (1961-65) before the link between thalidomide use during pregnancy and phocomelia was recognized.

Only in 1965 Reproductive toxicology studies in animals—thanks landmark address of Sir Austin Bradford Hill to the Royal Society – started to be considered part of the drug protocol.
Thalidomide

So far, the part of the story was quite known and just demonstrates that anti-animal testing groups used to lie on thalidomide, by inventing another story... (i.e., Thalidomide was safe when tested in animals, but detrimental in humans: ergo Animal Testing is useless)

As a matter of facts, Thalidomide turns out to be an argument in favor of more animal testing:

it was not tested on pregnant animals and this caused the tragedy

But the story of Thalidomide is not over .... and the best part is yet to come !

1) Why US never approved Thalidomide ?

2) Who discovered that Thalidomide was responsible for phocomelia?
Thalidomide

1) Why US never approved Thalidomide?

The German company wanted to sell thalidomide in the United States. So, in 1960, the company applied to the Food and Drug Administration (FDA) for approval.

Given thalidomide's popularity in Europe, FDA officials thought that approval for the drug would be straightforward...

Indeed, for its approval was chosen Dr. Frances Kelsey –at her second assignment for FDA. Her supervisor (Dr. Ralph Smith) told her: "Well, this is a very easy one. There will be no problems with sleeping pills."
1) Why US never approved Thalidomide?

But Dr. Frances Kelsey found deficiencies in the thalidomide application. In particular, she noted that:

- the drug affected experimental animals differently from humans. While thalidomide had no reported harmful effects on the animals, it also **DID NOT** have the beneficial effect of making them sleepy.

animals vs. humans different specificities and drug reactions led her to improve animal testing, not to discharge it as useless procedure!
1) Why US never approved Thalidomide?

Kelsey was particularly interested in **fetal safety** because during the 1940s she had worked on the **antimalarial drug quinine** and noted that **RABBITS EMBRYOS** did not metabolize quinine. Furthermore, the harmful effects of **German measles during pregnancy** had been recently recognized.

Then, in February **1961**, Kelsey read a letter in the British Medical Journal where a British physician reported that long-term use of thalidomide caused burning pain in the fingers and toes (by damaging nerves).
1) Why US never approved Thalidomide?

She suspected that a drug that damaged nerves could have wide-ranging effects on a developing fetus.

In graduate school, Kelsey had been intrigued by teratogens drugs that harm the fetus passing through the placental barrier (rabbit, armadillo), and she suspected that thalidomide was one of them.

Richardson-Merrell Company (now part of Sanofi) was called on to perform tests and report the results. They brought together more information, but Kelsey still found deficiencies so they resubmitted. Then, the company refused and demanded approval 6 (six!) times, and was refused each time.
1) Why US never approved Thalidomide?

In recognition of Kelsey's vigilance, she was the second woman to be awarded with the highest honor for a U.S. civilian by President John F. Kennedy in 1962:

the medal for Distinguished Federal Civilian Service.

And nearly 40 years later, Kelsey was once again honored. In 2000 she was inducted into the National Women's Hall of Fame in Seneca Falls, N.Y. Kelsey (together with Elizabeth Blackwell and Eleanor Roosevelt)

1st Conclusions

- Thanks to tests on rabbits Thalidomide did not enter in US
- Consequently, Reproductive Toxicology Studies in animals began (1965 ca)
- Biomedical researches have to be tenacious and **without prejudices**
Thalidomide today, a revival!

Initially the drug was banned internationally

Teratogenic between 20-36 days after fertilization

The precise mechanism of action for thalidomide is still partially unknown… Proposed mechanisms (more than 30)

Angiogenesis, Integrin regulation, Oxidative DNA damage, growth factor antagonism.

But it has now been reintroduced as a treatment for leprosy, oral ulcer for AIDS, new anticancer drug (multiple myeloma patients FDA 2006), as therapy for Behcet's disease (beh-chets) autoimmune disease, that causes inflammation in blood vessels, leading to numerous symptoms— which may include mouth sores, eye inflammation, skin rashes and lesions.
Thalidomide

But the story of Thalidomide is not over ....

and the best part is yet to come!

The 2nd backstory of Thalidomide...

2) Who discovered that Thalidomide was responsible for phocomelia?
Thalidomide

The Australian obstetrician William McBride (and the German pediatrician W. Lenz) suspected a link between birth defects in 1961.

McBride published a letter in *The Lancet*, in December 1961, noting a large number of birth defects in children of patients who were prescribed Thalidomide.

He was awarded a medal and prize money by the prestigious *L'Institut de la Vie* of the French Government. With the prize money, he built Foundation 41, a Sydney-based medical research foundation concerned with the causes of birth defects. He became a national and international hero (top 10 Austr. medical discov)
Bendectin 1956-83

McBride's involvement in the Bendectin/Debendox case is less illustrious but more instructive...

The Bendectin was a drug entered the US market in 1956 by Merrell Dow Pharmaceuticals to relieve nausea and vomiting during pregnancy.

Does this remind you something?

Bendectin was a drug marketed under the same indications of Thalidomide.

Even Bendectin (vitamin B6 + doxylamine, an antihistamine) became object of attention and considered by some, including McBride himself, responsible for birth defects. Because of the continuing causes to which it was confronted, Merrell Dow in 1983 withdrawn the product (although FDA concluded that there was no association between Bendectin and birth defects).
Jason Daubert and Eric Schuller, who were born with severe malformations, sued the Merrell Dow, a trial which was conducted by the famous celebrity lawyer Melvin Belli. They called as a witness (and a testimonial) the no less famous William McBride.

In 1981 McBride published a paper indicating that the drug Bendectin/Debendox (in the US/in the UK) caused birth defects.

His coauthors noted that the published paper contained manipulated data and protested. Also, McBride, as witness, repeatedly showed his fake data during multiple lawsuits followed by patients.

Eventually, the case was investigated and, as a result, McBride was expelled by the Australian medical register in 1993 for deliberately falsifying data. (5 years later he was reinstated to the medical register).
Bendectin 1956-83

The Bendectin case has several consequences.

1) There was an immediate increase in the rates of hospitalization for nausea and vomiting in pregnancy.

2) As a result, only 2 medications (oxytocin, cervidil) were approved between 1962 and 2010 for obstetrical indications by the FDA.

3) Leaving medical conditions untreated during pregnancy can result in adverse pregnancy morbidity for both the mother and baby.
Bendectin 1956-83
Bendectin 1956-83

<table>
<thead>
<tr>
<th>Category</th>
<th>Symptoms</th>
<th>Impact On Patient’s Life</th>
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</thead>
<tbody>
<tr>
<td>Mild</td>
<td>Nausea only</td>
<td>No effect on family life or employment</td>
</tr>
<tr>
<td>Moderate</td>
<td>Nausea and vomiting</td>
<td>Interferes with family life or employment</td>
</tr>
<tr>
<td>Severe</td>
<td>Persistent vomiting leading to dehydration</td>
<td>Requires IV hydration or hospitalization</td>
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- NVP hospitalizations
- Limb reduction deformities
- Bendectin tablets sold

William McBride, M.D.
The most important consequence!

4) From a legal perspective, the case through Daubert v. Merrell Dow Pharmaceuticals (1993) set a new standard for admitting expert testimony in federal courts.

Facing the manipulation of a gynecologist who was a world authority (McBride, the thalidomide hero), the judges realized that the rules they used were outdated, since they referred to a judgment of the Supreme Court (the Frey Rule of 1923), which stated that to admit evidence in court is sufficient to “established to have gained general acceptance” about the validity of the instrument used by the expert.

Daubert Standard shows an evidenced dislike of the “general acceptance” criterion.
Bendectin 1956-83
and
the Standard Daubert 2000

• Today Evidence must be **reliable** and **relevant**
  – Underlying methodology & procedure must be based on scientific knowledge
  – District court is gatekeeper – determines whether reasoning or methodology is scientifically valid, applying several factors
    • Has theory or methodology been tested
    • Has it been subjected to peer review
Bendectin 1956-83
and
the Standard Daubert 2000

2nd Conclusion
- If something like that were valid in Italy, it would be unthinkable
a legal action in defense of fake treatments (like Stamina affair),
or in defense of the alleged relationship vaccine-autism and also
attempts to advance “evidences” against animal testing.

- Then, the animal testing which supported Bendecting approval
also served to overcomes charlatanism and manipulations in
courts and to establish the admissibility of scientific evidence as
based on empirical data (and no more on expert authority)
1) History as a Tool in Science Education.

Telling stories is the best way to **understand science and to debunk fake science**.

Here are some recent interesting papers centred on history and story telling as valuable tools:

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**The Effects of Anti-Vaccine Conspiracy Theories on Vaccination Intentions**

Daniel Jolley*, Karen M. Douglas*
School of Psychology, University of Kent, Canterbury, United Kingdom

**Abstract**

The current studies investigated the potential impact of anti-vaccine conspiracy beliefs, and exposure to anti-vaccine conspiracy theories, on vaccination intentions. In Study 1, British parents completed a questionnaire measuring beliefs in anti-vaccine conspiracy theories and the likelihood that they would have a fictitious child vaccinated. Results revealed a significant negative relationship between anti-vaccine conspiracy beliefs and vaccination intentions. This effect was mediated by the perceived dangers of vaccines, and feelings of powerlessness, disillusionment, and mistrust in authorities. In Study 2, participants were exposed to information that either supported or refuted anti-vaccine conspiracy theories, or a control condition. Results revealed that participants who had been exposed to material supporting anti-vaccine conspiracy theories showed less intention to vaccinate than those in the anti-conspiracy condition or controls. This effect was mediated by the same variables as in Study 1. These findings point to the potentially detrimental consequences of anti-vaccine conspiracy theories, and highlight their potential role in shaping health-related behaviors.

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**Effective Messages in Vaccine Promotion: A Randomized Trial**

Brendan Nyhan, Jason Reifler, Sean Richey and Gary L. Freed
Pediatrics; originally published online March 3, 2014.
DOI: 10.1542/peds.2013-2365

**Effective Messages in Vaccine Promotion:** A Randomized Trial

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**Human Vaccines & Immunotherapeutics** 9(8), 1795–1801; August 2013; © 2013 Landes Bioscience

**Story and science**

How providers and parents can utilize storytelling to combat anti-vaccine misinformation

Ashley Shelby* and Karen Ernst
Moms Who Vax, Twin Cities, MN, USA

Keywords: vaccines, anti-vaccine, social media, Facebook, immunization, vaccine hesitancy, Andrew Wakefield, autism

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**PEDIATRICS**

**Effective Messages in Vaccine Promotion: A Randomized Trial**

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**Lessons from an online debate about measles–mumps–rubella (MMR) immunization**

Michelle S. Nicholson1, Julie Leask2,4,5

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**Conclusion 1**

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<th>1) History as a Tool in Science Education.</th>
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Fatal attraction: the intuitive appeal of GMO opposition

Stefaan Blancke¹, Frank Van Breusegem²,³, Geert De Jaeger²,³, Johan Braeckman¹, and Marc Van Montagu²,³,⁴

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³ Department of Plant Biotechnology and Bioinformatics, Ghent University, 9052 Ghent, Belgium
⁴ Institute of Plant Biotechnology Outreach–VIB, Incubation and Innovation Center, Ghent University, 9052 Ghent, Belgium

Detecting Emotional Contagion in Massive Social Networks

Lorenzo Coviello¹, Yunkyu Sohn², Adam D. I. Kramer³, Cameron Marlow³, Massimo Franceschetti¹, Nicholas A. Christakis⁴,⁵, James H. Fowler²,⁶,⁷

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Beliefs, behaviors and HPV vaccine: Correcting the myths and the misinformation

Gregory D. Zimet⁸,⁹, Zeev Rosberger⁸,⁹, William A. Fisher⁴, Samara Perez⁸,⁹, Nathan W. Stupiansky *

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Conclusion 2

2) We need **Evidence-based policy making.**

Difference between Facts vs. Opinions and the benefit for politics

Nature 18 APRIL 2013, VOL 496, p.269

*Look after the pennies.* Government decisions about where to spend and where to cut should be based on evidence, not ideology.

“A smarter way is to follow the path pioneered by evidence-based medicine.”

Nature 12 SEPTEMBER 2013, VOL 501, 159

*A standard for policy-relevant science*

Ian Boyd calls for an auditing process to help policy-makers to navigate research bias.

Policy. Twenty tips for interpreting scientific claims _Nature_ Nov 2013

Conference on Science Advice to Governments – Auckland, August 28-29, 2014
We lived in small bands of hunter-gatherers for millennia and millennia and is in this long period that our brain has adapted (cognitive evaluations and moral...
BIOLOGICAL EVOLUTION
Evolutive time

TECHNO-CULTURAL EVOLUTION
Cultural time
Technological time

Millions of years
(slow changes fixed in the genome)

Homo sapiens 2009

Few millennia or centuries
(quick cultural and environmental changes)

Biological time
Existential time
Evolutionary (or Darwinian) approach

WHY MISMATCH TO MODERNITY?
Because the modern (cultural and natural) environment is changing more rapidly than we (our genome) can adapt to it!! In other words, there has not been enough time for genetic evolution to reshape body and our brains (decision-making cognition) since we ceased to be hunter-gatherers.
Conclusion 3

We are not good to evaluate...

...the benefit/risk and the probability,

Our brain drives us to make bad decisions!

The evolutionary past must be considered

To elaborate a new form of education according to a brain which has...

.. a bounded rationality D. Kahneman
The exemplar case of EBOLA

The Zmapp, the experimental anti-Ebola drug administered to the 2 American volunteers, was obtained thanks to GMO tobacco leaves (Nicotiana benthamiana), and has previously been tested on animals, using mice (for creating monoclonal antibodies) and monkeys (in order to test the effectiveness). Also the 2 vaccines (GSK and Merck), which BigPharma gave for free, used animal testing....
Thanks for your attention!
Some problems of the near future

- Species specificity (thalidomide)

It is well known that thalidomide exhibits species-specific differences in its teratogenic actions. Many animal organisms have been used to study thalidomide’s actions, including chicks, rabbits, zebrafish, marine fish, armadillos, marsupials, hydra, and nonhuman primates. Also the timing appears to be central: in humans, thalidomide taken on the 20th day of pregnancy caused central brain damage, day 21 would damage the eyes, day 22 the ears and face, day 24 the arms, and leg damage would occur if taken up to day 28. Thalidomide did not damage the foetus if taken after 42 days gestation.

The future:

Personalized medicine (monoclonal antibodies)?