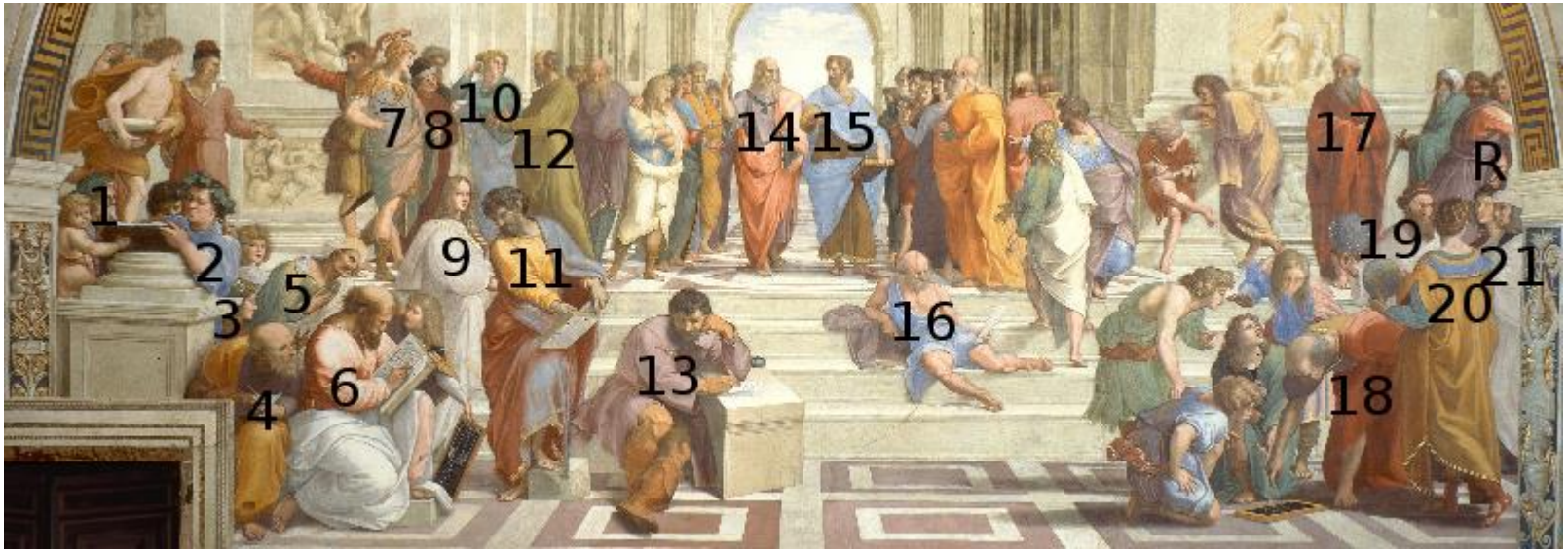
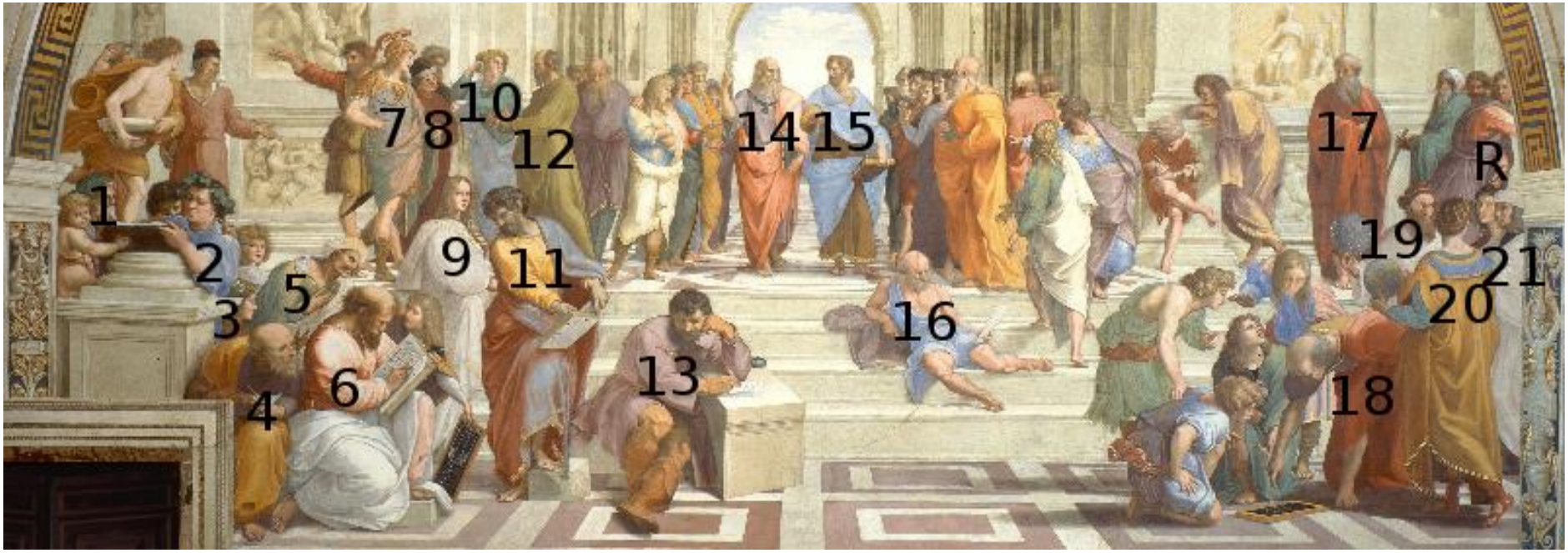
Ethics of clinical research

Olivier Jonquet

Raphaël *L'Ecole d'Athènes* (1510)



1-Zénon d'Elée
5-Averroès
6-Pythagore
7-Alcibiade/Alexandre le Grand
8-Xénophon
11-Parménide
12-Socrate
13-Héraclite
14-Platon
15-Aristote
16-Diogène
17-Plotin
18-Euclide
19-Zoroastre



1 : Zénon de Citium ou Zénon d'Élée
2 : Épicure
3 : Frédéric II de Mantoue
4 : Boèce ou Anaximandre ou Anaximandre
5 : Averroès
6 : Pythagore
7 : Alcibiade ou Alexandre le Grand
8 : Antisthène ou Xénophon
9 : Hypatie ou Francesco Maria della Rovere
10 : Eschine ou Xénophon
11 : Parménide
12 : Socrate
13 : Héraclite
14 : Platon
15 : Aristote
16 : Diogène de Sinope
17 : Plotin
18 : Euclide ou Archimède –
19 : Strabon ou Zoroastre
20 : Ptolémée
R : Raphaël
21 : Le Sodoma GA Bazzi

Aristote (384-322 BC)

- *Virtue is not natural, but is not against nature* (NE, 1103a24)

- *Life is contingency: vita in motu*

- Prudence is a cardinal virtue ; has its origin in reason

- Realistic moral : art of possible
  to keep within bounds
  prudence
  self developpement

What can I know?

What ought I to do?

What may I hope?

Immanuel Kant (1724-1804)

Kant : categorical imperative

- 1-*Act only according to that maxim whereby you can at the same time will that it should become a universal law without contradiction*
- 2-*Act in such a way that you treat humanity, whether in your own person of any other, never merely as a mean to an end, but always at the same time as an end.*
- 3-*Thus the third practical principes follows as the ultime condition of their harmony with practical reason : the idea of the very rational being as a universally legislating will*

Groundings of the Metaphysics of Morals

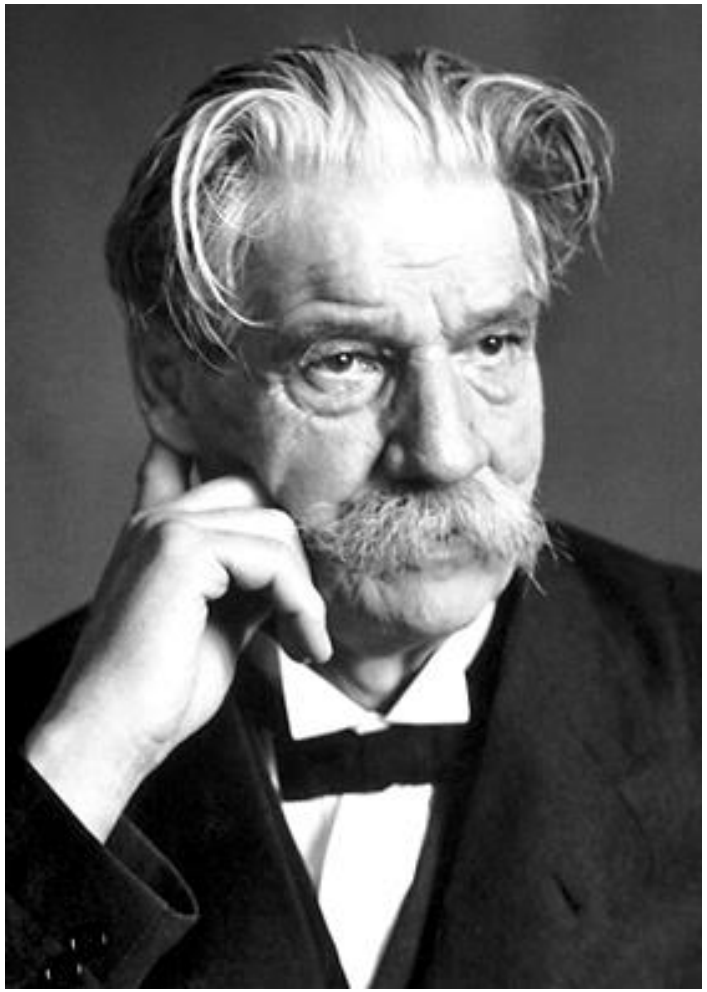
Paul Ricoeur (1913-2005)

- *The project of an accomplished life*
- *The goal of a good life with and for others within just institutions*
- *The shared admission of fragility*
- Inevitability of moral conflict (*Antigone-Creon*)

  Antigon is as inhuman as Creon
- *Dialogic dimension :* concrete wisdom that applies abstract rules to concrete cases and adapt moral and legal rules to concrete human needs and to the multiplicity of moral dilemnas

Jürgen Habermas (1929-), Emmanuel Levinas (1906-1995),

John Rawls (1921-2002)…



Ethics is recognition of our responsability towards anything living

Albert Schweitzer (1875-1965)

Mt 7,12
So in everything, do to others what you would have them do to you.

Lc 6,31
Do to others as you would have them do to you.

Rm 13,10
Love does no harm to a neighbor. Therefore love is the fulfillment of the law.

Fritz Jahr (1895-1963)
Pasteur luthérien allemand

Francis of Assisi

Jean-Jacques Rousseau

Bio-Ethyk ; eine Umschau ûber die ethschen Beziehungen des Menschen zu Tier und pflange

Bioéthique : a review of ethics relationships between men, animals and plants

***Kosmos : Handweiserfûr Naturfreunde*, 1927** *24(1):2-4*

Science , research

Methodologic groundings of science

- Science : *scire*
- Search objectivity, eliminate subjectivity
- Segmentation of the problem in sub independant problems
- No interaction between observer and observed
- Reproduction of results :

Particular facts are never scientific; only generalization can etablish science (Claude Bernard)

- Invariability
- A cause, an effect
- Build models of the explored reality
- Know the HOW of the world, not WHY
- Morally neutral

Why clinical research?

- Improve knowledge
  -on a disease (physiopathology, aetiology…)
  -on man

Improve treatments
  -drugs
  -devices
  …

Research on man (or woman…)

- Research activity with the goal to product a generalisable knowledge

  -activity : procedure, methodology

  -knowledge : distinct from care

  -generalisable, universal : from singular to general and from general to singular

Théophraste Bombast von Hohenheimdit : Paracelse (1493-1541)

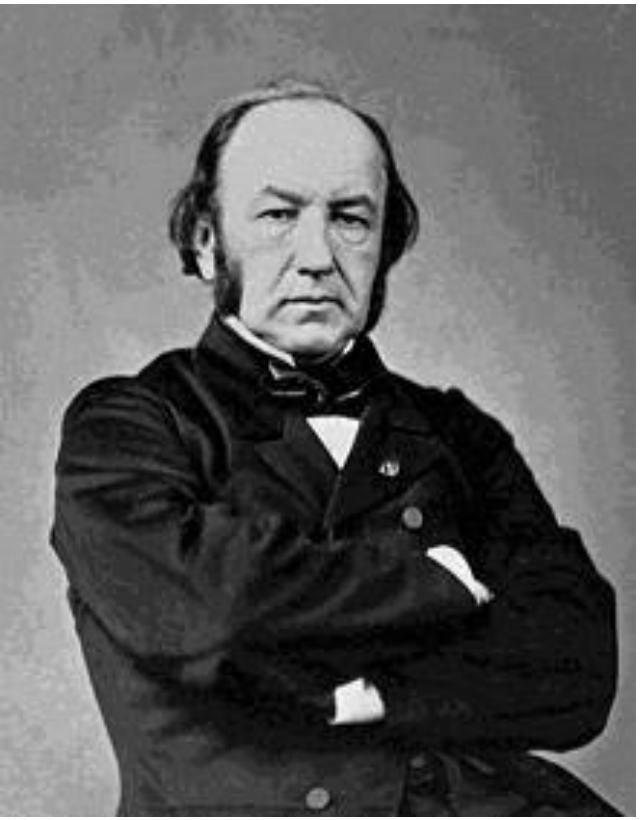
alterius non sit qui suus esse potest

Medicine

-of the man

-of the human being

-of one man



Claude Bernard (1813-1878)

Among the experiments that may tried on man, those that can only harm are forbidden, those that are innocent are permissible, and those that may do good are obligatory.

It is immoral then, to make an experiment on man when it is dangerous to him, even though the result may be useful to others.

There are some doctors who declare themselves against experimentation, *and only in favour* observation.(…)*experimentation cannot exist without observation. Experiment is only* provoked *observation.*

Every day physician make therapeutic experiments on patients and every day surgeon do vivisections…

Hippocratic aphorisms

- Ὁ βίος βραχὺς, Life is short
- ἡ δὲ τέχνη μακρὴ, Art is long
- ὁ δὲ καιρὸς ὀξὺς, Opportunity fleeting
- ἡ δὲ πεῖρα σφαλερὴ, Experience perilous
- ἡ δὲ κρίσις χαλεπή Decision difficult

SHOCK!!!

Courrier Adolf Hitler

ADOLF HITLER

BERLIN, den 1.Sept.1939.

Reichsleiter Bouhler und
Dr. med. Brandt

sind unter Verantwortung beauftragt, die Befug-
nisse namentlich zu bestimmender Ärzte so zu er-
weitern, dass nach menschlichem Ermessen unheilbar
Kranken bei kritischster Beurteilung ihres Krank-
heitszustandes der Gnadentod gewährt werden kann.

Adolf HITLER

Berlin le 1er septembre 1939

Monsieur le directeur d'empire BAULHER et
Monsieur le docteur en médecine BRANDT

se voient confier la responsabilité d'élargir les attributions
de médecins désigner nominativement, afin que des malades,
qui peuvent être considérés selon les connaissances humaines comme incurables
puissent bénéficier d'une mort gracieuse, quand leur état de santé devient
particulièrement critique

Signé Adolf HITLER

mention manuscrite : apparemment

m'a été remis par Baulher le 27/8/1940

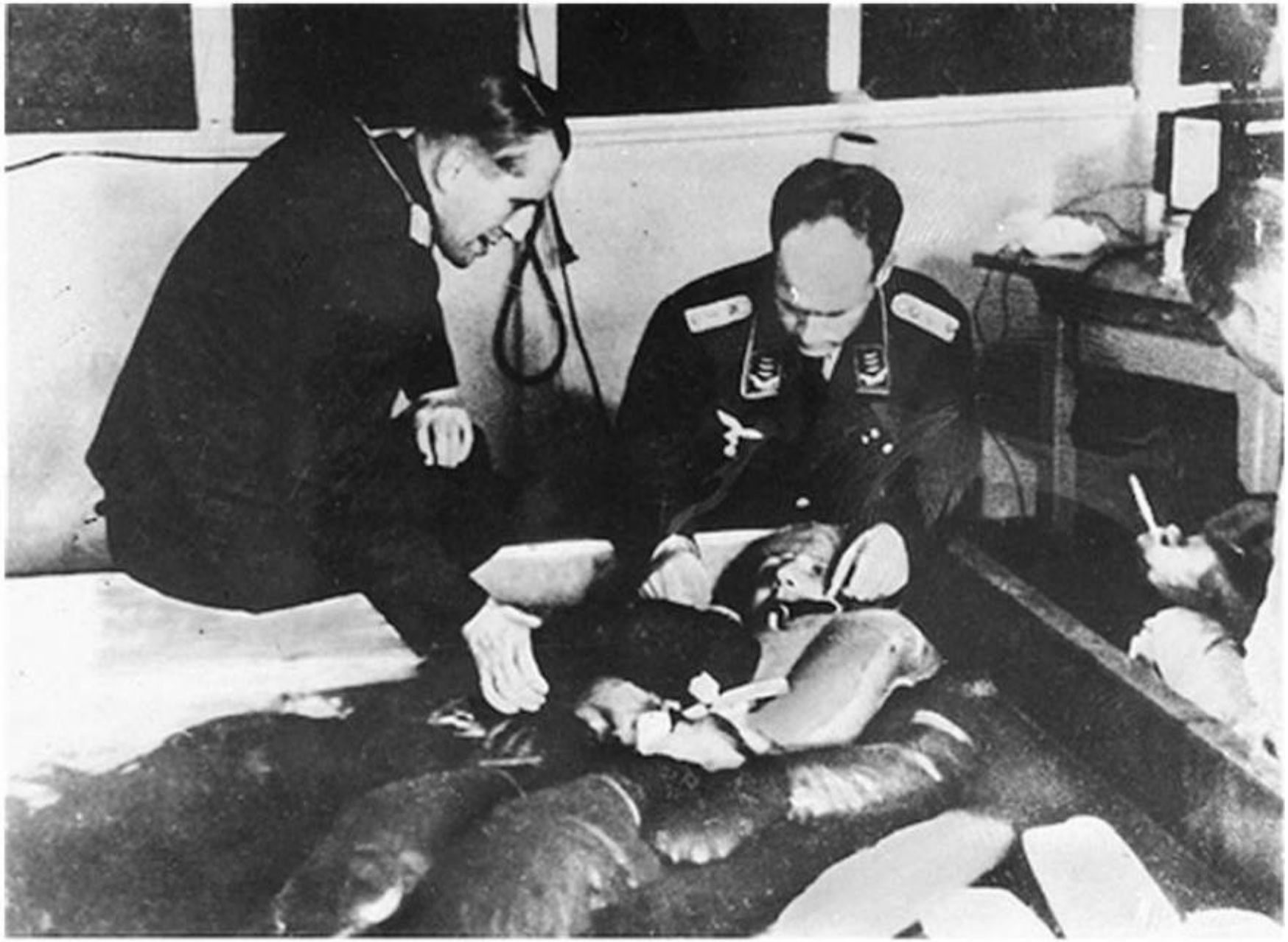
Signé : Dr Gütner

Gnadentod : mort gracieuse
Gnadenschuss : coup de grâce du fusillé
……..

Nuremberg trial 18/10/1945-1/10/1946

Nazi physicians trial Nuremberg 9/12/1946-21/08/1946

Dr Berthold Ostertag (1895-1975) Hôpital de la Charité Berlin



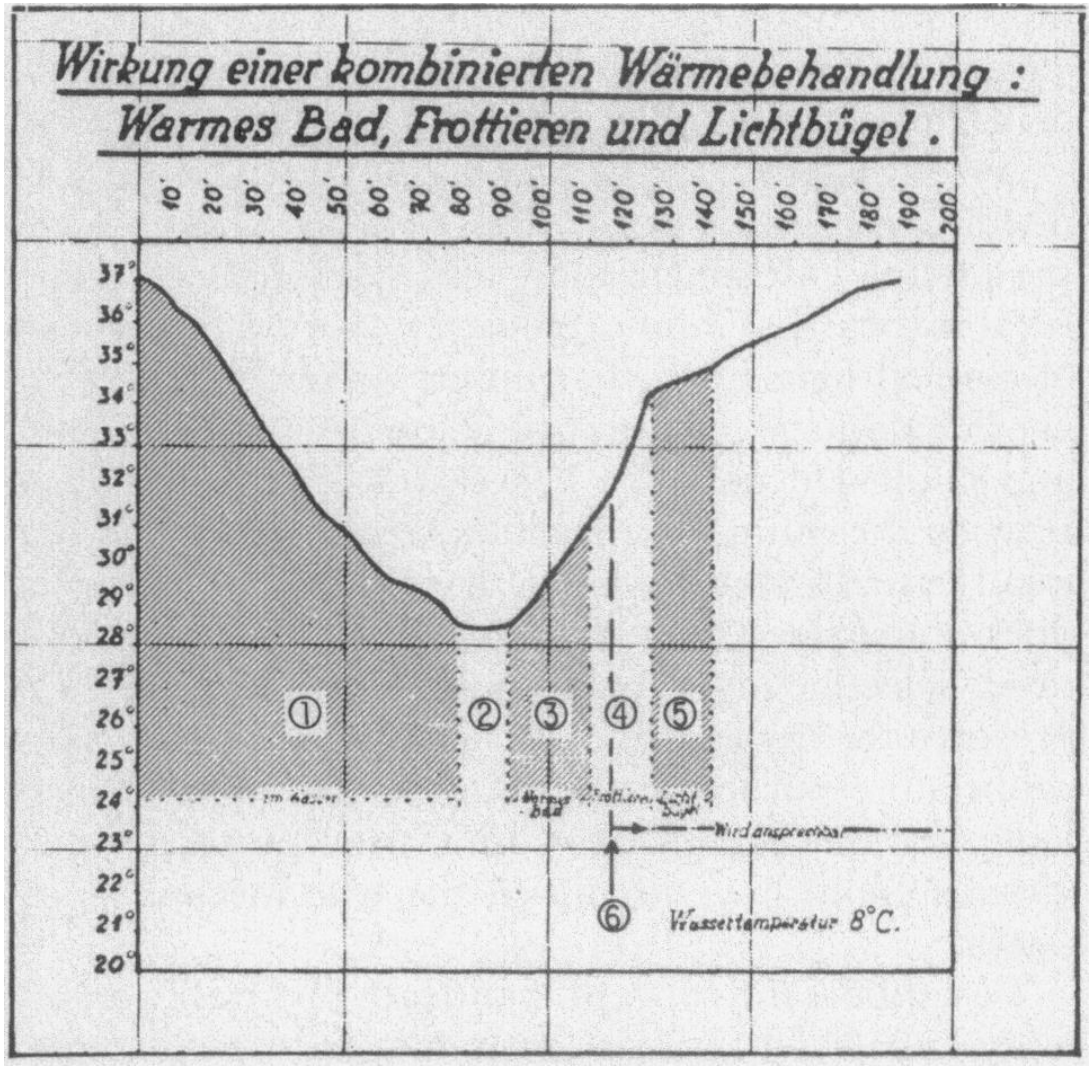
Hypothermia experiment Dachau : Dr Sigmund Rascher et Dr Ernst Holzloehner

SPECIAL ARTICLE

NAZI SCIENCE — THE DACHAU HYPOTHERMIA EXPERIMENTS

ROBERT L. BERGER, M.D.

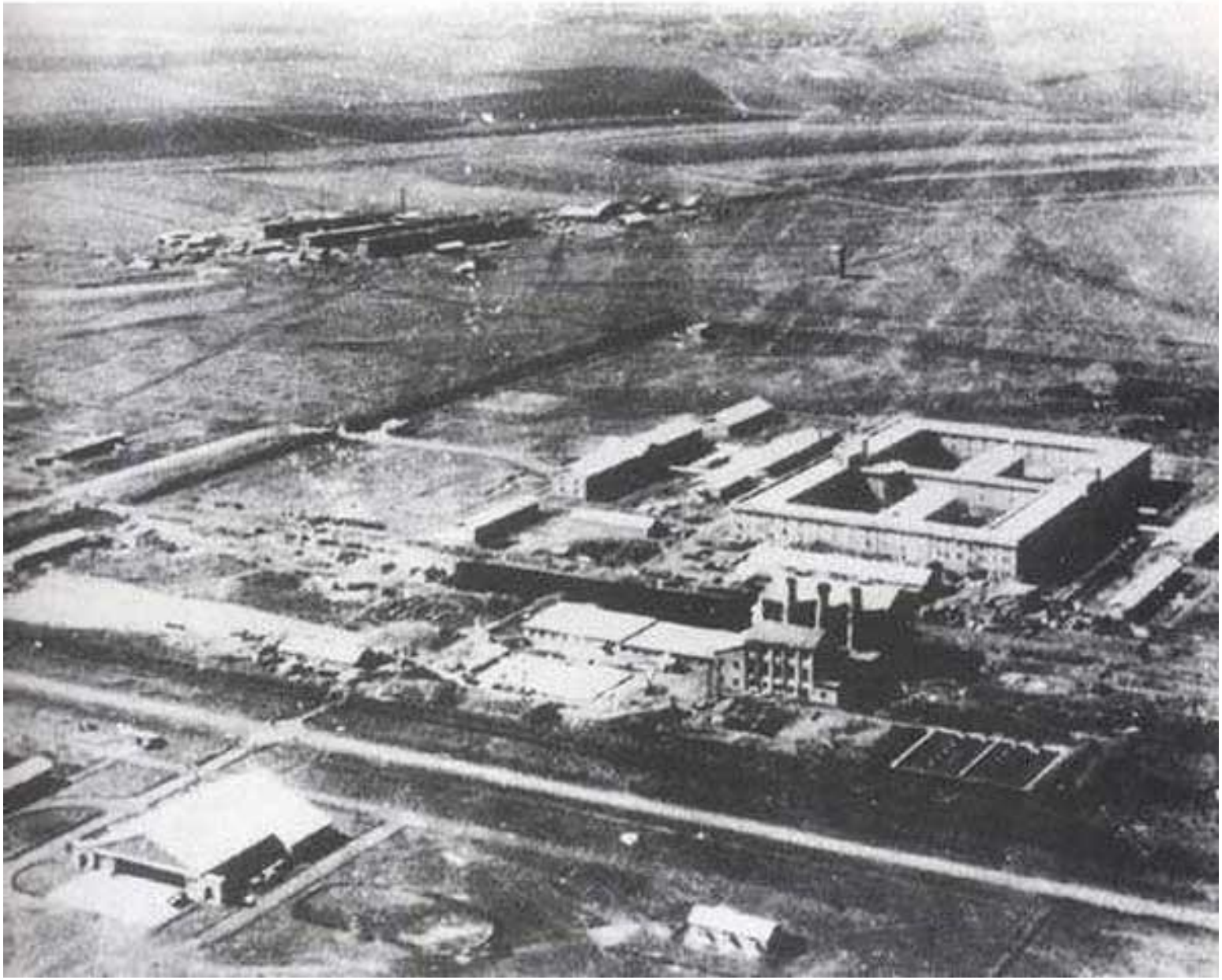
THE NEW ENGLAND JOURNAL OF MEDICINE May 17, 1990



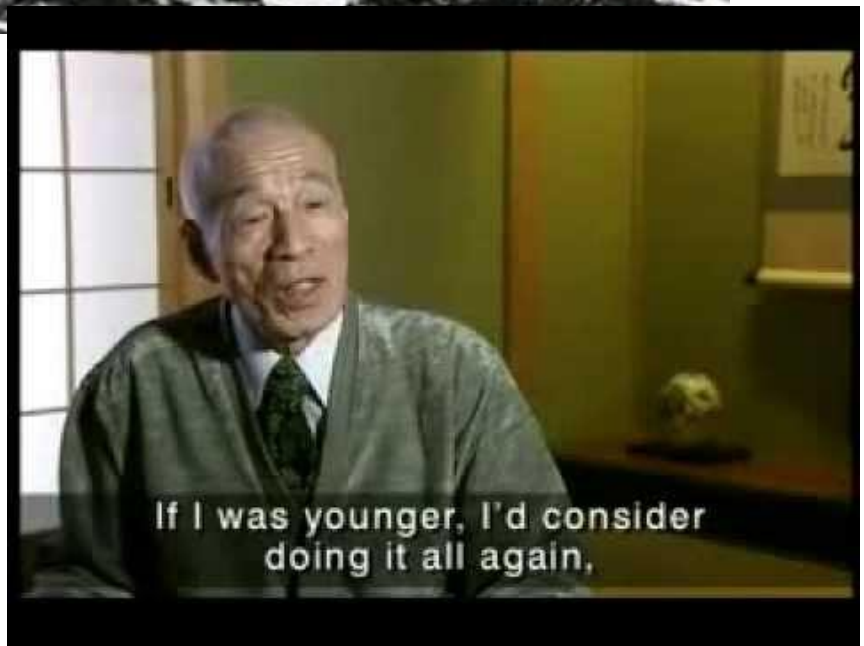
Miscellaneous

- Paludism
- Typhus
- Tuberculosis
- Sterilizations
- Poisons
- « Polygal » : hemostatic
- Gas gangrene

Don’t forget japanese!

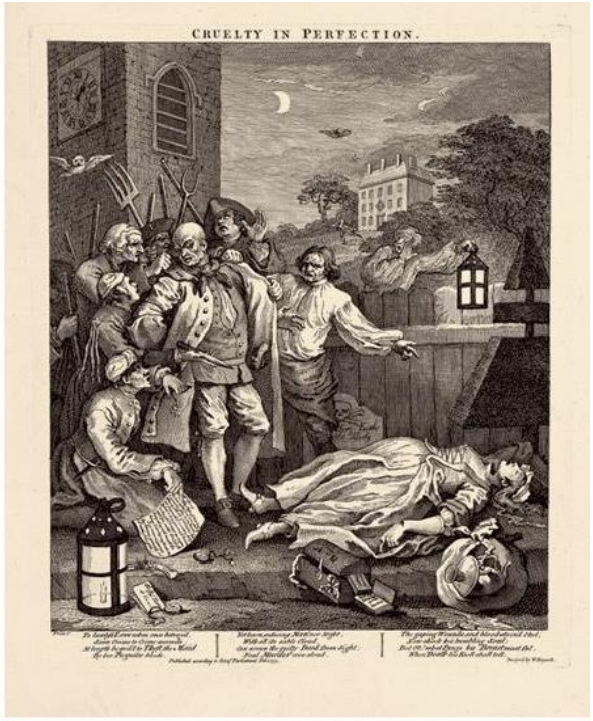


Unité 731 Pengfan (Mandchourie)

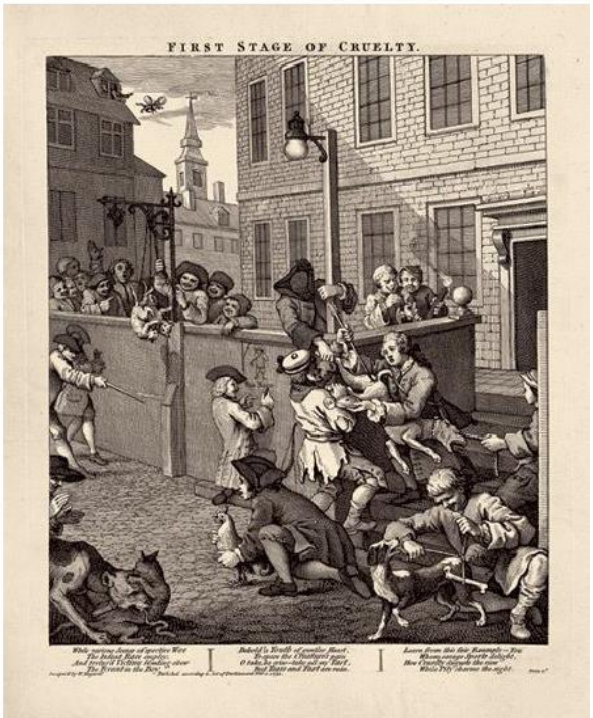


Shiro Ishii (1892-1959)

We come from far away



William Hogarth (1697-1764)



For the custom of tormenting and killing of beasts will, by degrees, harden their minds even towards men.

Locke (1632-1704)

Consent

Convicts
in corpore vili

Vivisections

- Hérophile (320-260 BC)

Fiat experimentum in corpore vili

Herophilus, ille medicus aut lanius (Celse)

- Diderot (1713-1784)

Is guilty dissection inhuman?

The archer of Meudon : first surgical lithotomy Germain Colot in front of Louis XI (1474)

History

- Trial *Slater v. Baker-Stapelton*

It appears from the evidence of the surgeons that it was improper to desunite the callous without consent ; this is the usage and law of surgeons

- Coley's toxins

After some deliberations, he consented

WB Coley (1862-1936)

History

- Louis Pasteur (1822-1895) *Lettre à l'empereur du Brésil*

- Sanarelli (1864-1940)

1897 five patients experiment injection of « bacillus » of yellow fever

- William Osler (1849-1919)

To deliberately inject a poison of known high degree of virulency into an human being, unless you obtain that man's sanction, is nort ridiculous, it is criminal (1898)

ONZIÈME ANNÉE. — N° 24 — 16 DÉCEMBRE 1859.

GAZETTE MÉDICALE DE LYON

ET RECUEIL DES ACTES DE LA SOCIÉTÉ IMPÉRIALE DE MÉDECINE

DIRIGÉE PAR LE DOCTEUR P. DIDAY

SECRÉTAIRE-GÉNÉRAL DE LA SOCIÉTÉ IMPÉRIALE DE MÉDECINE,

SECRÉTAIRE-GÉNÉRAL HONORAIRE DE L'ASSOCIATION DE PRÉVOYANCE DES MÉDECINS DU RHÔNE.

Journal bi-mensuel. — On s'abonne, à Lyon, chez VINGTRINIER, quai St-Antoine, 35 ; et Mme PHILIPPE, r. St-Dominique, 7. — Paris, chez SAVY fils, libraire, rue Bonaparte, 10. — Prix : Lyon, 15 fr. par an ; Départements, 17 fr. ; Étranger, selon les tarifs postaux. — Adresser lettres et paquets FRANCO à M. DIDAY, rue des Célestins, 5.

Tribunal correctionnel de Lyon (4e chambre).

Présidence de M. Baron, vice-président.

Audience du 8 décembre 1859.

BLESSURES VOLONTAIRES.

L'affaire dont nous allons rendre compte, avait attiré à l'audience une grande affluence de docteurs en médecine de notre ville, nous distinguons parmi eux MM. Rollet, Diday, Lacour, Valette et autres; l'honorabilité des prévenus, la position de l'un d'eux, aide-major à l'hospice de l'Antiquaille, le caractère et la qualification de la prévention, tout concourait à rendre intéressante la discussion qui allait avoir lieu. — A midi, l'huissier d'audience appelle l'affaire de M. le procureur impérial contre MM. Guyénot et Gailleton. — M. Roë, substitut, invite les prévenus à s'asseoir auprès de leur défenseur. — Voici en quelques mots le fait qui donne lieu à la poursuite.

Le 4 décembre 1858, un jeune enfant de la Charité, nommé B..., âgé de 10 ans, entra à l'hospice de l'Antiquaille pour être traité d'une teigne faveuse, confluente, qui intéressait tout le cuir chevelu; le malade présentait quelques symptômes de scrofules, sa santé générale était mauvaise. Pendant près d'un mois, la médication ordinaire appliquée à ce genre de maladie, était restée sans effet, lorsque le 7 janvier 1859, M. Guyénot, alors interne des vénériens, demanda au chef de service, M. Gailleton, l'autorisation d'inoculer au malade le pus d'accidents constitutionnels (plaques muqueuses). L'autorisation lui fut accordée et quatre piqûres furent faites au bras droit du malade. — Pendant un mois, aucun résultat ne se montra; le 10 février se manifestèrent deux ulcérations superficielles de deux millimètres de diamètre; dans le courant de mars apparut sur le tronc une roséole qui disparut après six jours de durée. Le 9 avril tout avait disparu, la teigne s'améliorait, se modifiait d'une façon heureuse.

Au mois d'août, la teigne avait complètement disparu; l'enfant se portait à merveille. M. Guyénot publia l'observation dans la *Gazette hebdomadaire de Paris* (15 avril 1859) (1).

M. l'avocat impérial a déclaré d'abord que les efforts de la science sont dignes du plus grand intérêt, mais que le droit d'expérimenter ne peut rester sans contrôle. Recherchant ensuite quelles sont les conditions d'une expérimentation légitime, M. l'avocat impérial admet comme indispensables les conditions suivantes : 1° La science et le titre de l'expérimentateur. 2° La guérison du malade comme le but unique, essentiel et fondamental; ainsi, par exemple, l'emploi d'un moyen nouveau dans une maladie désespérée et quand on a employé tous les autres moyens. 3. Quand l'expérience a un autre but que la guérison du malade, qu'elle n'est qu'une expérience scientifique, on doit avoir le consentement de l'intéressé.

Après avoir exposé ces principes qui serviront de bases à l'accusation, M. l'avocat impérial fait connaître les faits et reproche à M. Guyénot d'avoir expérimenté sans un titre de docteur, de ne pas avoir eu pour but la guérison du malade.

Arrivant ensuite à l'examen du fait lui-même, M. le substitut reconnaît tous les éléments du délit de blessures volontaires, soit dans la piqûre elle-même soit surtout dans ses conséquences.

Walter Reed (1901)

- Ethics of research requires

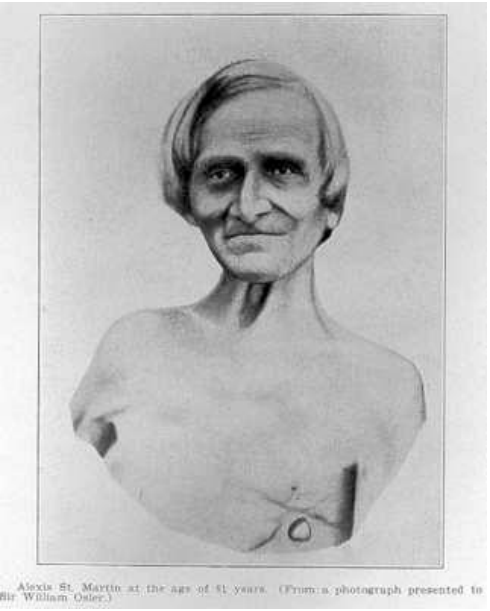
  self-experiment

  written consent

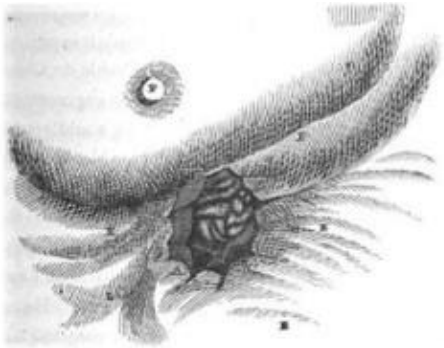
  remuneration, payment

  only adult

  mention in papers *with his full consent*



Alexis St. Martin at the age of 31 years. (From a photograph presented to Sir William Osler.)



The appearance which is presented when the valve was pushed back is shewn in the above figure.

A A A, are the edges of the aperture. B indicates the cavity of the stomach as seen when the valve is depressed. C, the valve itself. EEE, the cicatrix of the original wound. F, the nipple.

Alexis Saint Vincent (1794-1880)

Showing the mean time of digestion of the different Articles of Diet, naturally, in the Stomach, and artificially, in Vials, on a bath.

The proportion of gastric juice to aliment, in artificial digestion, was *generally* calculated at one ounce of the former to one drachm of the latter, the bath being kept as near as practicable at the natural temperature, 100° Fahrenheit, with frequent agitation.

Articles of Diet.	*Mean time of chymification*			
	In Stomach.		In Vials.	
	prep.	h. m.	prep.	h. m.
Rice,	boiled	1 00		
Sago,	do.	1 45	boiled	3 15
Tapioca,	do.	2 00	do.	3 20
Barley,	do.	2 00		
Milk,	do.	2 00	do.	4 15
Do.	raw	2 15	raw	4 45
Gelatine.	boiled	2 30	boiled	4 45
Pig's feet, soused,	do.	1 00		
Tripe, do.	do.	1 00		
Brains, animal,	do.	1 45	do.	4 30
Venison, steak,	broiled	1 35		
Spinal marrow, animal,	boiled	2 40	do.	5 25
Turkey, domesticated,	roasted	2 30		
Do. do.	boiled	2 25		
Do. wild,	roasted	2 18		
Goose, do.	do.	2 30		
Pig, sucking	do.	2 30		
Liver, beef's, fresh,	broiled	2 00	cut fine	6 30
Lamb, fresh,	do.	2 30		
Chicken, full grown,	fricas'd	2 45		
Eggs, fresh,	h'rd bld	3 30	h'rd bld	8 00
Do. do.	soft bld	3 00	soft bld	6 30
Do. do.	fried	3 30		
Do. do.	roasted	2 15		
Do. do.	raw	2 00	raw	4 15
Do. whipped.	do.	1 30	whipped	4 00
Custard,	baked	2 45	baked	6 30
Codfish, cured dry,	boiled	2 00	boiled	5 00

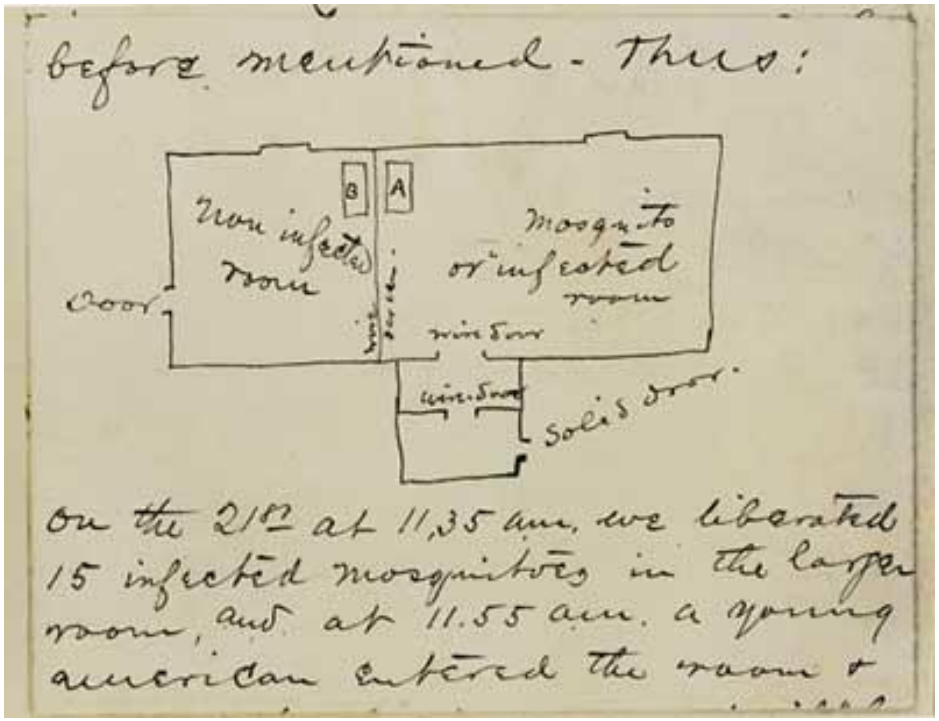
Bonaparte

Les pestiférés de Jaffa

Desgenettes

Figure 1.2. Walter Reed, standing in white uniform with colleagues, as Jesse Lazear inoculates James Carroll

Carlos Finlay (1833-1915) **Walter Reed (1851-1902)**



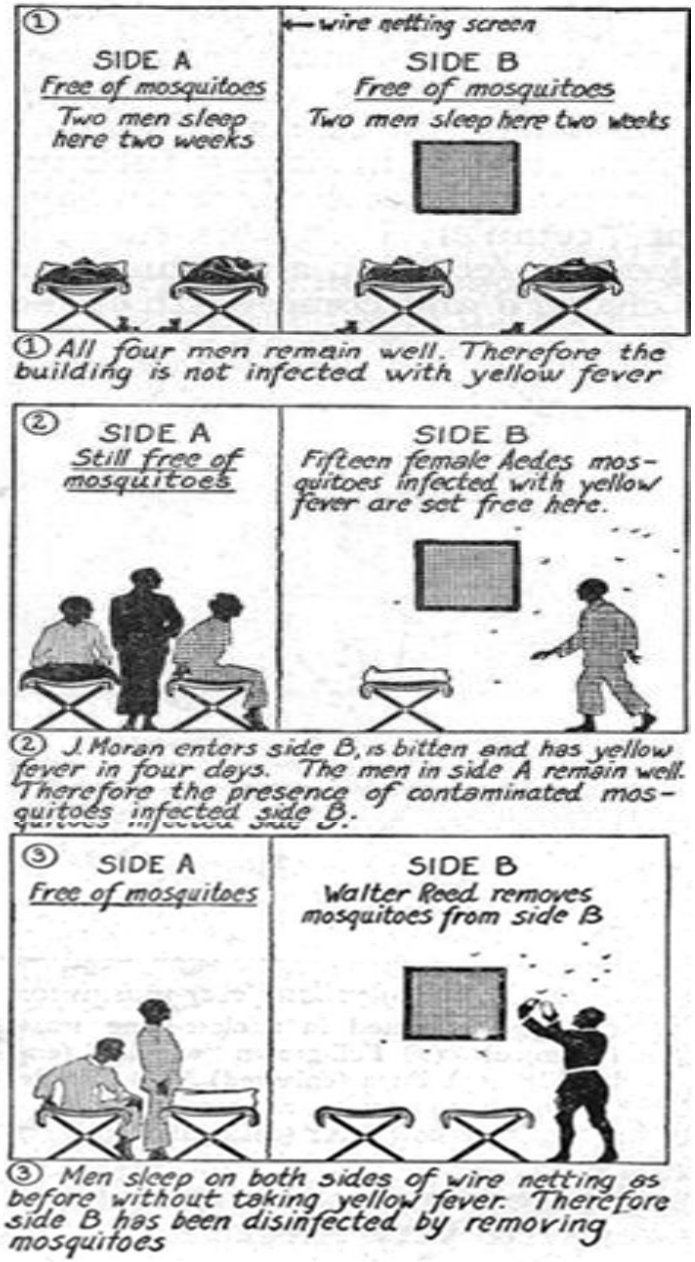
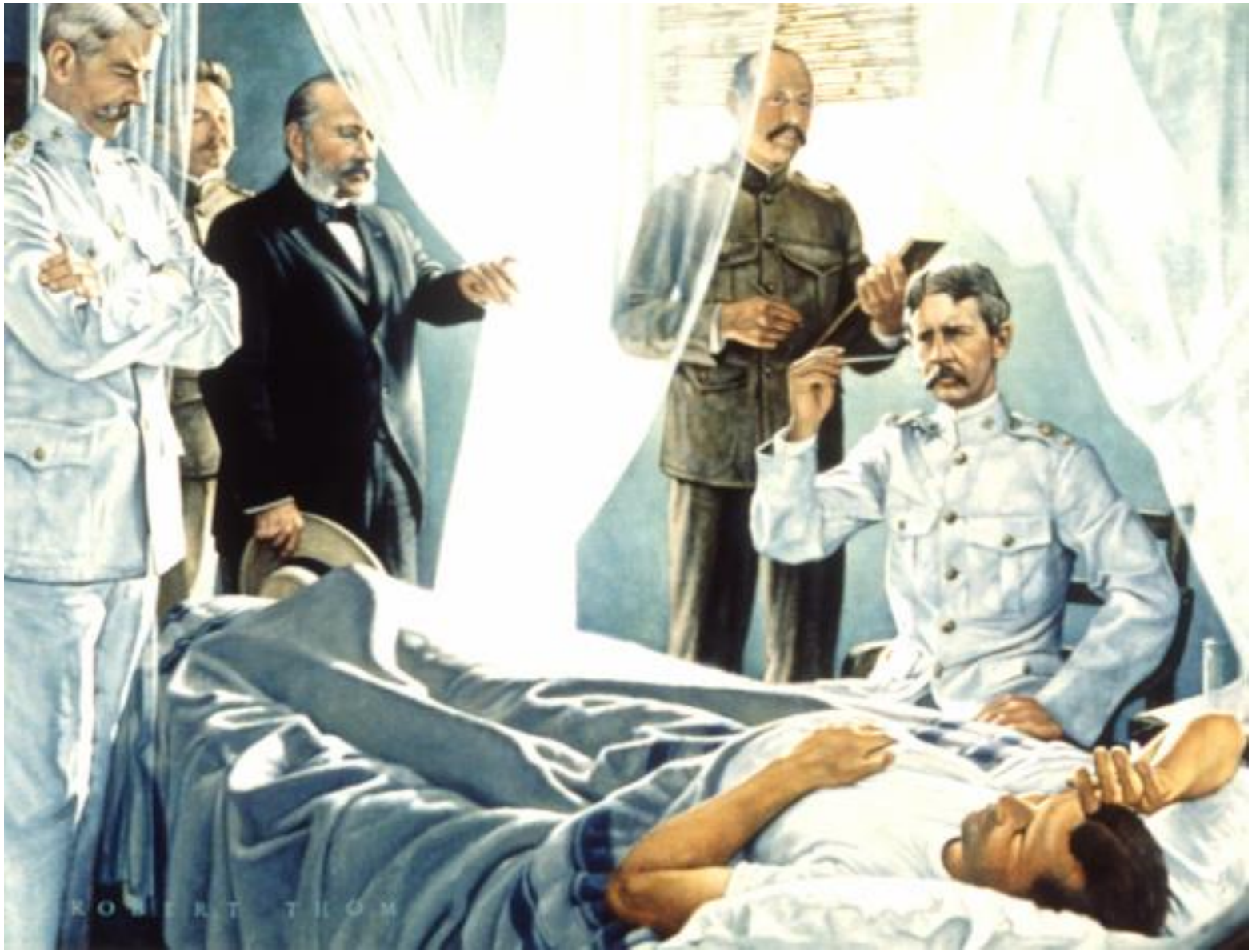


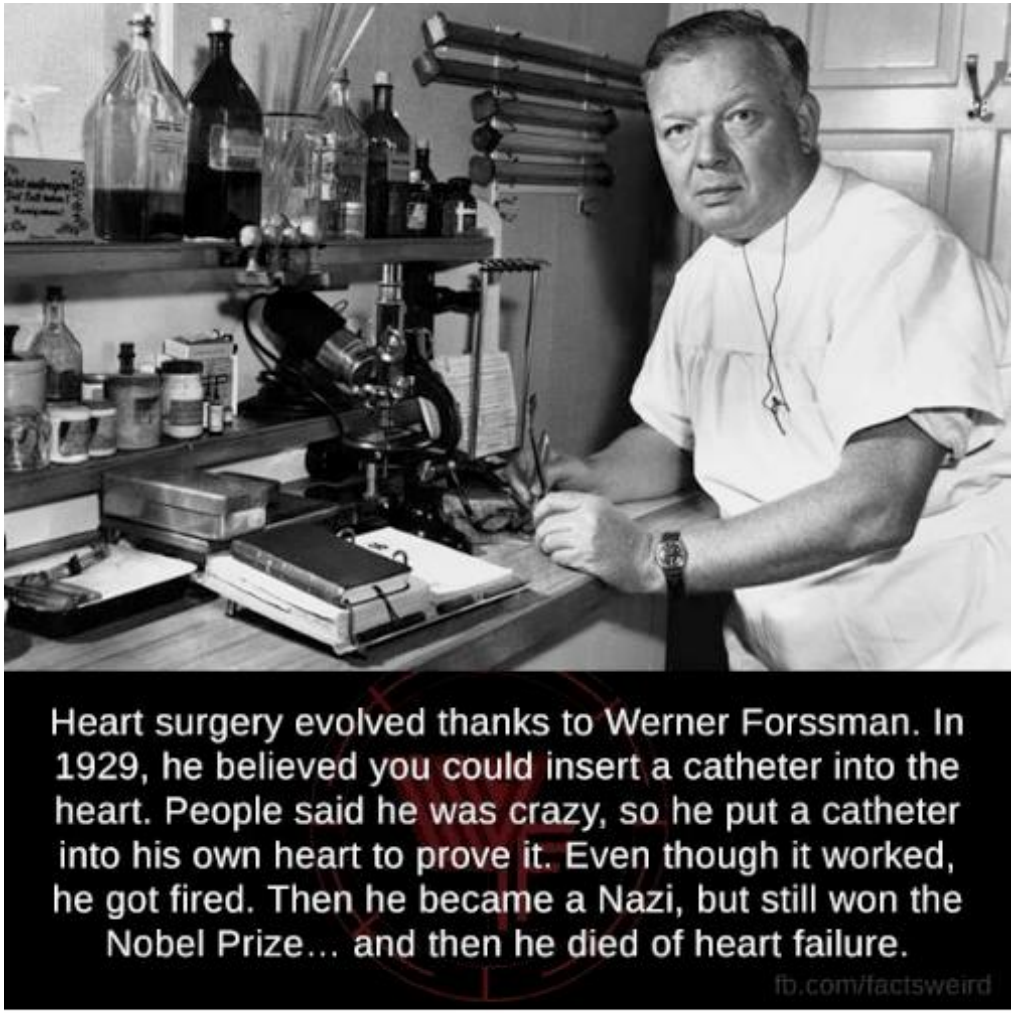
Figure 1.1. Illustrated Depiction of Yellow Fever Experiment. Source: Papers of Jefferson Randolph Kean, MSS 628, Special Collections, University of Virginia Library, Charlottesville, Va. Reproduced with permission.



Carlos Finlay (1833-1915)

Walter Reed (1851-1902)

Werner Forssman (1904-1979)
First cardiac catheterism (with ureteric catheter)



Consent

- *Agree with*
- From latin *consentire : feeling with*
- *Consensus* (Cicero 106-43 BC): in accordance with oneself, others and nature
- Implies a sympathy between two persons and not between a person and a project or a paper (of full consent...)
- Ethical involvement
- But is not sufficient (dwarf tossing)!

Expérience de Milgram (1960)

Public Announcement

WE WILL PAY YOU $4.00 FOR ONE HOUR OF YOUR TIME

Persons Needed for a Study of Memory

*We will pay five hundred New Haven men to help us complete a scientific study of memory and learning. The study is being done at Yale University.

*Each person who participates will be paid $4.00 (plus 50c carfare) for approximately 1 hour's time. We need you for only one hour: there are no further obligations. You may choose the time you would like to come (evenings, weekdays, or weekends).

***No special training, education, or experience is needed. We want:**

Factory workers	Businessmen	Construction workers
City employees	Clerks	Salespeople
Laborers	Professional people	White-collar workers
Barbers	Telephone workers	Others

All persons must be between the ages of 20 and 50. High school and college students cannot be used.

*If you meet these qualifications, fill out the coupon below and mail it now to Professor Stanley Milgram, Department of Psychology, Yale University, New Haven. You will be notified later of the specific time and place of the study. We reserve the right to decline any application.

*You will be paid $4.00 (plus 50c carfare) as soon as you arrive at the laboratory.

TO:
PROF. STANLEY MILGRAM, DEPARTMENT OF PSYCHOLOGY, YALE UNIVERSITY, NEW HAVEN, CONN. I want to take part in this study of memory and learning. I am between the ages of 20 and 50. I will be paid $4.00 (plus 50c carfare) if I participate.

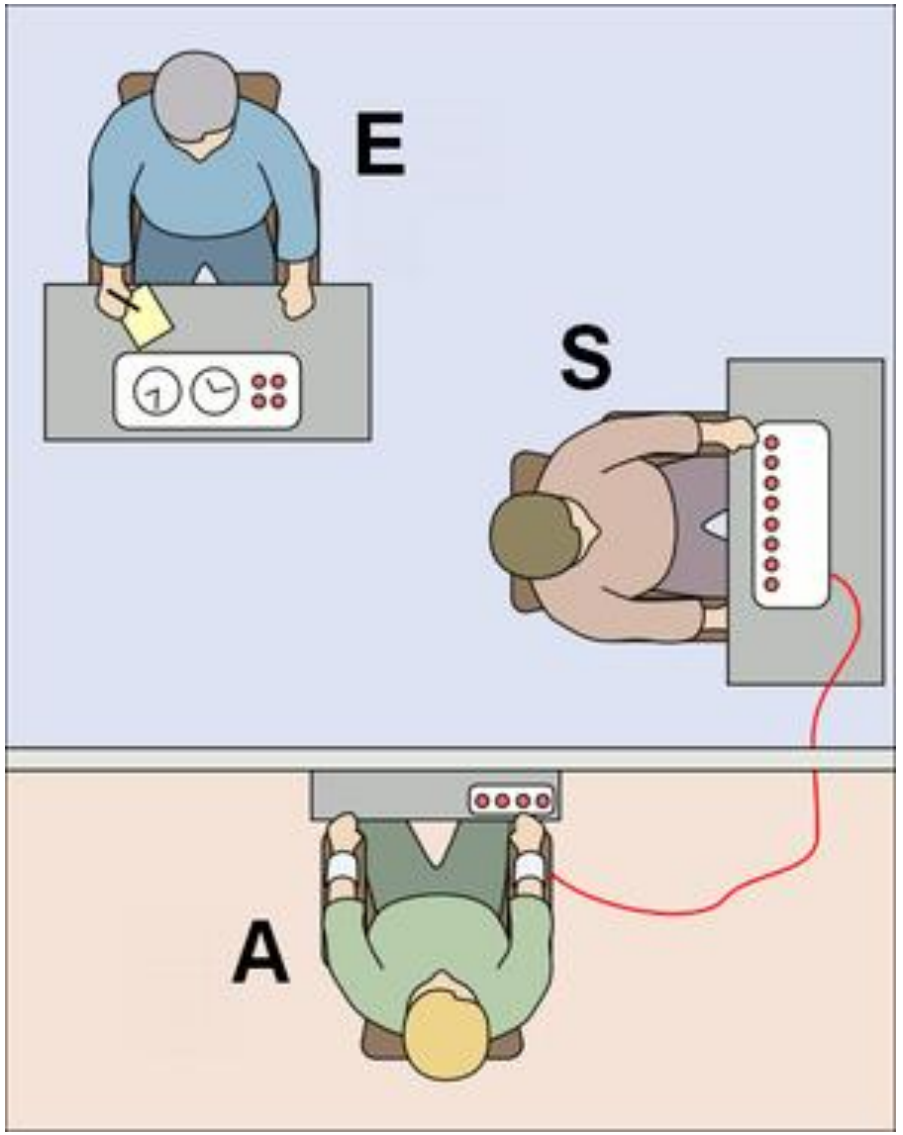
NAME (Please Print). . . . . .

ADDRESS . . . . . .

TELEPHONE NO. . . . . Best time to call you . . . . . .

AGE . . . . . OCCUPATION . . . . . SEX . . . . . .
CAN YOU COME:

WEEKDAYS . . . . . EVENINGS . . . . . WEEKENDS . . . . . .



Dignity : Immanuel kant

What is related to general human inclinations and needs has a market price*;*

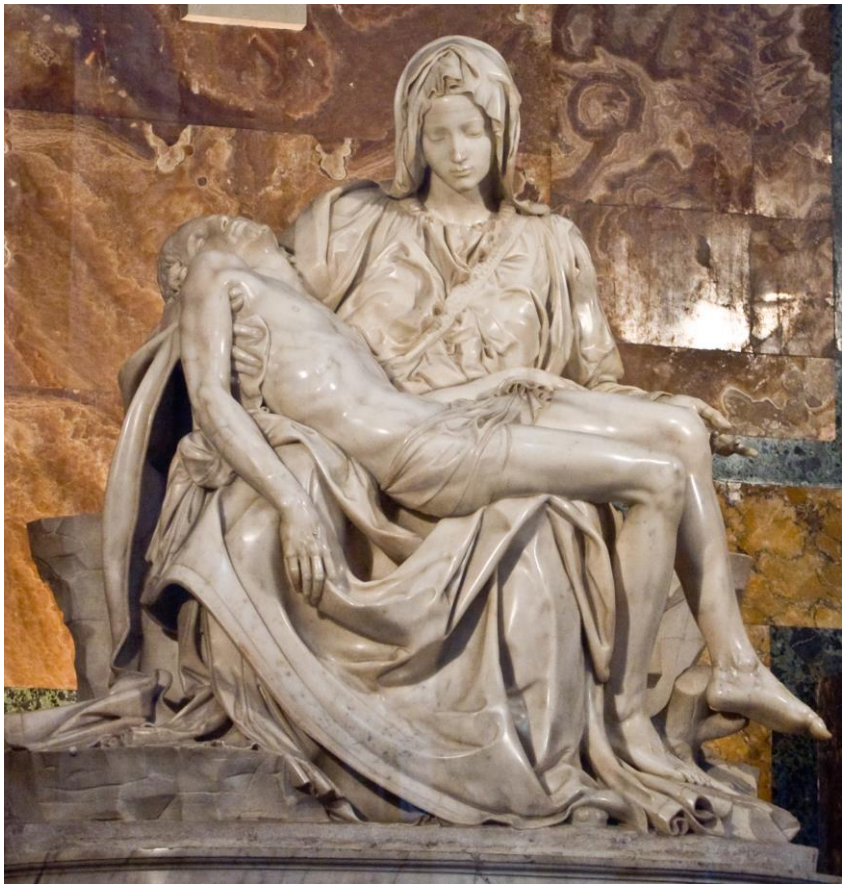
That which, even without presupposing such a need, conforms with a certain taste has a fancy price;

But that which constitutes the condition under which alone something ***can be an end in itself has not merely a relative value, that is, a price, but an inner value, that is*** **dignity.**

Morality, and humanity insofar as it is capable of morality, is that which alone has dignity

Information

- Give a *form* to a *substance* (Aristote)
- Help patient to be shaped (*en forme*), in accepted way (dans les *formes*)



Michelangelo (1475-1564) *Pieta*

End of the second world war (1939-1945)

Nazi physicians trial Nuremberg 9/12/1946-21/08/1946

Nuremberg code

1-Required is the voluntary, well-informed, understanding consent of the human subject in a full legal capacity.

2-The experiment should aim at positive results for society that cannot be procured in some other way.

3-It should be based on previous knowledge (like, an expectation derived from animal experiments) that justifies the experiment.

4-The experiment should be set up in a way that avoids unnecessary physical and mental suffering and injuries.

5-It should not be conducted when there is any reason to believe that it implies a risk of death or disabling injury.

Nuremberg code

6-The risks of the experiment should be in proportion to (that is, not exceed) the expected humanitarian benefits.

7-Preparations and facilities must be provided that adequately protect the subjects against the experiment's risks.

8-The staff who conduct or take part in the experiment must be fully trained and scientifically qualified.

9-The human subjects must be free to immediately quit the experiment at any point when they feel physically or mentally unable to go on.

10-Likewise, the medical staff must stop the experiment at any point when they observe that continuation would be dangerous.

Special Communication

World Medical Association Declaration of Helsinki
Ethical Principles for Medical Research Involving Human Subjects

World Medical Association

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington, DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/

All is right?

Tuskege (Alabama)

- From 1932, forty years follow-up of 400 syphilitic black people and 200 free subjects
- Aim : understand natural course of the disease
- But : 1932 Salvarsan®(Paul Ehrlich Nobel prize 1908)

  1944 Penicillin
- 1969 CDC continues experiment
- 1972 investigations by newspapers…
- 1997 Pdt Clinton apologizes : *clearly racist study*…

Willowbrook

- Center for mentally retarded children
- Children were intentionnaly given hepatitis in an attempt to track development of hepatitis
- Follow-up by NYC university
- They justified their deliberate infections and exposures by claiming that given that there was a high rate of infection in the institution it was practically inevitable that the children would become infected.
- Natural history of a disease…

The Willowbrook Letters: Criticisms and Defense. **The Lancet**, April 10, May 8, June 5, and July 10, 1971

- After, Belmont report

Belmont report : *Principles of bioethics*
(Beauchamp and Childress 1978)

- **Autonomy** – one should respect the right of individuals to make their own decisions

  Nonmaleficence – one should avoid causing harm

  Beneficence – one should take positive steps to help others

  Justice – benefits and risks should be fairly distributed

In France

- Nothing until 1988…

- Huriet-Serusclat Law defines conditions for ethical research

Developping countries?

The New England
Journal of Medicine

Volume 331 NOVEMBER 3, 1994 Number 18

REDUCTION OF MATERNAL–INFANT TRANSMISSION OF HUMAN IMMUNODEFICIENCY VIRUS TYPE 1 WITH ZIDOVUDINE TREATMENT

EDWARD M. CONNOR, M.D., RHODA S. SPERLING, M.D., RICHARD GELBER, PH.D., PAVEL KISELEV, PH.D.,

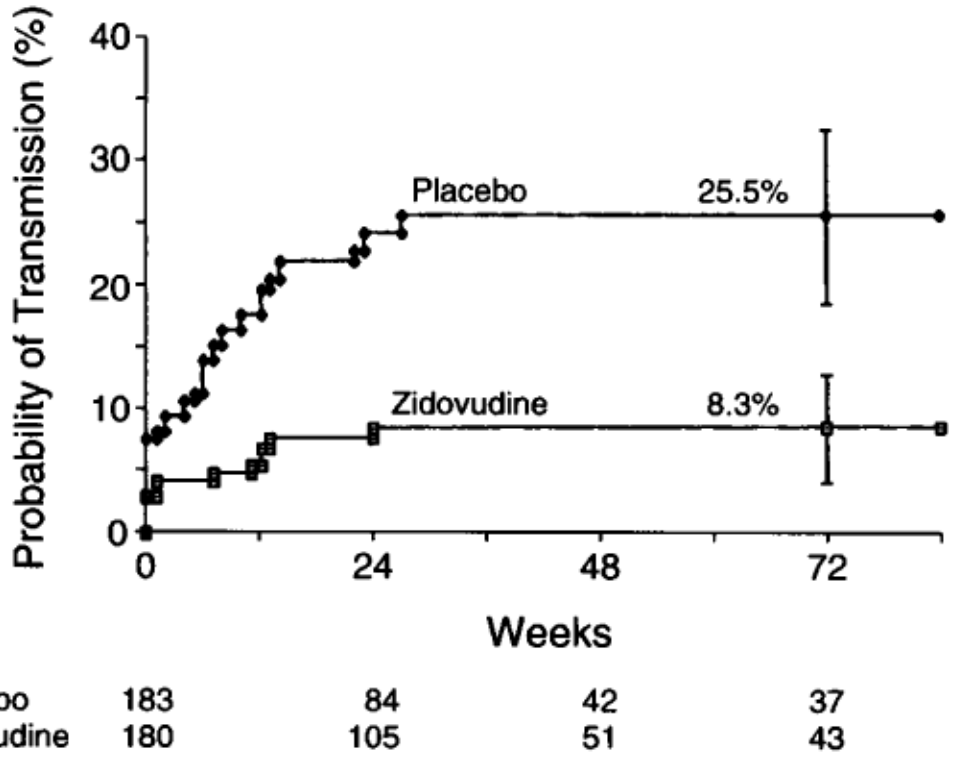
Table 3. Alternative Efficacy Analyses.*

VARIABLE	ZIDOVUDINE	PLACEBO	ALL
Infants >32 wk			
Births (no.)	150	149	299
Infection status (no.)			
Indeterminate	29	22	51
Defined	121	127	248
HIV-infected	9	31	40
Transmission rate (%)†	7.4	24.4	16.1
Infants ≥1 yr			
Births (no.)	95	104	199
Infection status (no.)			
Indeterminate	12	15	27
Defined	83	89	172
HIV-infected	7	20	27
Transmission rate (%)‡	8.4	22.5	15.7

*In these analyses, two positive cultures define HIV infected, and at least two negative cultures (one obtained at ≥24 weeks) and no positive cultures define the absence of HIV infection. P values were determined with the chi-square test.

†P = 0.002 for the comparison between groups.

‡P = 0.03 for the comparison between groups.



Short-course zidovudine for perinatal HIV-1 transmission in Bangkok, Thailand: a randomised controlled trial

THE LANCET • Vol 353 • March 6, 1999

Nathan Shaffer, Rutt Chuachoowong, Philip A Mock, Chaiporn Bhadrakom, Wimol Siriwasin, Nancy L Young, Tawee Chotpitayasunondh, Sanay Chearskul, Anuvat Roongpisuthipong, Pratharn Chinayon, John Karon, Timothy D Mastro, R J Simonds, on behalf of the Bangkok Collaborative Perinatal HIV Transmission Study Group

Methods In a randomised, double-blind, placebo-controlled trial, HIV-1-infected pregnant women at two Bangkok hospitals were randomly assigned placebo or one zidovudine 300 mg tablet twice daily from 36 weeks' gestation and every 3 h from onset of labour until delivery. Mothers were given infant formula and asked not to breastfeed. The main endpoint was babies' HIV-1-infection status, tested with HIV-1-DNA PCR at birth, 2 months, and 6 months. We measured maternal plasma viral concentrations by RNA PCR.

Findings Between May, 1996, and December, 1997, 397 women were enrolled; 393 gave birth to 395 live-born babies. Median duration of antenatal treatment was 25 days, and median number of doses during labour was three. 99% of women took at least 90% of scheduled antenatal doses. Adverse events were similar in the study groups. Of 392 babies with at least one PCR test, 55 tested positive: 18 in the zidovudine group and 37 in the placebo group. The estimated transmission risks were 9·4% (95% CI 5·2–13·5) on zidovudine and 18·9% (13·2–24·2) on placebo (p=0·006; efficacy 50% [15·4–70·6]). Between enrolment and delivery, women in the zidovudine group had a mean decrease in viral load of 0·56 log. About 80% of the treatment effect was explained by lowered maternal viral concentrations at delivery.

Interpretation A short course of twice-daily oral zidovudine was safe and well tolerated and, in the absence of breastfeeding, can lessen the risk for mother-to-child HIV-1 transmission by half. This regimen could prevent many HIV-1 infections during late pregnancy and labour in less-developed countries unable to implement the full 076 regimen.

Lancet 1999; **353:** 773–80

Short-course oral zidovudine for prevention of mother-to-child transmission of HIV-1 in Abidjan, Côte d'Ivoire: a randomised trial

Stefan Z Wiktor, Ehounou Ekpini, John M Karon, John Nkengasong, Chantal Maurice, Sibailly T Severin, Thierry H Roels, Moise K Kouassi, Eve M Lackritz, Issa-Malick Coulibaly, Alan E Greenberg

THE LANCET • Vol 353 • March 6, 1999

Methods From April, 1996, to February, 1998, all consenting, eligible HIV-1-seropositive pregnant women attending a public antenatal clinic in Abidjan were enrolled at 36 weeks' gestation and randomly assigned placebo or zidovudine (300 mg tablets), one tablet twice daily until the onset of labour, one tablet at onset of labour, and one tablet every 3 h until delivery. We used HIV-1-DNA PCR to test the infection status of babies at birth, 4 weeks, and 3 months. We stopped the study on Feb 18, 1998, when efficacy results were available from a study in Bangkok, Thailand, in which the same regimen was used in a non-breastfeeding population.

Findings

breastfed. Among babies with known infection status at age 3 months, 30 (26·1%) of 115 babies in the placebo group and 19 (16·5%) of 115 in the zidovudine group were identified as HIV-1 infected. The estimated risk of HIV-1 transmission in the placebo and zidovudine groups were 21·7% and 12·2% (p=0·05) at 4 weeks, and 24·9% and 15·7% (p=0·07) at 3 months. Efficacy was 44% (95% CI −1 to 69) at age 4 weeks and 37% (−5 to 63) at 3 months.

Interpretation Short-course oral zidovudine was safe, well tolerated, and decreased mother-to-child transmission of HIV-1 at age 3 months. Substantial efforts will be needed to ensure successful widespread implementation of such a regimen.

Problems

- Developping countries
- Obligation to ensure access of beneficial treatments for research participants at the conclusion of clinical trials.
- Research with captive populations : prisoners, students, soldiers
- Research with identifiable and targetes communities
- Research with healthy volunters
- Research with fetuses, embryos, and stem cells
- Research with childrens
- Resarch with ethnic and minority populations
- Research involving economically disadvantaged participants

And now…

COVID vaccination

Human Challenge Studies to Accelerate Coronavirus Vaccine Licensure

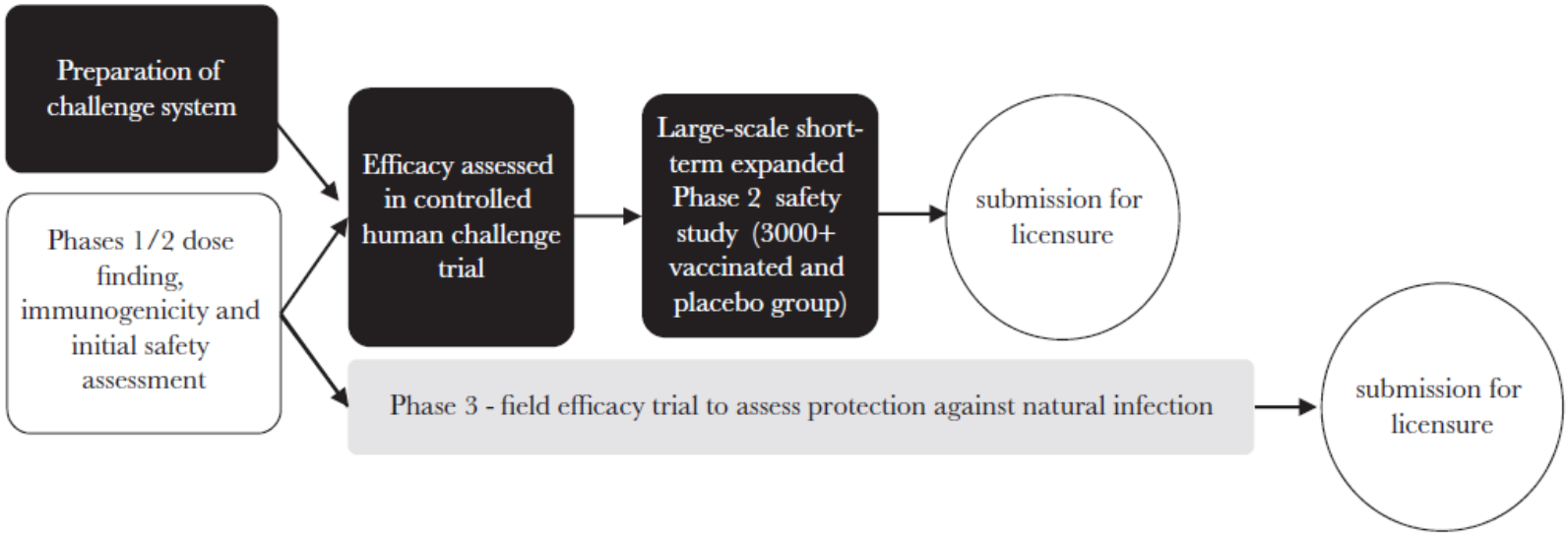
The Journal of Infectious Diseases® 2020;221:1752–6

Nir Eyal,[1,2,3] Marc Lipsitch,[4,5] and Peter G. Smith[6]

[1]Center for Population-Level Bioethics, Rutgers University, New Brunswick, New Jersey, USA, [2]Department of Philosophy, Rutgers University, New Brunswick, New Jersey, USA, [3]Department of Health Behavior, Society and Policy, Rutgers School of Public Health, Piscataway, New Jersey, USA, [4]Center for Communicable Disease Dynamics, Department of Epidemiology, Harvard T. H. Chan School of Public Health, Boston, Massachusetts, USA, [5]Department of Immunology and Infectious Diseases, Harvard T. H. Chan School of Public Health, Boston, Massachusetts, USA, and [6]MRC Tropical Epidemiology Group, London School of Hygiene & Tropical Medicine, London, UK

Controlled human challenge trials of SARS-CoV-2 vaccine candidates could accelerate the testing and potential rollout of efficacious vaccines. By replacing conventional phase 3 testing of vaccine candidates, such trials may subtract many months from the licensure process, making efficacious vaccines available more quickly. Obviously, challenging volunteers with this live virus risks inducing severe disease and possibly even death. However, we argue that such studies, by accelerating vaccine evaluation, could reduce the global burden of coronavirus-related mortality and morbidity. Volunteers in such studies could autonomously authorize the risks to themselves, and their *net* risk could be acceptable if participants comprise healthy young adults, who are at relatively low risk of serious disease following natural infection, if they have a high baseline risk of natural infection, and if during the trial they receive frequent monitoring and, following any infection, the best available care.

Keywords. coronavirus; vaccines; human challenge studies; randomized controlled trials; risk-taking; ethics.



Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine

Fernando P. Polack, M.D., Stephen J. Thomas, M.D., Nicholas Kitchin, M.D., Judith Absalon, M.D., Alejandra Gurtman, M.D., Stephen Lockhart, D.M., John L. Perez, M.D., Gonzalo Pérez Marc, M.D., Edson D. Moreira, M.D., Cristiano Zerbini, M.D., Ruth Bailey, B.Sc., Kena A. Swanson, Ph.D., Satrajit Roychoudhury, Ph.D., Kenneth Koury, Ph.D., Ping Li, Ph.D., Warren V. Kalina, Ph.D., David Cooper, Ph.D., Robert W. Frenck, Jr., M.D., Laura L. Hammitt, M.D., Özlem Türeci, M.D., Haylene Nell, M.D., Axel Schaefer, M.D., Serhat Ünal, M.D., Dina B. Tresnan, D.V.M., Ph.D., Susan Mather, M.D., Philip R. Dormitzer, M.D., Ph.D., Uğur Şahin, M.D., Kathrin U. Jansen, Ph.D., and William C. Gruber, M.D., for the C4591001 Clinical Trial Group*

This article was published on December 10, 2020, at NEJM.org.

DOI: 10.1056/NEJMoa2034577

Table 2. Vaccine Efficacy against Covid-19 at Least 7 days after the Second Dose.*

Efficacy End Point	BNT162b2		Placebo		Vaccine Efficacy, % (95% Credible Interval)‡	Posterior Probability (Vaccine Efficacy >30%)§
	No. of Cases	Surveillance Time (n)†	No. of Cases	Surveillance Time (n)†		
		(N=18,198)		(N=18,325)		
Covid-19 occurrence at least 7 days after the second dose in participants without evidence of infection	8	2.214 (1,7411)	162	2.222 (17,511)	95.0 (90.3–97.6)	>0.9999
		(N=19,965)		(N=20,172)		
Covid-19 occurrence at least 7 days after the second dose in participants with and those without evidence of infection	9	2.332 (18,559)	169	2.345 (18,708)	94.6 (89.9–97.3)	>0.9999

* The total population without baseline infection was 36,523; total population including those with and those without prior evidence of infection was 40,137.

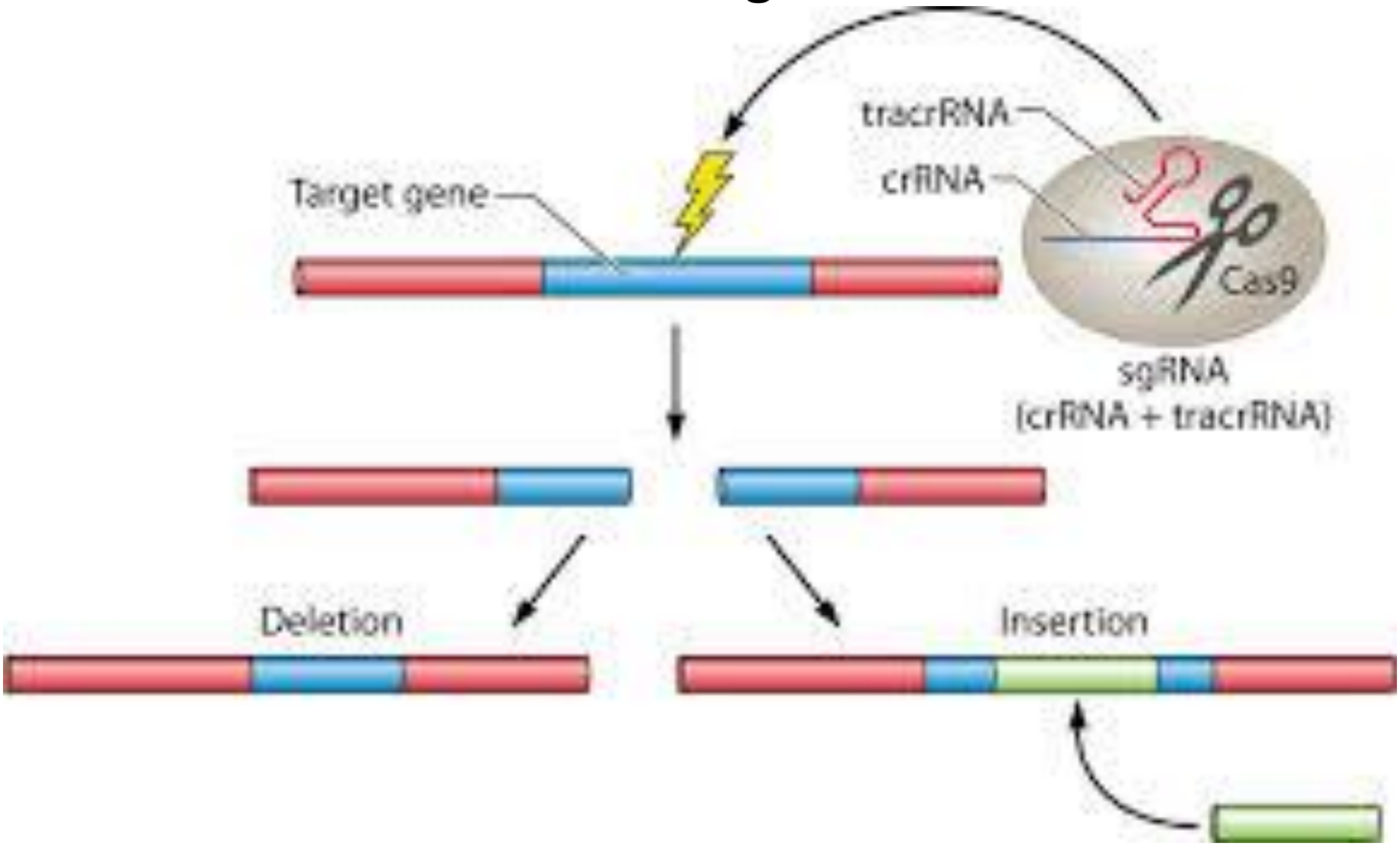
† The surveillance time is the total time in 1000 person-years for the given end point across all participants within each group at risk for the end point. The time period for Covid-19 case accrual is from 7 days after the second dose to the end of the surveillance period.

‡ The credible interval for vaccine efficacy was calculated with the use of a beta-binomial model with prior beta (0.700102, 1) adjusted for the surveillance time.

§ Posterior probability was calculated with the use of a beta-binomial model with prior beta (0.700102, 1) adjusted for the surveillance time.

BIOETHICS

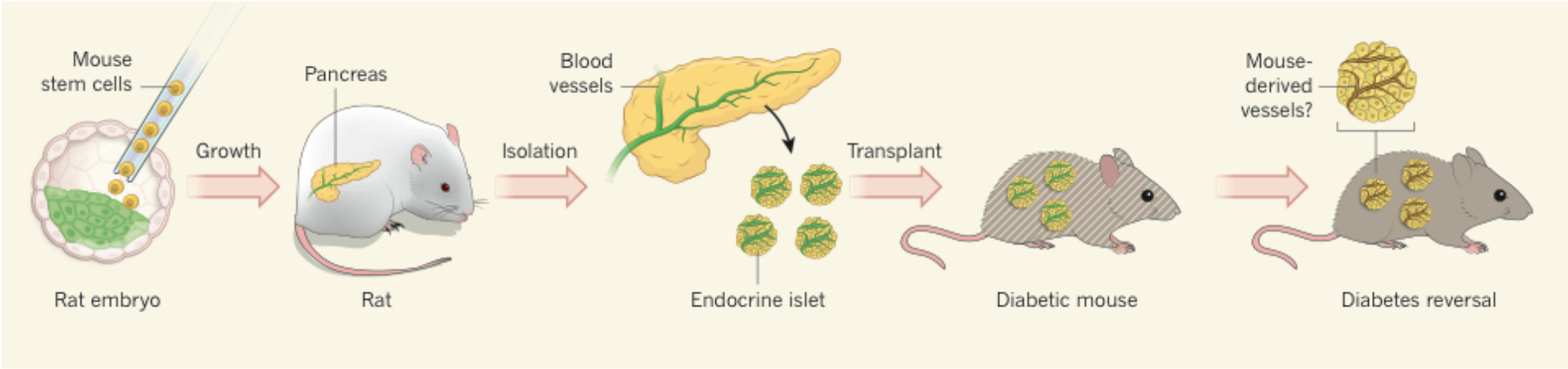
Genetics changes?



CRISP PR cas9

Interspecies pancreas transplants

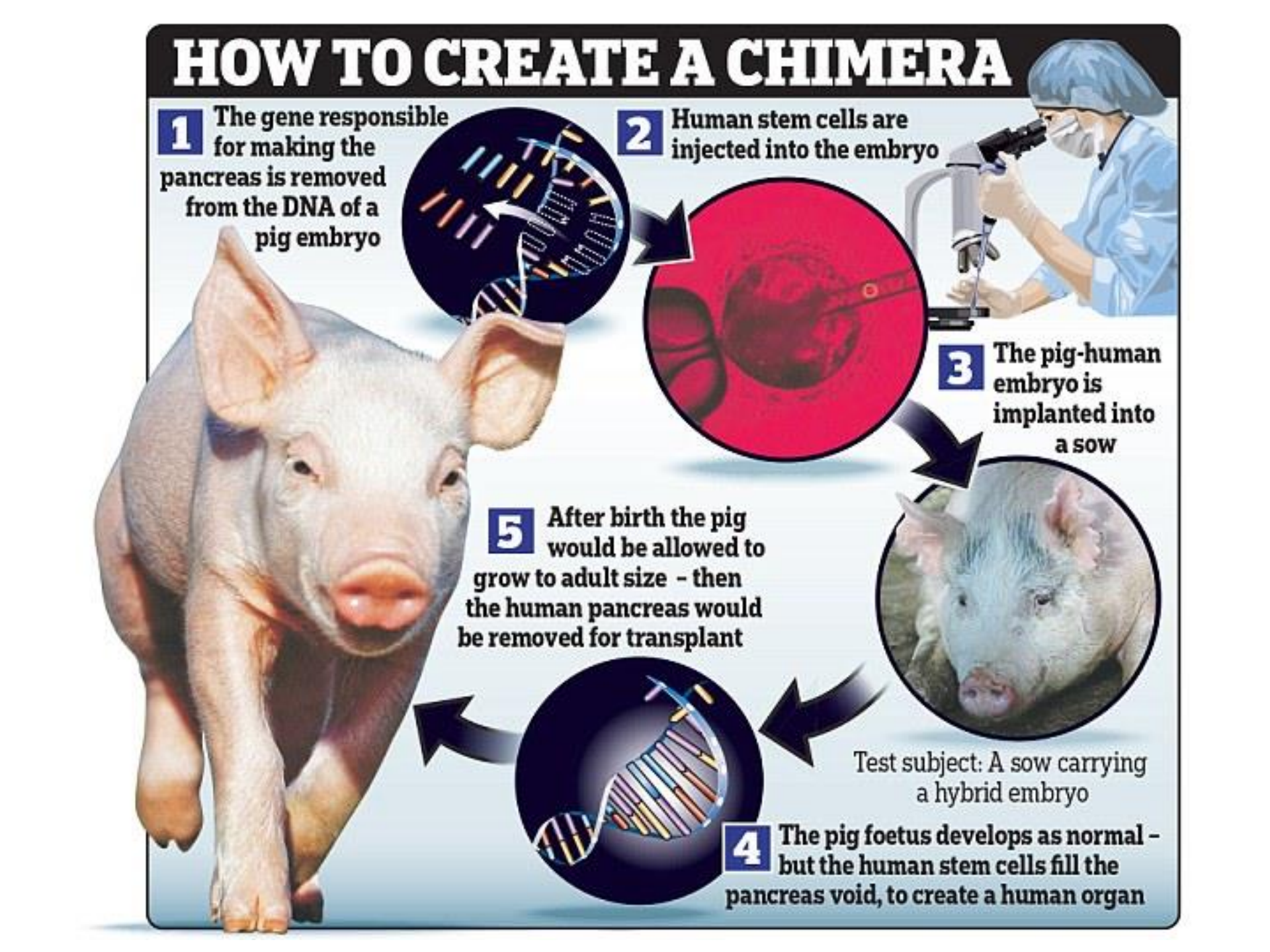
A mouse pancreas grown in a rat controls blood-sugar levels when transplanted into a mouse that models type 1 diabetes. This achievement provides a tantalizing glimpse of how organs could be grown for therapeutic use. **SEE ARTICLE P.191**



Interspecies organogenesis generates autologous functional islets

Tomoyuki Yamaguchi[1]*, Hideyuki Sato[1]*, Megumi Kato-Itoh[1], Teppei Goto[2], Hiromasa Hara[2], Makoto Sanbo[2], Naoaki Mizuno[1], Toshihiro Kobayashi[1]†, Ayaka Yanagida[1], Ayumi Umino[1], Yasunori Ota[3], Sanae Hamanaka[1], Hideki Masaki[1], Sheikh Tamir Rashid[4,5], Masumi Hirabayashi[2] & Hiromitsu Nakauchi[1,5]

HOW TO CREATE A CHIMERA



Ethics of clinical research is a continuous challenge…

Exemple IHU de Marseille : hydroxychloroquine in treatment of COVID

DÉMARCHES RÉGLEMENTAIRES EN FONCTION DU PROJET

Recherche sur la personne humaine en vue du développement des connaissances biologiques et médicales

Promoteur

Catégorie 1 Recherches interventionnelles	Catégorie 2 Recherches interventionnelles à risques et contraintes minimes	Catégorie 3 Recherches non interventionnelles
Lcode Sté Publique jusqu'en oct. 2018 puis Règlement EU	Loi Jardé	
Recherche sur des médicaments *(RE : intervention à risque et faible intervention)*	**Recherches ne portant pas sur des médicaments** *(autres produits de santé et hors produits de santé)*	**Recherches à risque minime ❶** *Hors produits de santé ou produits de santé dans les conditions habituelles d'utilisation*	**Recherches observationnelles**
Enregistrement (n°EudraCT)	Enregistrement (n°ID-RCB)		
Autorisation ANSM *(ou UE pour le RE)*	**Autorisation ANSM**	**Information ANSM (Envoi du résumé et avis du CPP)**	
Avis du CPP *(Avis éthique de chaque Etat membre pour RE)* Information et **Consentement écrit** libre et éclairé	**Avis du CPP** Information et **Consentement écrit** libre et éclairé	**Avis du CPP** Information et **Consentement exprès** (écrit ou oral) libre et éclairé ❷❸	**Avis du CPP** Information et **déclaration de non opposition** libre et éclairé ❷
CNIL : Engagement de conformité **MR001** Ou autorisation CNIL	**CNIL** : Engagement de conformité **MR001** Ou autorisation CNIL	**CNIL** : Engagement de conformité **MR003** Ou Engagement de conformité MR001 si consentement Ou autorisation CNIL
Assurance		

❶ Définies par arrêté du 18/11/2016 (
❷ Consentement écrit : Recherches entrant de le champ de la loi Bioéthique
❸ Dérogation au consentement exprès en situation d'urgence

⚠ Les recherches portant sur des données existantes avec changement de finalité et des éléments biologiques existants ne font pas parties des recherches sur la personne humaine telles que définies dans ce tableau

ansm

DIRECTION DE L'INSPECTION [redacted]

RAPPORT PRELIMINAIRE D'INSPECTION

Nom, adresse et coordonnées des inspectés	**Fondation IHU – Méditerranée Infection** 19-21 Bd Jean Moulin 13005 Marseille **Assistance Publique - Hôpitaux de Marseille** 80, rue Brocher 13354 Marseille
Essai(s)	**Recherche de Tropheryma whippleï comme agent de gastro-entérite chez le jeune enfant** *Codelacronyme donné par le promoteur : NA* **Pathologies associées au voyage et acquisition de pathogènes et de bactéries multirésistantes chez les étudiants en médecine effectuant un stage pratique hors de France** *Codelacronyme donné par le promoteur : BMRSTUD*
Date(s) d'inspection	18/11/2021 et 22 au 26/11/2021
Date du rapport préliminaire d'inspection	19 janvier 2022
Inspecteur(s)	[redacted]
Accompagnant(s)	[redacted]
Références	Référence de la mission : 2021-GCP-27 Date de la lettre de mission : 12/11/2021

cofrac INSPECTION

Accréditation n° 3-1094

Portées disponibles sur www.cofrac.fr

ate inspection: 18 au 26/11/21
ortée: recherche impliquant la personne humaine
ssentiellement deux projets de recherche et une mise en
uvre de traitements expérimentaux « hors recherche »)
U/FMI/APHM

Date: 2022 (porte sur la période 2017-2022)
Portée: Gouvernance, organisation, fonctionner
institutionnel
IHU/FMI

Pr Philippe Van De Perre

Rapport ANSM

- Inspection motivée par diverses alertes sur des manquements et incohérences méthodologiques dans des publications scientifiques et à des allégations diffusées dans la presse
- Objectif principal: vérifier l'adéquation des mesures prises dans la mise en œuvre de la RIPH, avec les dispositions législatives et réglementaires
- La réunion d'ouverture et la visite des locaux se sont déroulés dans un climat détestable (incluant agressions verbales et insultes) portant atteinte au respect dû à la fonction des inspecteurs
- Au centre des investigations: le **droit des patients**
- **Ecart critique** ★ **= portant atteinte au droit des patients**

Pr Philippe Van De Perre

Deux essais cliniques et un traitement expérimental « hors recherche »

- **Tropheryma whipplei associated with diarrhoea in young children**

(Clin Microbiol Infect 2016) - **TW**

- **Acquisition of multidrug-resistant bacteria and colistin resistance genes in French medical students on internships abroad**

(Travel Med Infect Dis 2021) - **BMRSTUD**

- Traitement expérimental de patients atteints de TB multi résistante, par de nouvelles combinaisons d'antibiotiques

Pr Philippe Van De Perre

Rapport ANSM : constats

- **Confusion récurrente dans d'identité du promoteur** (IHU?, FMI?, IHU/FMI?, investigateur?, APHM?)
- **Méconnaissance des obligations réglementaires en matière de RIPH**
- **Inadéquation formelle du Comité d'Ethique Interne (CEI) de l'IHU MI (composition, tdr, documents à fournir, rapport).** Divergence des avis fournis par le CEI P/R à ceux envoyés à l'ANSM. Contestation de la véracité de signature de certains avis (faux en écriture?). Utilisation inappropriée d'une jurisprudence des avis CPP.
- **APHM non informée de recherche promue par l'IHU MI dans ses propres locaux**
- **Nombre important de projets RIPH 3 sans avis CPP (recommandés par le CEI). Concerne plusieurs centaines de patients**

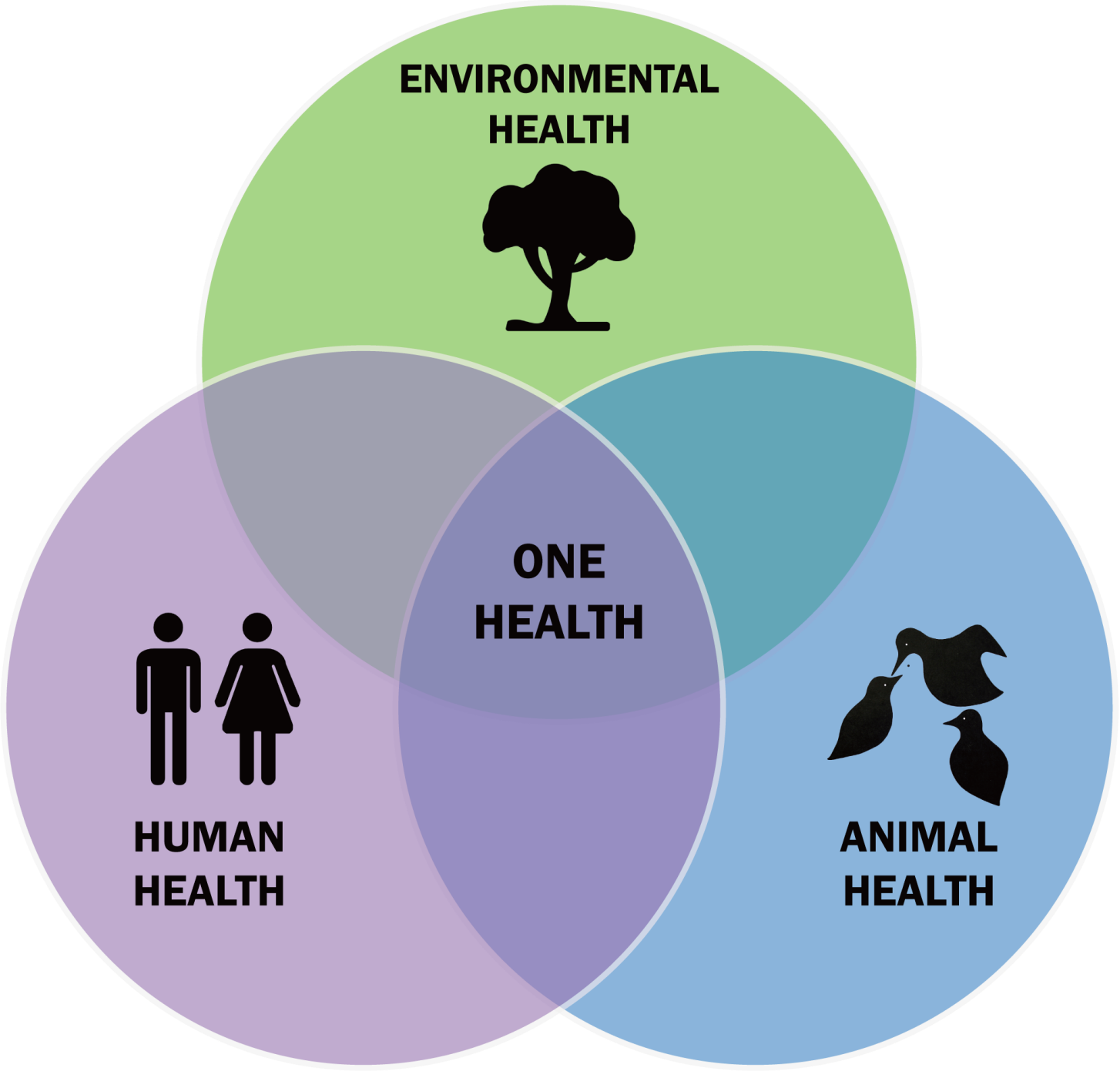
Pr Philippe Van De Perre

Rapport ANSM : synthèse et conclusions

- 15 écarts dont 8 critiques et 7 majeurs
- 7 remarques dont 6 majeures
- Mépris délibéré de la réglementation, en particulier catégorisation RIPH inappropriée (en faveur RIPH3 « observationnelle » ou « hors loi Jardé), RIPH sans avis favorable CPP, anomalie ou absence de recueil du consentement, …
- Atteinte aux droits des patients par mise en œuvre de traitements antituberculeux expérimentaux, sans justification et sans information des patients, nombreux EIG, …
- Atteintes caractérisées et réitérées aux droits des patients

DECISIONS: Suites pénales et mesures administratives
ARRET des inclusions et de la mise en œuvre de nouveaux essais cliniques

Pr Philippe Van De Perre


ENVIRONMENTAL HEALTH
ONE HEALTH
HUMAN HEALTH
ANIMAL HEALTH