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Cheaper, Faster, Development of More Effective New Treatments

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Abstract:
An historical review of the 'strategic' development or accidental discovery of new therapeutic interventions demonstrates that 'evidence' is needed to confirm progress. As early as 1940 Carl Popper provides a prescription for 'Logic of Discovery'. A study will only provide new scientific information if it has a 'falsifiable' null-hypothesis.
If the null-hypothesis is proven to be 'false', another falsifiable hypothesis needs to be formulated and tested. The first time a null hypothesis is confirmed is not enough to accept the null-hypothesis. Each positive confirmation of the null hypothesis increases the chance the investigators move in the right direction.
The use of double blind randomized trials as recommended by FDA and EMA have no falsifiable null hypothesis. If the study collects enough patients' one arm will always be better than the other arm at a probability of < 0.05, but a repeat study -almost never done- could show the other arm of the study is the best one with same low p-value.
Radiolabeled Immunoglobulin Therapy (RIT) in patients with poor prognosis solid tumors, allows for the introduction of a falsifiable 'null-hypothesis' and the determination of radiation dose effect curves for normal tissues surrounding the tumor as well as tumor dose effect curves, without exposing the patient to unpredictable risks and increasing the chance for a beneficial tumor response.

Harnessing Military Excesses

At the end of the nineteenth century physicians become uncomfortable with the limitations to their diagnostic and therapeutic options:
a. Taking a history,
b. Doing a physical exam,
c. Inspecting bodily fluids and
d. Recommending bed rest, diet changes, blood letting and observation.

The Hippocratic advice: '*Do no harm*' is followed religiously. Patients with acute life-threatening diseases are watched in the hope that in ten days the patients will survive by 'crises and lysis'. Many of the patients do not.

Experimenting with new treatments in animals or even human beings was considered unethical and contrary to the Hippocratic Oath. Four wars in the 19th and 20th century illustrate the stepwise increasing destructive power and cruelty caused by new weaponry. (Table 1) At the battlefield surgeons and; nurses at the battle field start to realize doing nothing but just observing, wounded soldiers and wounded innocent bystanders/citizens is unacceptable. The medical treatment of wounded soldiers and innocent bystanders is improved.

Table 1: The Spoils of War

War	Military escalation	Social/Health care improvements
Crimean War, 1853-1856	Better explosives. (Nobel sr.), use of railways and telegraph for more efficient warfare.	Nursing, triage of wounded soldiers, (Florence Nightingale). Better anesthetics, plaster casts, enhanced amputation methods, (N.I. Pirgov) First War Correspondent, (Leo Tolstoy)
Franco-Prussian War, 1870-1871	Improved command structures, guns, and cannons.	Prisoners of war should receive the same treatment as the soldiers of the invading Army.
World War I 1914-1918	First use of tear gas & nerve gas. Citizens/hostages are used to extract money and to decrease violence against the invading Army.	Gasmasks; Accident with transportation of nitrogen mustard lead to the discovery of the first human chemotherapeutic agent: Nitrogen mustard.
World War II 1939-1945	Bombarding civic centers, Atomic Warfare Extermination of Jews in gas-chambers, euthanasia of children with genetic 'undesirable' genetic disorders.	Nuclear energy ('Atoms for Peace'), International Atomic Energy Commission, Bone marrow transplantation. The Nuremberg Code for experimentation with human beings.

Tsar Nicolas II responds by organizes 2 Peace Conferences in The Hague, the Netherlands in 1899 and 1907. US, Theodor Roosevelt, is a co-sponsor in 1907. An international arbitration court is proposed to adjudicate conflicts before they escalate into wars. Its deliberations are ignored, The Austrian Baroness Bertha von Suttner-Kinsky, a dedicated pacifist, writes a best seller in 1899, entitled 'Die Waffen nieder' (*Lay down your arms*). She is a revered celebrity at both Peace Conferences.

Origins of the Nobel Prize

Alfred Nobel Jr. is a chemist, engineer and inventor. He owns laboratories in twenty different countries and holds more than 350 patents, most of them on the use of different forms of explosives. All European countries are stocking his expensive explosives and have made Alfred and his brothers very wealthy. Alfred's main interest is in making, nitroglycerin based explosives more powerful and less dangerous to handle by preventing premature, unscheduled explosions. An explosion in Nobel's own laboratory kills several people, including his youngest brother.

Nobel has other interests, such as blood transfusions, which he starts to study in dogs in a laboratory in France. When he hears his brother Ludvig is dying from cardiac failure in Cannes, France, Alfred hurries to Cannes to resolve old business conflicts with his brother before he dies. The day after Ludvig's death, a French newspaper publishes a necrology entitled '*Le Marchand de la mort est mort*' (The merchant of death is dead) assuming in error it is Alfred, who has died, not Ludvig. Alfred does not like to be labeled a 'merchant of death'. Alfred corresponds for years with Baroness Bertha Von Suttner-Kinsky. In 1981 Alfred writes to Bertha:

'Perhaps my factories will put an end to war sooner than your congresses: on the day that two army corpses can mutually annihilate each other in a second, all civilized nations will surely recoil with horror and disband their troops. Good wishes alone will not ensure peace.'

Albert continues to work hard, is lonely, and suffers from depressions. In Paris, his doctors try to convince him to take nitroglycerine for his heart trouble! October 25, 1896 Alfred writes to his friend, Ragnar Sohliman:

'My heart trouble will keep me here in Paris for another few days at least, until my doctors are in complete agreement about my immediate treatment. Isn't it the irony of fate that I have been prescribed N/G/I (Nitroglycerine) to be taken internally!'

Alfred Nobel refuses to be treated with nitroglycerine and dies December 10, 1896 at the age of 63, in San Remo, Italy. Alfred modified his will a year before his death. He informs Bertha, he did so. Bertha answers: 'Whether I am around then or not does not matter, what we have given, you and I, is going to live on'

The whole world is surprised when Nobel's modified will is made public. The French Government is disappointed by not being able to collect substantial inheritance taxes. Alfred has donated 96% of his financial assets to be used for a series of prizes for those who confer the 'greatest benefit to mankind' in 5 different categories.

'I hereby appoint as Executors of my testamentary dispositions, Mr. Ragnar Sohlman, resident in Bofors, Väland (Sweden) and Mr. Rudolf Lilljequist, Oslo. (Norway).' In 1893 Sohlman had become Nobel's assistant. The execution of Nobel's will makes Sohlman and Lilljequist very wealthy men.

Sweden and Norway

In 1900 Swedish King Oscar II promulgates the Nobel Foundation statutes. Each year the Nobel Assembly at The Karolinska Institute Institutet, (a Medical University) selects the Nobel Prize winners. The Assembly consists of fifty professors from various medical disciplines at the University.

The Norwegian Nobel Committee, consisting of 5 members appointed by the Norwegian Parliament awards the yearly Peace Prize in a ceremony in Oslo. All Nobel prizes are awarded on December 10, the day Nobel died, in the presence of Norwegian or Swedish Royalty.

Baroness Von Suttner is the first *woman* to receive a Nobel Prize, the Nobel Prize for Peace in 1905.

Nobel upgrades his name from being '*the merchant of death*', to being the provider of yearly, prestigious Prizes in 5, later 6 different disciplines,' which are still being awarded more than 100 years later.

Negative aspects of the Nobel Prize tradition are the competition and jealousy it can generates among scientists. With all his wealth and patents Alfred Nobel probably provides the wrong role model for those academicians, who want to cash in on their inventions, before sharing them for an affordable price with people who might benefit from their inventions.

The first Nobel Peace Prize is awarded in 1901 to Henri Dunant, the founder of the Red Cross and Frédéric Passy, the founder of the French Peace Society. Nobel Prizes are only given to living people and to not more than three recipients per category per year. There are 5 categories: Physics, Chemistry, Physiology or Medicine, Literature and Peace. In 1969 Economics is added as a sixth category.

Institut Pasteur

In the second part of the 19th century Pasteur and his co-workers make milk, wine and beer safer by 'pasteurization', partial sterilization of a substance/liquid at a temperature and for a period of exposure that destroys microorganisms without major chemical alteration of the substance. In addition, Pasteur discovers an effective vaccine for rabies by performing research in animals as well as human patients. He dies in 1895 and therefore no Nobel Prize for Pasteur. However, the Pasteur Institute remains involved in research in treatment and vaccination for many different microorganisms all over the world and collects a respectable number of Nobel Prize winners.

In 2008 Luc Montagnier and Françoise Barré-Sinoussi from the Pasteur Institute receive the Nobel Prize in Physiology or Medicine for their discovery of an AIDS virus.

Three early Nobel Prize winners improve Health Care

In 1926 GB Shaw receives the Nobel Prize for Literature. Two physician-investigators, Paul Ehrlich from Germany and Christian Eijkman from The Netherlands, win their Nobel prizes in Physiology or Medicine in 1908 and 1929, respectively. This trio independently defines the need for 'Public Health' (Shaw) and research in experimental animals to 'translate' observations made in animals to human patients (Ehrlich and Eijkman).

Public Health matters

In 1906 GB Shaw writes '*the Doctors Dilemma*,' a play about ethical problems encountered by a physician/surgeon trying to cure patients with advanced tuberculosis. In his, as usual for him, long preface to the play Shaw's explains his position on Public Health[1]. Shaw summarizes his preface in 14 statements; three of them reproduced in Table 2. Thereafter Public Health officers, employed by the British Government, take center stage. Due to their good work the average lifespan of British citizens gradually increases from 40 to 78 years of age, because air and sewer systems are cleaner, drinking water is safer, more people eat a balanced diet, children are vaccinated for common infectious diseases, and the workplace is safer, etcetera. The single payer Public Health System Law takes effect in Britain in 1948, two years before Shaw's death.

Table 2: Shaw's advice

1. Nothing is more dangerous than a poor doctor, not even a poor employer or a poor landlord.
(…)
12. Do not try to live forever. You will not succeed.
(…)
14. Take the utmost care to get well born and brought up. This means that your mother must have a good doctor. Be careful to go to a school where there is what they call a school clinic, where your nutrition and teeth and eyesight and other matters of importance to you will be well attended to. Be particularly careful to have all this done at the expense of the nation, as otherwise it will not be done at all, the chances being about forty to one against you being able to pay for it directly yourself, even if you know how to set about it. Otherwise you will be what most people are at present: an unsound citizen of an unsound nation, without sense enough to be ashamed or unhappy about it.

Doctor's Dilemma

In 1906 Shaw needs to invent a dilemma for his play. A surgeon/friend of Shaw helps him fantasize about a new 'miracle cure' for Tuberculosis. The macrophages of the patient will eat and digest all the patient's tubercle bacilli, if those bacilli are covered by the right amount of 'opsonins' at the right time of day. We now know opsonins do exist and are IgG antibodies. In 1972 Edelman and Porter get the Nobel Prize for Physiology or Medicine for defining the chemical structure of IgG[2].

In 1906 there are thousands of patients in London, England with incurable, advanced tuberculosis. The dilemma created for Shaw is one of choice: The available amount of opsonins is limited; not more than a handful of patients can be treated. How does a Doctor select the most deserving patient and treats the selected patient at the right time of the day? Shaw subtitles his play '*A Tragedy*' but fills his play with funny and entertaining dialogues. The play runs for two years in London's West End. Real treatments for Tuberculosis do not become available till much later. In 1952 Samuel Waksman gets the Nobel Prize for the discovery op streptomycin[3]. He is forced to share his Nobel Prize money with one of his collaborators, Schatz.

In the preface to his play Shaw underlines his aversion to using 'Biometrica'/Statistics or animal research. Shaw describes research in animals as 'Vivisection', 'Experiments in Torture'.

Ehrlich and Eijkman probably never read or saw Shaw's play. They ignore Shaw's condemnation of experimental animal research and statistics, but follow instead Pasteur's by doing experiments in animals and using statistics when necessary. A significant increase in average human lifespan does not have to be confirmed by experimental animal studies, statistics or studies with several arms, one arm receiving placebo treatment. No need for a control group of citizens for example continuing their lives without receiving the benefits offered by Public Health officers.

Ehrlich and Eijkman

Ehrlich claims his successes are due to the first four Gs in Table 3: *Geld* (Money), *Gluck* (Luck), *Geduld* (Patience), *Geschick* (Talent). The attractiveness of the 4G acronym is lost in translation: MLPT.

Table 3: Ehrlich's 4 four Gs plus 1

Number of G	In German	In English	Ehrlich's Solution
1	Geld	Money	Emperor Wilhelm I and II
2	Gluck	Luck	Animal model for syphilis
3	Geduld	Patience	Salversan and Neosalversan found after more than 600 and 900 animal trials respectively
4	Geschick	Talent	See text
5	Gewin	Profit	No, others profit from Ehrlich's 'intellectual property'

The micro-organism which causes syphilis cannot be grown in vitro. The Japanese assistant of Ehrlich, Shiga, uses a rabbit model for syphilis, to study the therapeutic potential of arsenic salts. The first arsenic salt modification that is efficacious in the rabbit model is arsenic salt modification 606, named Salversan. Later superseded by the more water-soluble neo-salver-

san, modification 914.

Clearly, Ehrlich and Shiga do possess the fourth G, *Geduld*, (Patience) in abundance. Please note Ehrlich is not interested in making a profit, the fifth G in Table 2, *Gewin*, because the German Emperors Wilhelm I and II provide Ehrlich with a salary and enough funds to build and run his laboratory[4].

Polyneuritis endemica perniciosa (PEP)

In 1883 Christiaan Eijkman, wants to become a doctor but his family lacks the financial means to allow him to go to Medical School in the Netherlands. He signs up for a much cheaper education in microbiology in the Army of the Dutch Indies. In 1886 he secures his own microbiology laboratory and proceeds to search for microorganisms that produce toxins that might cause PEP. He fails to identify such toxins.

A lab assistant of Eijkman tells him chickens in his lab show signs of PEP. Eijkman performs histological studies of tissues of chicken and human patients with PEP, confirming the histological similarities of PEP in the two different species. A random change in the food provided to the laboratory chickens appears to cure the animals of PEP. The change? Feeding the chicken unpeeled (brown) rice rather than peeled (white) rice. Inmates of prisons in the Dutch Indies also get PEP sometimes, but only in prisons where white rice is served.

Eijkman is convinced something in the husk of rice protects against PEP, or '*beriberi*', as it known locally, the Singhalese word for '*extreme weakness*'. The chemical structure of Vitamin B-1, thiamine, the curative organic material in the rice's husk, is not elucidated till 1932. In 1929 Eijkman and Sir Frederic Gowland Hoper share the Nobel Prize in Physiology or Medicine for the discovery of vitamins, organic chemical compounds, which the organism cannot synthesize in sufficient quantities and must obtain in its diet[5]. Taking Vitamin B-1 prevents beriberi.

Intellectual Property

Directors of commercial enterprises do not want to employ people, who, like Nobel, invent things, submit patents and become very rich by selling their new inventions to anybody with enough money to buy their invention. The employers of individuals with Nobel like talents claim the employer owns the ideas/minds of their employees because the employer pays them a salary. The legal buzzword for this strange claim is: '*Intellectual Property*.' The employer claims he owns the mind of his employee! The reality of scientific progress/discovery of new inventions is different: many new ideas are born while an employee/scientist is half-asleep or dreaming at home, not while he is fully awake, performing his duties for the company.

Investigator driven Research

In 1930 Dr. Karl Landsteiner is awarded the Nobel Prize for Physiology or Medicine for his discovery of the most important human blood groups, the ABO system and the Rhesus system, which enable the transfusion of blood from healthy human volunteers whenever patients loose large amounts of blood during surgery, giving birth, after traffic accidents, or warfare[6]. Fortunately, blood can be stored for days and transfused to the properly selected recipients in due time.

In most countries, blood banks are not for profit institutions. Landsteiner and his employer, Rockefeller Institute for Medical Research in New York, never receive any financial reimbursement for the life-saving technology they developed. Before Landsteiner left for New York, he worked in a Hospital in the Hague, the Netherlands, where he was not reimbursed for his Research.

Cancer Chemotherapy

Fifty years ago, North American oncologists defined 5 sequential phases in clinical cancer research. The clinical-medical investigator follows these 5 phases in the proper order, till the new drug eventually appears to be safe and effective. Only about 5% of all new drugs reach the finish line, phase 4.

Table 4: The different phases of drug discovery

Phase	Aim	Description	% of total R&D costs
0	Preclinical Research	Translating new basic science into clinical applications by way of lab research and studies in experimental animals	31
1	Toxicity, Side effects	Determination of optimal dose and route of administration usually in small and large animal research, sometimes in healthy volunteers and eventually in end stage human patients, i.e. patients having no other therapeutic options	14
2	Activity	Study of new drug in a small group of patients with one specific form of cancer or a new treatment given to a well-defined group of patients with another –not cancer- disease	15
3	Randomized trial	Double blind new vs. existing therapy or placebo. Large numbers of patients studied in many institutions for long periods of time	30
4	Post Marketing analysis	Determine side effects of drug/therapy after prolonged use. Study of interactions with other medications	10

Randomization: Longer studies, Higher Costs, and Lower rewards

Academic ethicists and statisticians demand randomized phase 3 trials between two new drugs or between a drug and a placebo. Such studies need to be continued till one arm of the study is better than the other arm with a Probability value, p-value, of less than 0.05.

In addition, the two study arms need to provide 'Equipoise' to patients: similar risks for beneficence and side effects. Those demands can only be met by entering hundreds of patients in each arm. This will increase the number of institutions that need to participate in the study and escalate study duration and costs. The best arm is the drug with the fewest side effects and the best therapeutic results. Due to equipoise the two arms have similar low, efficacy. Usually less than 1 of 5 patients in the 'best' study arm benefits from the new drug.

Another compelling reason for the pharmaceutical industry to perform randomized double-blind phase 2 and 3 studies is that the Food and Drug Administration (FDA) in the United States will only allow the Pharmaceutical industry to market

a new drug if it performs well in at least two phase 3 studies. Fortunately, the European Medical Association and the World Medical Association are not convinced double blind randomized phase 2 or 3 studies are necessary or that placebo arms are necessary or ethically justifiable.

Professor David Sackett, who introduced the term 'Evidence based medicine' for the first time, is concerned as well. In 1996 he states in the British Medical Journal: '*Evidence based medicine is not 'cookbook medicine'*. Some questions about therapy do not require randomized trials, successful interventions for otherwise fatal conditions. In that case we must follow the trail to the next best external evidence and work from there.'

Sidney Farber, a pathologist/clinician in Boston, Massachusetts.

In 1949 Dr Farber notices the cytology of bone marrow aspirates of children with Acute Lymphocytic Leukemia (ALL) are similar to the cytology of bone marrow aspirates of patients with a folic acid deficiency anemia. Farber decides to treat children with ALL with folic acid. Unfortunately, folic acid administrations make the ALL cells grow faster. Instead, anti-folic acid treatment with methotrexate decreases the number of leukemic cells. Due to the rarity of ALL in children Sidney Farber starts to raise money for a National Co-operative Pediatric ALL group. After a number of well-designed group studies most children with ALL are cured. March 1973 Dr Farber dies in his office from a heart attack. In 1974 the building in which Dr Farber worked is named after him.

In 1977-1978 Huib Vriesendorp spends a year as a clinical fellow in adult medical oncology in the Sidney Farber Cancer Center. His friend and co-fellow in Adult Medical Oncology, is an Englishman, Bruce Ponder.

Bruce assisted John Cairns write his book, '*Cancer and Society*'[7]. Cairns calculates the increase in average lifespan of citizens in the Western World when someone, somewhere finds a cure for all forms of cancer. The average life span of human beings in the 'developed world' will increase by a measly 12-24 months, because cancer is mostly a disease of the elderly. (Figure 1) A cure for cancer will produce significant increases in life span for children in developed countries.

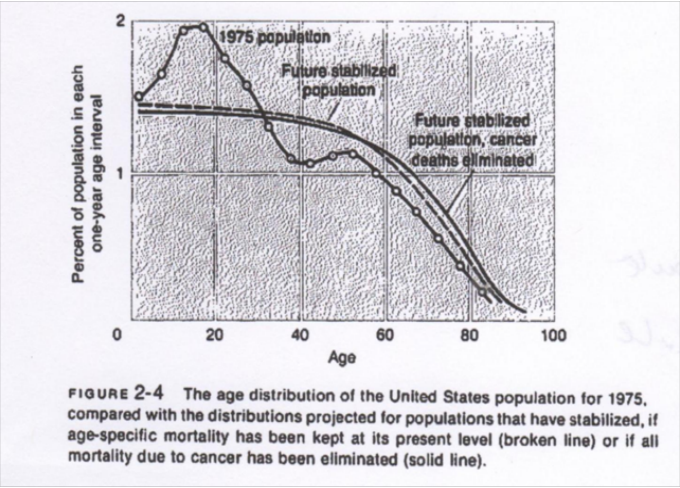

FIGURE 2-4 The age distribution of the United States population for 1975, compared with the distributions projected for populations that have stabilized, if age-specific mortality has been kept at its present level (broken line) or if all mortality due to cancer has been eliminated (solid line).

Figure 1: From John Cairns, Cancer: Science and Society, W.H. Freeman & Co, San Francisco, 1978

John Cairns' message does not get a lot of traction among the Medical Oncology Fellows or their attending physicians in 1977-1978 in the Sidney Farber Cancer Center. They continue to administer new or old chemotherapeutic agents, observing tumor responses and normal tissue toxicity. The attending physicians emphasize the steep dose-effect curves of cancer chemotherapy as evidence for the need to use high doses of chemotherapy. "*No pain, no gain*."

Three D, not Two D

To this day medical oncology fellows have good as well as bad days. The dose effect curves for normal tissue toxicity are as steep as the dose effects curves for tumor shrinkage. The pharmacokinetics and bio-distribution of phase 1 and 2 drugs for cancer are investigated in cancer patients without potentially curative options. Unfortunately, the globally accepted prescription unit for cancer chemotherapy is per meter square body surface area, recommended in 1966.... and still used in 2018. (8) This is disappointing and hard to understand or justify.

The 'no pain no gain' attitude correctly assumes dose effect curves for cancer drugs, and normal tissue damage are both steep, but very few chemotherapists, if any challenge the use of Body Surface Area (BSA) as the universal dose for cancer chemotherapy. It is impossible to measure a drug dose in a surface. Just as it is impossible to catch fish in a frozen pond. Fish just like cancer chemotherapy need a 3D volume to swim in.

In 1987 Vriesendorp, Vriesendorp and Vriesendorp, (a unique author list, that gets honorable mention in the Canadian website for 'Improbable Results') recommend changing the dosing of cancer chemotherapy from 2D to a 3D unit which can be determined objectively without a slide rule: kg bodyweight (BW)[9].

This will decrease overdosing chemotherapy in small children, women and men, because smaller individuals have a higher Body Surface Area/ Bodyweight ratio. Taller, heavier individuals will be under-dosed when body surface is used as a prescription unit. Pediatric oncologists find another solution. They decrease chemotherapy dosed for children on BSA by a factor 2.

In 1966 Freireich et al. to recommended BSA as the proper dose unit for human cancer patients based on preclinical toxicology studies in mouse, rat, hamster, dog, monkey and phase 1 studies in adult human patients. The same 'equitoxic' dose can be given in all species if the drug dose is given per meter2 BSA[8].

The logical next question would have been: 'does the dosing of cancer chemotherapy per BSA, provide the same plasm a drug levels in the different species analyzed by Freireich et al. Vincent De Vita performed extensive pharmacokinetics studies in animals and patients, but did not compare chemotherapy serum levels in experimental animals and human patients[10].

Serum levels are higher in smaller animals/human beings due to the higher body surface/body weight ratio in smaller individuals. Most new chemotherapeutic agents cause bone marrow toxicity. All species experience the same amount of hematological toxicity because smaller species have more hemopoietic stem cells and can tolerate higher doses of total body irradiation than human patients[9].

Carl Popper

In 1935 Popper publishes a book entitled:' *Logic der Forschung* ', which is translated into English and published by

Hutchinson & Co, in London, England in 1959, as '*Logic of Scientific Discovery*[11]. In 1946 Medawar and Popper meet and become friends. Medewar introduces Popper to the scientific community in Great Britain. Medawar describes Popper's logic as:

'The generative act in scientific discovery is the formulation of a hypothesis followed by tests /experiments in which the logical implications and consequences of the hypothesis are examined. Such experiments have one of two outcomes:

1. Results of the experiment square with the hypothesis.
2. Results are inconsistent with the hypothesis. The hypothesis is invalid and must be discarded.'

Popper's logic of scientific discovery starts to bridge the gap between the arts and sciences. Other philosophers had created a gap between poets, writers, artists in general, who were perceived as 'creative thinkers' and scientists who were considered to be just 'collectors of facts'. Popper's philosophy abolishes the old and artificial difference between artists and scientists.

Popper insists a new hypothesis can never be definitively proven to be correct. Testing the hypothesis should never end unless the hypothesis is proven to be incorrect. After each positive test the chance increases, the hypothesis is the right one. Proper is critical of hypotheses/questions, which are doing an inventory, e.g. 'How deep is the ocean'. This is going to be a long and an expensive study, most of the world is covered by Oceans. The result? Deep is deep and sometimes deeper.

An important example of non–falsifiable studies are the comparison of two new drug regimens, or comparing a new drug regimen to a placebo, in double blind randomized studies. Eventually one arm will be better than the other arm with a p value of < 0.05, but provide little to no benefits to future patients. The costs of double blind randomized trials are astronomical and do not deserve to be called 'level one' – the best possible- evidence, because the hypothesis of the study is not-falsifiable. In the unlikely event of repeating the same double blind randomized trial, the other arm might be the better arm. Studies that end in a draw: the two arms are not different from each other, are also not helpful. Both arms provide only small benefits to study patients.

In contrast single arm phase2 studies with a falsifiable null hypothesis: "this new drug will only be useful, if it provides benefits in a least one out of four patients". If this is indeed the case, no double blind randomized trials are needed. If the null hypothesis is not confirmed, i.e. only 1 in 5 patients benefits from the drug. The drug should be dropped from further analysis.

Peter Medawar wins a Nobel Prize

In 1960 Peter Medawar and Frank Macfarlane Burnet share the Nobel Prize in Physiology and or Medicine for their discovery of 'Acquired Immunological Tolerance.' Skin grafts of another mouse strain are accepted for long periods of time in mice that receive immediately after birth a high dose of spleen cells of the skin donor mouse strain.

Medawar is an eloquent speaker and writer. 'I cannot give any scientist of any age better advice than this: the intensity of the conviction that a hypothesis is true has no bearing on whether it is true or not.'

'Scientific reasoning is a kind of dialogue between the possible and the actual, between what might be and what is in fact the case.' 'A scientist is not a man, who cranks some well-oiled machine of discovery.' 'Scientists who think science consists of unprejudiced data gathering without speculation are merely cows grazing on the pasture of knowledge.' (12)

Medawar also quotes Charles Darwin, who wrote to one of his friends: 'How odd it is that anyone should not see that all observations must be for or against some view if it is to be of any service'.

Medawar dies in 1987 after multiple invalidating strokes. Later 'Acquired Immunotolerance' appears not to be tolerance, but graft prolongation followed by rejection, The prolonged skin allograft or kidney allograft survival is due to chronic Graft Versus Host Disease/immunosuppression induced by the transfusion of allogeneic spleen cells. (13)

Darwin loses his Christian faith

Darwin summarized his geology studies and collections of biological specimens on the Galapagos islands more than 20 years after his return to England. In 1859 Darwin publishes, reluctantly, his book 'On the origin of Species by means of Natural selection or the Preservation of Favoured Races in the Struggle for Life'.

He had lost his Christian face in 1830, noting 'I found it more and more difficult with free scope given to my imagination to invent evidence which would suffice to convince me. This belief crept over me at a very slow rate, but was at last complete.' At least some inventories, when properly analyzed produce workable, and testable null-hypotheses. To this day fundamental Christians across the globe insist Darwin was dangerously wrong. The Bible, a multi-authored book, tells the 'true' story. Scientists and Christians and other religious movements still need to learn to agree to disagree.

The Art of Creation

In 1964 Koestler writes a book entitled: '*The art of creation*'[13] , which moves him into the crosshairs of Medawar, a friend of Popper, who perhaps more clearly enunciated 'the scientific discovery' process. Medawar reviews 'The art of creation': 'Dreams bring out the worst in Koestler, (...) those who enjoy slopping around in the amniotic fluid should pause for a moment to entertain (perhaps only unconsciously in the first instance) the idea that the content of dreams may be assemblages of thought elements that convey no information whatsoever.'

Koestler responds: 'No doubt most dreams are self-addressed messages, whose information content is purely private and meaningless to others. But equally undeniable is the fact –which Medawar chooses to pass in silence- that dreams, hypnagogic images and other forms of unconscious intuitions proved decisive in the discoveries of dozens of scientists and mathematicians, Ampère, Gauss, Kekeulè, Leibnitz, Poincarè, Fechner, Otto Loewi, Planck, Einstein to mention only a few. '

Where do we go from here?

The authors are convinced the R&D of new drugs, new therapies can be improved. We recommend implementing recommendations of Popper, Medawar and Koestler which are in sequence:

1. Formulate a hypothesis. We agree with Koestler that sometimes the best hypotheses are sometimes born at night, when

scientists are half awake.
2. Test the hypothesis rigorously, especially the hypothesis, that passes the first or second test.
3. Discard hypotheses that cannot be 'falsified'.
4. Pay attention to costs and conflicts of (financial) interest.
5. Follow the Hippocratic advice: In the first place do no harm.

By 2016 the R&D of a new drug/therapy has become more complicated than in 1908. Today's Doctors are no longer leaders in medicinal drug development, like Ehrlich, Eijkman were earlier.

In 2018 doctors have delegated their financial and managerial matters to others: such as CEOs of global pharmaceutical firms or health insurance companies and financial officers of hospitals. Such individuals live by a new version of the 'golden' rule[14]:

'*The guy with the gold makes all the rules*.'

The *old* golden rule used by Boy Scout leaders was: '*the golden rule is to be nice*'.

Taxpayers/patients still consider physicians the right people to decide what is good or bad for them and often willingly follow the advice of their doctors and underline their agreement with their physician by signing an informed consent form.

One of the reasons for this lingering public trust is that doctors have an international ethical code of behavior, the Physicians Charter, derived from the original oath of Hippocrates, which includes: "*Do no harm* (to your patient)" and "*Make sure you do not have direct or indirect financial conflicts in the delivery of your patient care*. "

By 2016 three new 'dilemmas' have joined the 'artificial' dilemma created by Shaw in 1906:
1. Are Physician/Investigators still willing to initiate their own clinical research or do they prefer to follow blindly the rules of the guy with the gold?
2. Are Physician/Investigators able to deal with the ever-growing body of hard to understand and interpret Rules and Regulations that clinical investigators need to adhere to (at great emotional and financial costs also for patients)?
3. Are Physician/Investigators still interested in forming a multi-disciplinary, open source, investigative group operating without a profit motive?

Phase2Therapy

The company P2T, founded in 2013, is ambitious and wants to try and change the current new drug/new therapy research culture. P2T wants to make better drugs and new treatment methods available to patients faster and at lower costs. This P2T tries to do so by assisting clinical medical investigators in the design and execution of short lasting phase 2 studies.

P2T will enhance knowledge transfer by making results of P2T studies available to others on login and password while the study is still on going. P2T harbors knowledge (*intellectual property*) of scientists based in the Netherlands, the United States, Great Britain, and Switzerland. This diversity in languages spoken, talents, educational backgrounds and cultures is essential to P2T's success. It is a not-for-profit organization and obtains its operating costs by way of donations, grants and crowd sourcing.

Radiolabeled Immunoglobulin Therapy (RIT) for solid tumors

Vriesendorp and coworkers reported on their studies with radiolabeled rabbit immunoglobulin reactive with human ferritin in patients with end-stage Hodgkin's disease[15-19]. Other liquid tumors, leukemias and lymphomas have benefited from RIT.

P2T recommends a new two-step RIT approach for patients with *poor prognosis solid tumors* such as recurrent, inoperable adeno carcinomas of the exocrine pancreas (PaCa) and patients with a GlioBlastomaMultiforme (GBM).

The first step is the intra-tumoral administration of monoclonal humanized IgM reactive with Tenascin-C and labeled with Indium-111, a gamma emitter. Gamma Camera scans are performed 2, 24, 48, 72, and 120 hours after administration. Blood samples are taken and the same time points. If the gamma camera images indicate uptake in primary tumor and for PaCa patients in draining lymph nodes the patient will proceed to the second step.

Step 2 is the re-administration of the immunoconjugate labeled with Yttrium-90, a beta emitter. Blood and urine samples will be taken at the same time points as for the Indium-111 labeled Tenascin-C administration. In prior nude mice studies with human tumor xenografts the biodistribution of the radioimmunoconjugate was followed for one week. It appeared to be identical for both radiolabels. Both radioimmunoconjugates distributed rapidly within the tumor.

The gamma camera scans for Indium-111 labeled radioimmunoconjugates will be used to calculate radiation doses received by the tumor, radiation sensitive normal tissues surrounding the tumor, by the Y-90 labeled immunoconjugate. Tumor size, tumor staging and survival of the patients will be correlated to tumor volume and lymph node involvement.

This approach will allow for the re-introduction of the Hippocrates paradigm: '*Doctor do no harm*' for patients with poor prognosis solid tumors.

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