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A physicist's view of the similarities and differences between tuberculosis and cancer

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HIGHLIGHTS

- Responses of organs to TB and cancer are similar.
- In TB people died before childbearing age, in cancer after.
- It is harder to fight domestic intruders than external ones.

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ABSTRACT

In 2015 in the United States 612,000 persons died from cancer whereas only 470 died from tuberculosis (TB), a disease which was the main cause of death around 1900. How can one explain such a huge discrepancy in treatment progress? A statistical and medical comparison between TB and cancer will give some clues.

What makes the question of particular interest is the fact that TB and cancer also share important features. Both TB and cancer can affect several organs, e.g. the lungs, brain, bones, intestines, skin. What in cancer is called "malignant neoplasm" (tumor) is called "granuloma" in TB. By isolating malignant cells from the rest of the body, such clusters protect the host's organism but at the same time they are "secure beachheads" from where malignant cells can wander off to new locations. Thus, metastatic tumors have a TB parallel in the form of secondary granulomas.

To investigate this parallel more closely we use the age-specific response of organs. Called spectrometric analysis in a previous paper (Berrut et al. 2017), this method provides information about how fast tumors develop and how serious they become. A characterization of the response to TB of organ j is given by the following (age-dependent) death ratio:

$$T_j(t) = (\text{death by TB of type } j \text{ at age } t)/(\text{all TB deaths at age } t).$$

The development of cancer tumors can be described by similar profile functions $C_j(t)$.

It appears that for the same organ $T_j(t)$ is similar in shape to $C_j(t)$. In other words, the idiosyncrasies of each organ are more determinant than the functional differences between TB and cancer. Such observations bring to light vulnerabilities in the way the immune system provides protection to various organs.

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1. Introduction

The paper has the following starting point and motivation.

1.1. How to measure the role of the immune system in cancer?

People who, due to organ transplantation, undergo long-term imunosuppression provide an insight into the role of the immune system in the development of cancer. Several studies have shown a 3-fold increased risk of cancer[1] compared with the general population of same age and sex [1,2].

Nonetheless, in present-day cancer research there is a marked tendency to overlook the role of the immune system. As an illustration consider the following argument ([3], p. 281).

> The increase in cancer incidence with age indicates that cancer is the result of a multistep accumulation of cellular changes; if caused by one-step changes, cancer would occur with same likelihood at any moment in life.

However, if (as is likely) the immune system becomes less effective with age, then a mutation occurring in old age will have a greater impact. As a matter of fact, there are many infectious diseases whose likelihood also increases with age.

One of the main goals of the present paper is to estimate the capacity of the immune system to identify and eliminate cancer cells. It will be seen that the comparison with TB will guide us in this task.

1.2. Possible role of stem cell mutations in TB

It has been recognized for more than a century that some organs (and the corresponding tissue types) give rise to cancers much more frequently than others. Mutations can occur at three levels: (i) genes (ii) stem cells (in diverse degrees of differentiation) (iii) Differentiated cells in specific organs, an assumption in line with the classical somatic mutation "theory" of cancer.

Thanks to the work of Miguel Lopez-Lazaro (see [3]) we know that gene mutations play only a small role in explaining differential cancer risk across organs.

In recent years there has been renewed interest in this question in relation with a better understanding of mutations arising during DNA replication in stem cells. In a pioneering work Cristian Tomasetti and Bert Vogelstein ([4], Fig. 1) showed that the likelihood of cancer across organs is compatible with the number of stem cell divisions which is itself a proxy for the number of mutations. This explanation is also supported by the great variability in degrees of differentiation observed in high malignancy cancer cells [5].

The parallel between tuberculosis and cancer developed in the present paper includes the responses of organs respectively to the two diseases. As, at first sight, the role of mutations seems less obvious for TB than it is for cancer, such correlations would tend to emphasize organ-specific idiosyncrasies of the immune system rather than the role of mutations. The bulk of this paper was written without having in mind the stem cell mechanism. In order to make our observation consistent with this mechanism, a natural conjecture is that predisposition to TB is also somehow connected with the number of stem cell mutations. This conjecture would extend the role of this mechanism beyond cancer per se.

1.3. Physicist view

What in the title is meant by the expression "a physicist view" is that our investigation relies on reasoning by comparison and analogy. Nowadays, researchers seem reluctant to use this approach, perhaps because it is not found sufficiently "scientific". However, as shown in the Appendix, it appears that historically this form of exploration has played a key-role in the development of physics. Although analogies alone cannot solve a problem, they can suggest conjectures which may turn out to be essential steps.

Moreover, the concepts that we introduce, e.g. learning curve, endogenous versus exogenous intruders, comparison to animal species, are certainly uncommon in papers written by biologists.

1.4. Sharp contrast in death rate changes

In the early 20th century in Europe and the United States tuberculosis (TB) was the first cause of death. Cancer came only in fourth position after cardiovascular and cerebrovascular diseases. In 1900 in the United the death rate of TB (all forms) was 194 per 1000 whereas for cancer it was only 64 per 1000. Nowadays, although remaining a substantial cause of death in old age, tuberculosis has been virtually eliminated in young and middle-aged patients. In contrast, despite intensive research, progress in cancer treatment was very limited.[2]

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[1] This incidence figure is averaged over all cancers; note that, surprisingly, there is no increase for brain, breast and prostate cancers.

[2] One reads that around 1990 only 25% of the people diagnosed with cancer survived more than 10 years, whereas 30 years later that percentage had climbed to 50% [6]. However, if tumors can be diagnosed earlier in their development due to improved imaging devices, the survival time will increase so to say mechanically even if the treatment itself is not much improved.

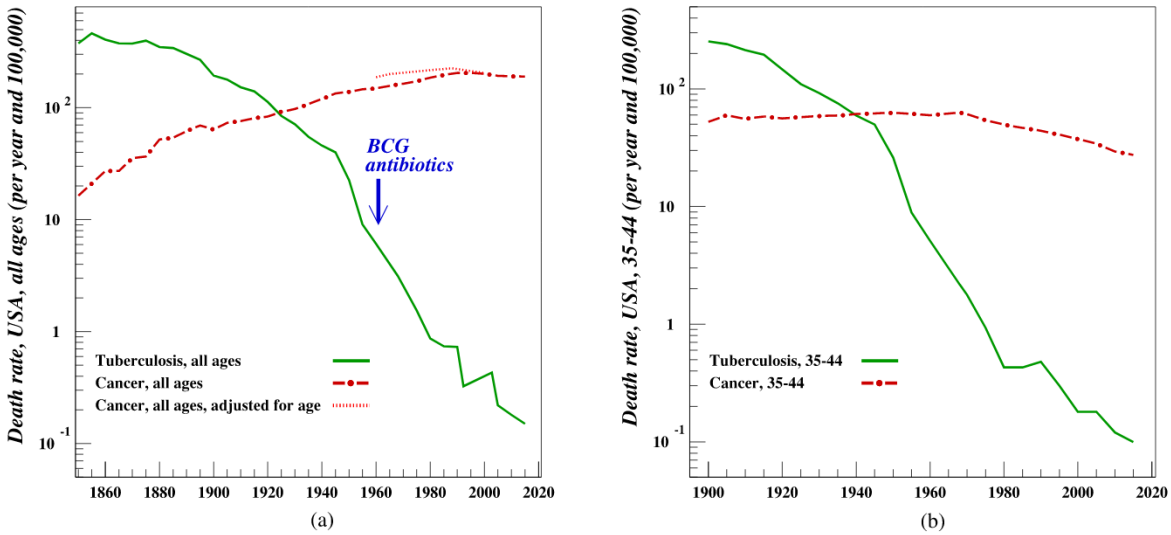

Fig. 1a,b. Comparison between the death rates of TB and cancer in the United States, 1850–2015, The TB death rate was divided by 30 even before the introduction of the BCG vaccine and of antibiotics in the 1950s. Note that age-adjustment for the cancer curve that takes into account the increase in the number of elderly people makes in fact little difference.
Source: 1850–1899: Statistique internationale du mouvement de la population (1907); 1900–1940: Linder and Grove [7]; 1940–1960: Grove and Hetzel [8]; 1968–2015: CDC Wonder databases, compressed mortality; 1968–1978, 1979–1998, 1999–2016. 1950–2002 (adjusted for age): National Vital Statistics Report Vol. 50, No 15, 16 September 2002. The respective ICD (International Classification of Diseases) codes for TB and cancer are as follows. 1968–1998: ICD8 and ICD9: 010–019, 140–239; 1999–2016: ICD10: A16–A19, C00–D48.

Figs. 1a and 2 tell us that for TB and measles much progress was achieved even before the introduction of vaccination. For TB there was a reduction of the death rate by a factor 30 and for measles by a factor 100. However, the factors which brought about such reductions did not trigger similar changes for cancer mortality. Why?

At the end of this paper, after considering several other factors we are led to the (provisional) conjecture that a key difference is the following.

> In 19th century TB or measles cases, the death of the affected persons occurred before child birth age which means that inappropriate immunity systems were not transmitted to the next generation. In contrast, then as well as now, death by cancer occurred well after child birth age.

As this conjecture should apply also to other diseases than TB and cancer, it should be possible to test it, at least if appropriate long term data can be found.

Fig. 1a,b shows a dramatic difference between the death rate changes of the two diseases. How can one possibly explain it?

1.5. Outline of the paper

The argument of the paper comprises the following steps.

- Usually the invasion of an organism by a disease takes place in successive stages characterized by different responses of the immune system. This will be discussed in the first section.
- If TB and cancer were two completely different diseases their comparison would be of little interest. In the second section it is shown that in fact the two diseases share many similarities.
- The next section focuses more specifically on how TB and cancer impact different organs.
- In the last section before the conclusion we propose a testable conjecture which accounts for the huge difference observed in the efficiency of exo-immunity versus endo-immunity.

2. Effectiveness of the immune system

2.1. Successive lines of defense

One can distinguish two phases in the action of the immune system against pathogens or cancer cells (for the sake of brevity let us call them "intruders") as schematized in Fig. 3a.

(1) The first phase is between the moment when the organism comes in contact with a few intruders and the moment when the intruders are sufficiently numerous to become detectable. For TB one can consider that the organism comes

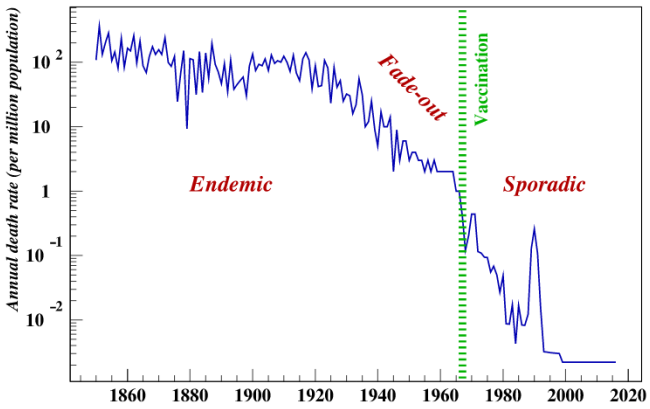

Fig. 2. Natural history of the death rate of measles in the United States. This graph complements Fig. 1a for another infectious disease. Measles differs from TB in two ways. (i) It is not due to a bacterium but to a virus, hence antibiotics are ineffective. Nevertheless the fall of the death rate was quite as impressive with a division by a factor 1000. (ii) The time constant of measles from infection to recovery or death is of the order of one month, that is to say at least 10 times shorter than the time constant of TB which is of the order of one year. This is certainly what explains the fact that the death rate fluctuations are much larger for measles than for TB. Note that in 1989–1991 there was a measles outbreak which particularly affected California, Chicago and New York. In 2001 and 2007 there were serious measles outbreaks in Japan.
Source: For 1850–1899 the data are for the state of Massachusetts which is the only state to have data going back to 1850. For 1900–1930 the data are for the registration states Bur [9]. After 1930 the data cover the whole country (except Alaska and Hawaii until statehood). 1850–1899: Statistique internationale du mouvement de la population (1907); 1900–1940: Linder and Grove [7]; 1940–1960: Grove and Hetzel [8]; 1961–1967: Mortality statistics in the United States 1967 p. 1–7 Bur [10]; 1968–2015 : CDC Wonder databases, compressed mortality 1968–1978, 1979–1998, 1999–2016. The respective ICD (International Classification of Diseases) codes for measles are as follows. 1968–1998: ICD8 and ICD9: 055; 1999–2016: ICD10: B05.

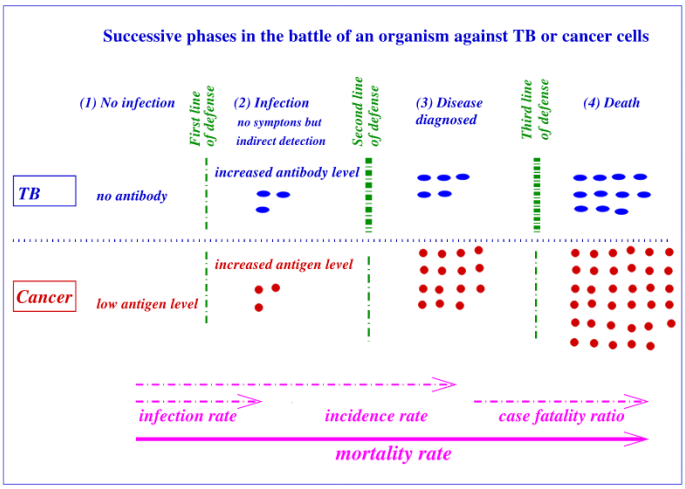

Fig. 3a. Successive lines of defense of a human organism against "intruders", TB mycobacteria or cancer cells. The distinction between phase (2) and (3) would correspond to HIV versus AIDS or latent TB versus developing TB. 90% of TB infected persons remain without symptoms. Antibody fight intruders by marking them for destruction by macrophages. In a general way antigens are foreign or abnormal bodies; for instance in the case of breast cancer, the cancer antigen CA 15.3 are proteins released by cancer cells; for healthy persons the concentration of CA 15.3 is low but not zero for it is thought that this protein is also produced (albeit in small quantity) by normal breast cells.

in contact with the mycobacteria through vaccination (although these are of course in attenuated form). For cancer, the occurrence of cancer cases in early childhood suggests that organisms come in contact with abnormal cells soon after birth. Statistically, this phase is described by the incidence rate which is the number of cases divided by the population. Fig. 3b shows that, averaged over age, control is lost in about 1000 cases per 100,000 for cancer as compared to only 3.3 cases per 100,000 for TB. It is mostly in this phase that the battle against cancer is lost.

In short for cancer the incidence rate is much larger than for TB especially in old age.

(2) In the second phase the number of intruders continues to grow until eventually this increase leads to death. Statistically, this phase is described by the case-fatality ratio which is the probability of death for a person who was diagnosed with the disease. It is given by the death rate divided by the incidence rate. Fig. 3c shows that for cancer the case-fatality ratio is moderately larger than for TB.

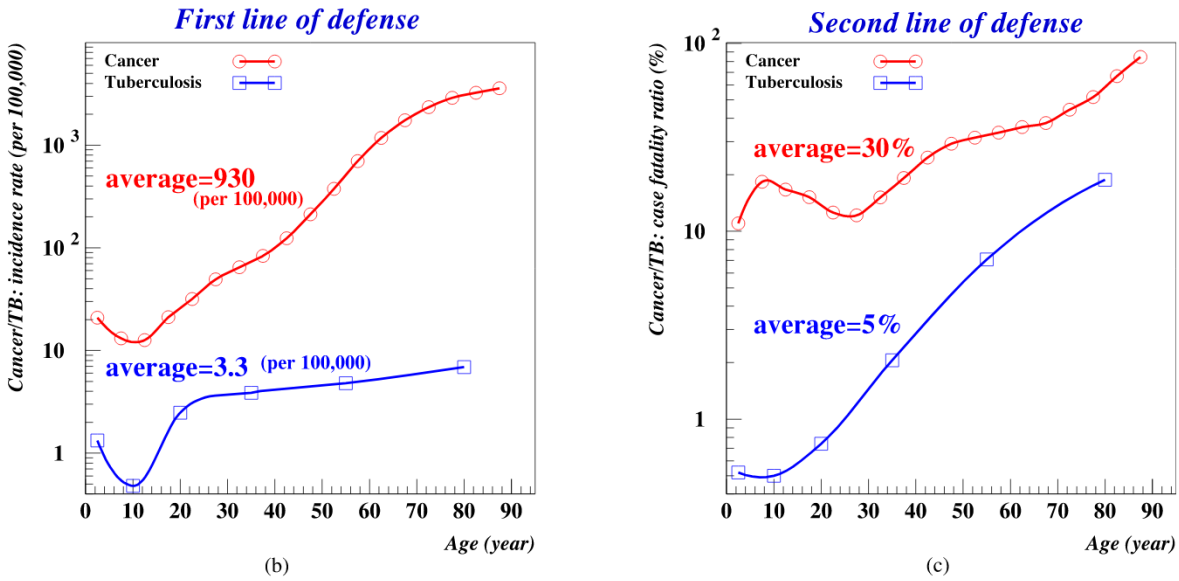

Fig. 3b,c. Comparison of the incidence rate and case fatality ratio for TB and cancer. (b) The incidence rate is the ratio: persons diagnosed with the disease divided by population. (c) The case fatality ratio is the ratio: deaths caused by the disease divided by persons diagnosed with the disease; it is given by the death rate divided by the incidence rate. It represents the probability of death for a person who is known to be ill in the respective age interval. The fact that both the incidence rate and the case fatality ratio increase with age shows that as they age organisms becomes less and less able to fight the disease successfully. More precisely, for TB it is the fatality ratio which increases fastest with age, whereas for cancer it is the incidence rate which shows the largest increase.
Source: The data are for males. TB (2014): CDC (Centers for Disease Control, USA). Cancer (2013–2015): Cancer Research UK. The data are for all forms of cancer (C00–C97).

Taken together the curves in Fig. 3b,c show that it is the weakness of the first and second line of defense against cancer which is the main factor in the huge difference seen in Fig. 1a.

The graphs of Fig. 3b,c can be further illustrated by the following facts.

• Fig. 3c shows that for cancer the case-fatality ratio is of the order of 30%.[3] This is a proportion which is higher than for most infectious diseases. Thus, for measles in the outbreak of 1989–1991 in California and New York it was less than 1%. As a more significant comparison, the case fatality ratio of TB for South African HIV-infested persons is about 20% [11]. Moreover, for most infectious diseases the case-fatality ratio decreases with age whereas for cancer it increases with age.[4]

• In an epidemic usually only a small proportion of the population is infected by the pathogens (in the sense of producing antibodies). On the contrary, the production of abnormal cells occurs in all organisms which means that the theoretical infection rate is 100%.

• With respect to infectious diseases any population comprises two components: (i) the susceptibles that is to say the persons who are not immunized and (ii) those who are immunized. The proportion of the second group increases with age. On the contrary, for cancer nobody seems to be immune.

In summary, the previous points together with the upcoming discussion suggest that human organisms are not well equipped to fight cancer. Hence the huge difference displayed in Fig. 1a,b.

2.2. History of infectious diseases: successive stages from endemic to eradication

The history of infectious diseases like smallpox, measles or TB usually comprises 4 phases, each of which may last from a few decades to a few centuries. Despite covering a broad time span of 166 years, the graphs of Figs. 1a,b and 2 probably miss the initial epidemic phase.

(TB1) **Epidemic phase.** When the prevalence of the infectious agent (whether bacteria or viruses) in a population is fairly low, few people have been able to develop an immunity. In this phase the disease manifests itself in the form of periodic epidemic surges.

[3] The cancer data in Fig. 3c are for the UK. US data lead to very similar results. Data from the US National Cancer Institute for the years 2011–2015 give an incidence rate of 439 per 100,000 and a death rate of 163 per 100,000 which leads to a case fatality ratio of 31%.

[4] For instance, it is reported by Dales et al. [12] that for measles during the outbreak of 1989–1991 in California and New York City, the case fatality rate was divided by a factor 100 between the age intervals (0,1 year) and (5 y,15 y).

(TB2) **Endemic phase.** As the outbreaks become more frequent infection becomes more prevalent with the result that the disease tends to become endemic. An endemic equilibrium state is reached when the death rate of the disease has become fairly stationary. Whereas for rare diseases such a stationary death rate can be quite low, in TB in the 19th century it was fairly high.

(TB3) **Fade-out phase through immunity of survivors and offspring.** When the prevalence of a disease is as high as it was for TB in the late 19th century, there are more and more survivors who develop an immunity which means a correlative fall in the number of susceptibles. In this process the transmission of immunity from mother to child through breast-feeding played an important role as was proved by the German biologist Paul Ehrlich in the early 20th century.

As a result of a decreasing concentration of pathogens in the environment, the death rate of the disease starts to fall. A "spontaneous" decrease of this kind was indeed observed for measles as well as for TB during several decades prior to the introduction of effective remedies in the 1950s.

(TB4) **Eradication phase.** With the disease held in check by vaccination and other remedies and if there is no other carrier which can constitute a "safe haven" for the pathogens involved, the decrease will go on and will end only when the disease is totally eradicated worldwide, a success so far reached for only few diseases of which, back in 1980, smallpox was the first.

2.3. What makes cancer more difficult to cure than TB

Now, let us come to the crucial question of why the cancer death rate curve is almost flat. Our reasoning comprises the following steps.

(C1) **Deviant cells are ubiquitous** It seems natural to admit that the incidence of a disease represents an equilibrium between two opposite forces: the prevalence of infectious agents in the environment and the strength of the immune system with respect to this specific disease. If there are no pathogens there will be no disease. As we have seen, this corresponds to the situation when a disease has been eradicated. Cancer corresponds to a completely opposite situation for the analogue of the pathogens are abnormal cancer cells which grow in a boundless way. As such deviant cells appear continuously in the body of each and every individual, cancer resembles a disease brought about by a widespread pathogen.

(C2) **Is there a learning curve with regard to the elimination of abnormal cells?** Now, we need to gauge the strength of the immune system with respect to cancer cells. Individuals who have recovered from smallpox will never become ill again which means that their immune system has been notably strengthened with respect to this disease. Similarly, it was shown by Paul Ehrling that mice which are fed small but increasing dosages of a poison (e.g. ricin or abrin) become resistant to this poison. Is there a similar strengthening mechanism for the immune system against cancer?

It is the task of the killer T-cells to identify and target abnormal cells. This includes cells infected by viruses or bacteria as well as cancer cells. As the first abnormal cells appear soon after birth (as seen by the occurrence of some forms of cancer in newborns), the existence of a learning process would mean that the immune system will be more and more able to remove them. However, the fact that after the age of 10, the death rate of cancer starts to increase and that it continues to go up steadily with age suggests that no equilibrium is reached. In a population of 100,000 30-year old persons the immune system will loose its war against abnormal cells in approximately 30 cases; at age 40 and 50 that war will be lost in 60 and 120 cases respectively (for data about age-specific death rates see [13]). In fact, we do not need to know whether the immune system improves or deteriorates with age; what the previous numbers show is that the imbalance between the rate of apparition of new abnormal cells and the capacity of the immune system to remove them increases with age. In other words, with respect to cancer, the human immune system reveals a structural weakness.

(C3) **Cancer in dogs** In the previous sentence we used the expression "*human* immune system" which raises the question of whether this weakness is special to humans or, on the contrary, is shared by other mammal species. Pet dogs are one of the animals for which there are data.[5]

> Dogs can develop a variety of cancers and most are very similar to those found in humans. Cancer is the leading cause of death in dogs. It is estimated that 30% of domestic dogs will develop cancer, which is the same incidence as in humans.

Fig. 4 shows that the trend of the age-specific cancer death rate for a group of 345 Rottweiler dogs is mostly upward. Although this is a fairly small group the results give a preliminary indication that the pattern is roughly similar to what is observed in humans. In other words, the weakness of the immune systems with respect to cancer is shared by dogs. Probably other mammals would reveal the same pattern if appropriate data were available.

(C4) **Poor performance of cancer immunotherapy and chemotherapy** For infectious diseases the main method of treatment was to strengthen the immune system through vaccination. Quite understandably, the same approach was tried for cancer. Paul Ehrlich (1854–1915), William Coley (1862–1936) and others developed cancer immunotherapy.[6]

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[5] It seems that the only animals for which the causes of death are identified with sufficient accuracy as a function of age are pet dogs and cats. The sources are: Khanna et al. [14], Gardner et al. [15], Wikipedia article entitled "Cancer in dogs".

[6] Interestingly, Ehrlich told his sponsors that cancer research meant basic research and that a cure could not be expected soon.

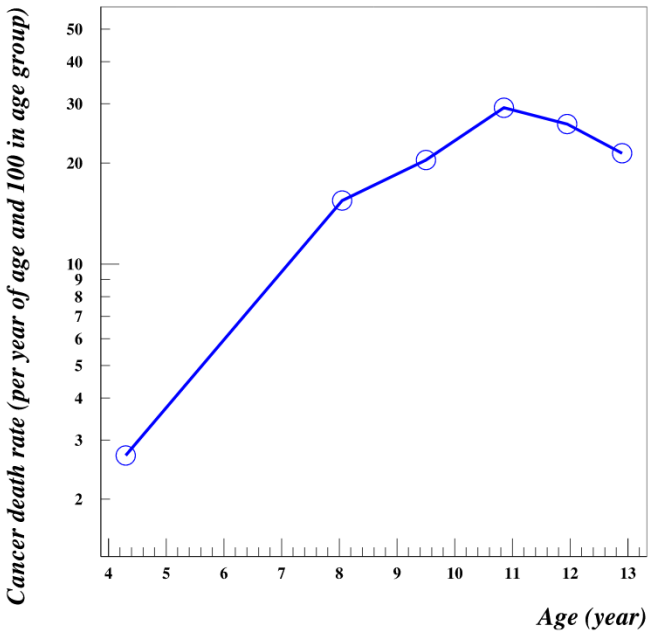

Fig. 4. Cancer death rate for pet dogs as a function of age. The data are based on information provided by veterinarians for a cohort of 345 Rottweiler dogs. The death rate increases more slowly in old age than for humans. However, in order to assess more reliably the death rate in old age one would need a larger sample. Here at the age of 12.5 years there were only 35 dogs still alive. Between the ages of 4 and 10 there is an exponential increase described by $\mu \sim \exp(\alpha t)$, $\alpha = 0.43$ year^{-1} which corresponds to a doubling time of 1.6 year; this is almost the same as for humans when renormalized with respect to the respective life spans, i.e. 1 dog-year equal some 6 human years.
Source: Cooley et al. [16].

They were able to prove that the mechanism of removal of abnormal cells by the immune system is fairly similar to the elimination of pathogens. However, despite notable progress (for which Ehrlich was awarded the Nobel prize in 1909), attempted cures were much less successful than for smallpox, rabies or other infectious diseases.

Ehrlich was not only a pioneer in immunotherapy but also in chemotherapy. Around 1910 he discovered the first effective drug treatment for syphilis. However, when tried for cancer, the approach of chemotherapy once again proved less effective than for infectious diseases.

In short, the component of the immune system tasked with fighting abnormal cells (let us call it the *endo immune system*) turned out to be weaker and more difficult to strengthen than the component (let us call it the *exo immune system*) destined to fight pathogens. In a parallel developed below, this difference can be seen as similar to the one between fighting a foreign war and a guerrilla war.

In spite of the differences emphasized in the previous discussion, the main argument of our paper is that better insight can be gained by *comparing* the two diseases. On the one hand, as shown below, they share many similarities but on the other hand with respect to treatment they are dramatically different.

2.4. Questions

Here are some of the questions that can be raised.

(1) Both TB and cancer do exist in dormant mode. In latent TB the persons are infected with the TB bacteria which however do not multiply; as a result they are not ill and not contagious. This state can last for years. Even without treatment less than 10% of these persons will develop the disease during their lifetime. Similarly, dormant cancer cells are mutated cells which, however, do not multiply. As explained below, dormancy is a very common occurrence in many microorganisms. Would it not be of interest to examine if there are common dormancy mechanisms? TB and cancer might be a good point where to start such a comparative study.

(2) Both TB bacteria and cancer cells form clusters. It is a way for them to be protected against anti-bodies.

In a sense this is a network problem in which the bacteria or cancer cells are the nodes; such networks would have the ability to branch out and nucleate to form secondary networks. Naturally, to define such networks in a meaningful way would require a knowledge of key-parameters such as density and interaction strength.

(3) Whether in TB or in cancer, the creation of new clusters (i.e. metastasis) is conditioned by the same steps. (i) First bacteria or cells must be able to leave the initial cluster. In cancer tumors this means being able to cross the extra cellular matrix, a layer of protein molecules which surrounds the tumor and separates it from adjoining tissues. (ii) While on

their way the bacteria or cancer cells must either not be detected or be able to ward off anti-body strikes. (iii) Finally, an appropriate niche must be found. Our subsequent analysis suggests that TB myco bacteria and cancer cells have the same preferences, namely the lungs and the other organs that we examine but that they both avoid skeletal muscles.

In the next section additional explanations are provided about the mechanisms involved in the previous points.

3. Similarities between TB and cancer

3.1. Similarities in treatment

The situations of the two diseases with respect to treatment appear fairly similar.

Drugs are available which kill the agents responsible of the disease, *Mycobacterium tuberculosis* on one hand and cancer cells on the other hand. The mechanism of action of antibiotics and drugs used in chemotherapy are very much the same in the sense that both drugs are only effective when the bacteria or cells are in division stage.

3.2. How intruders evade drugs: formation of clusters and dormancy

There are two main mechanisms through which TB bacteria and cancer cells can protect themselves. One is to form tight clusters that anti-bodies cannot penetrate. The second is to form dormant cells which cease dividing but survive in a quiescent state while waiting for appropriate environmental conditions. Among microorganisms this a very common mechanism. For instance, in *C. elegans* it is called the *dauer* stage, in the rotifer *Brachionus plicatilis* the so-called diapausing eggs may remain in an arrested stage for long periods until conditions become more favorable [17]. Similarly, the thick-shelled eggs of *Artemia salina* (a species of brine shrimp) can remain in a dormant state for years.

In other words, TB and cancer treatments are confronted to similar problems: how to break into clusters and how to get rid of the dormant cells.

3.3. What about vaccination?

The BCG (Bacille Calmette Guérin) vaccine was first used on humans in 1921 in France but it was not until after World War II that it received widespread acceptance elsewhere. As it arrived at the same time as the antibiotics it is difficult to distinguish clearly their respective roles. The analogue of vaccination was the development of immunotherapy. It was indeed tried but with little success.

3.4. Role of environmental factors

Between 1850 and 1950 TB mortality rate had fallen from 350 to 40 per 100,000. What were the *main* factors at work in the 100 years until 1950? An honest response is that we do not really know.

- Often environmental factors such as cleaner cities and better housing conditions are mentioned.
- Almost simultaneously working conditions improved substantially. For instance in England the "Graham's Factory Act" of 1844 stated that children 9–13 years could not work for more than 9 h a day. This was a first step which was followed by others. Incidentally, it can be observed that the laws passed prior to the establishment of the "Factory Inspectorate" in 1833 remained largely unenforced.

It is clear that children working in coal mines or in cotton factories were easy targets for TB.

- There was also the development of social security which made treatment in sanatorium widely available. This meant preventing contagion and allowing the organisms of patients to fight the disease in the best conditions possible. In a sense it was an immunotherapy treatment. In contrast, for cancer no similar sanatorium stays have been tried.[7] Would it not put the immune system in better conditions to fight cancer cells?

3.5. Worsening environmental conditions for cancer

With respect to cancer, environmental conditions rather deteriorated. One may mention food additives, pesticides used in agriculture or X-rays. Except the last one, most of these factors are not easy to quantify. An introduction to the X-ray issue can be found in n Roehner ([18], p. 42–45).

It is not easy to assess the effect of environmental factors for this requires long-term studies. Over a period of 50 years the incidence rate can change for several reasons. Medical diagnosis is very dependent upon available imaging means. For instance, between 1982 and 1989 the incidence rate of breast tumors smaller than 1 cm increased from 10 to 40 per 100,000 women whereas in the same time interval, the incidence of tumors of more than 3 cm remained unchanged at a level of 35 per 100,000 [19].

[7] In fact, in the 1930s "cancer sanatoriums" have been in existence, for instance in Switzerland, and often in relation with the approach of medicine based on homeopathy.

3.6. Similarities in histopathological patterns

Despite being caused by bacteria, TB lesions are very complex with a wide range of microbiological features (this applies even to people who, although infected, do not develop any signs of the disease). Among them one can mention: solitary nodules in the lung parenchyma (that is to say in the active part of the lung tissue), infection limited to lymphatic nodes, vasodilatation, fibrinous exudate, giant cells, necrotic cells [20,21]

Such a chaotic picture is not too different from what is seen in cancer. One should remember in this respect that the clearest feature of cancerous tissues is the great variety of cells in various stages of differentiation, a state called anaplasia (which means cells moving backward). Quantitative studies have even shown that the higher is cell variability the more severe is the malignancy and the shorter the survival time [5]. In other words the histology of cancer cells provides a good (yet nowadays somewhat neglected) predictor of recurrence and survival time.

3.7. Similarities between granulomas and tumors

The mechanism of TB propagation in an organism can be closely investigated in experimental TB induced in animal models. Zebrafish (*Danio rerio*) appear as a particularly convenient model [22]. The development of granulomas are a key feature of human TB and zebrafish studies provided a dynamic insight into what, hitherto, was largely seen as static structures. Granulomas are preferentially formed in fatty tissue and they are the first step through which infection can be clearly identified. In short, they play the same role as primary tumors in cancer. Moreover, observations on zebrafish showed that infected macrophages can detach from established granulomas and wander off to other organs to form secondary granulomas. Clearly, such a process parallels the dissemination of cancer cells which leads to secondary tumors.

3.8. Similarities in reprogramming mechanisms

At first sight, TB and cancer appear as very different diseases. Whereas TB is due to the proliferation of a bacteria, *Mycobacterium tuberculosis* (*MT*), cancer results from the boundless reproduction of body cells which have freed themselves from the controls generated by their neighbors. TB starts with a foreign pathogen whereas in cancer it is a body cell which spins out of control.

However, if we look at it more closely, the mechanisms are not too different for indeed through a kind of reprogramming process pathogens are able to twist the behavior of host cells (in the case of viruses) or macrophages (in the case of bacteria) which try to eliminate them. For instance, once a bacterium has been "imprisoned" into a vesicle of a macrophage,[8] a common trick (used for instance by *MT* or *Legionella pneumophila*) is to prevent the injection into the vesicle of enzymes which would kill the pathogen. In short, by manipulating their host successful pathogens are able to use it as a vehicle for proliferation.

Another connection is the fact that it was estimated [23,24] that about 16% of worldwide cancers are triggered by viruses or bacteria: for stomach cancer it is Helicobacter pylori, for lymphoma it is the Epstein-Barr virus, for cervical cancer it is the papilloma virus, for liver cancer it is hepatitis B or C.

One knows that the formation of a tumor is a multistage process; so is also the development of TB as illustrated by the following features. (i) In only 10% of infected persons will TB manifest itself. The other 90% will remain asymptomatic. (ii) As already mentioned as TB develops, one sees the formation of granulomas which are nodules of a diameter of about 3 mm in which pathogens and neutralized macrophages are clustered together.

3.9. Similarities in spreading mechanisms

Primary cancer tumors can spread to many organs. The same holds for TB.

- Although pulmonary TB is the most frequent, TB can also develop in other parts of the body: bones, skin, intestines, meningitis, genito-urinary organs. On the other hand there are some locations (e.g. skeletal muscles) where the development of both cancer and TB is uncommon.
- Although fairly rare, TB of the breast (tuberculosis mastitis) does occur and it is far more frequent (about 20 times) in women than in men [25]; it is particularly likely in reproductive age. As a matter of fact, being irregular and hard, TB breast lesions may be indistinguishable from breast carcinoma [26].
- One of the most important properties of cancer cells is their ability to spread to other organs where they may form secondary tumors. As already observed, there is a parallel in TB in the sense that the granulomas can migrate to other organs such as the liver or the kidneys. In developed form such cases are called miliary TB; they represent 20% of the extra-pulmonary cases.

In the following section we document how TB and cancer impact various organs. It will be seen that there are common patterns.

[8] The diameter of a human macrophage is about 20 micrometers which is 10 times more than the length of *MT* bacteria.

4. Similarities in how TB and cancer impact body organs

4.1. Purpose

If, as argued above, there is indeed a connection between the growth of TB and cancer in various organs, can it be that these links manifest themselves by similar responses of the organs? How can one design an operational procedure that will unravel such possible links?

It turns out (see Fig. 5a) that among the set of persons who die from cancer at an age t the probability $C_b(t)$ that this cancer will affect the brain is highest around the age of 10 years: $C_b(10) = 23\%$. At older ages this probability falls off sharply. At the age of 25 it is down to 5%, and at the age of 50 to 1%.

Fig. 5a also shows that the probability $T_b(t)$ for developing TB affecting the brain is also maximum at the age of 10 and falls off in older ages even more sharply than $C_b(t)$. Subsequently, for the sake of brevity, a curve such as $C_b(t)$ will be called the *age-profile* of brain cancer.

It could well be that the similarity in the age-profiles $C_b(t)$ and $T_b(t)$ is merely a coincidence. However, if for a number of other organs the same similarity is observed, it may suggest that some organ-specific factors are at work which account for similar responses for the two diseases.

What can be the practical interest of these observations? Taken alone, they will not give us a full fledged explanation of why such brain diseases appear at that specific age. However, they suggest that the idiosyncrasies of the organ under consideration play a more important role than the nature of the disease itself. For instance, as far as brain diseases are concerned, the screening defects of the blood–brain barrier may be the key.[9] In other words, in this shield versus sword issue, our observation will tend to focus attention on the macrobiological properties of the shield.

4.2. Method

In the previous subsection we defined our objective and we broadly delineated how the observation will be organized. Presently, we will explain how in practice it can be implemented.

The main difficulty is the following.

As we wish to explore the affinity a disease (α) has for a specified organ (S) we would need incidence data rather than mortality data. As a matter of fact, mortality data mix two very different effects (i) the prevalence of α in S (ii) how effectively this specific disease can be cured. As an extreme case, for a disease whose cure rate is 100% or which simply is not a deadly disease (as for instance is the case of most forms of herpes) it is altogether impossible to get any information about incidence from mortality data.

Because nowadays in all developed countries TB is cured in very effective ways,[10] it is impossible to use present-time data for our investigation. On the other hand, if we consider US data from the early 20th century there will also be two difficulties. (i) The international classification of diseases will be very different from the present-day classification and it will be much less detailed. Thus for TB there will be only 5 types and they will include labels such as "Pott's disease" (TB of the spine) or "White swellings" (TB of the joints) with which we are no longer familiar. (ii) In 1910, only 58% of the US population was included in the federal death registration area. This would reduce the number of deaths by a factor of two. Starting from 1933, the death registration area included 100% of the population. This led us to the methodological choice of using data from the period 1934–1945.

In 1934 there were substantial numbers of deaths in almost all types of TB or cancer except for a few. We have been using averages over a number of successive years in order to reduce the statistical fluctuations. Naturally, the fluctuations are conditioned by the number of deaths. As an illustration, one can mention the case of skin TB for which there were less than 10 deaths in almost all age groups except in the oldest ones. In this case the smoothing process required to take averages over 10 successive years that is to say from 1934 to 1943.

4.3. Results

If one can assume that the death records have been filed correctly, all disease locations documented in US mortality data are for *primary* lesions. The comparison between the profiles of TB types and cancer types is shown in Fig. 5a,b.

As a matter of curiosity, one may wish to know to what extent the cancer profiles of 1934 differed from those of 2015. Of the 7 profiles, only two were markedly different, namely (i) cancer of the respiratory system and (ii) skin cancer. For (i) in 2015 there was only one peak near the age of 65. The narrow peak centered on the age of 20 does no longer exist. For (ii) it is so to say the opposite in the sense that in 2015 in addition to the surge beyond the age of 75 there is also around the age of 25 a major peak which reaches the level of 4%.

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[9] Some of the "holes" of this barrier are described in Kim [27, p. 33–34] and Sorge and Doran [28]. For instance, the barrier can be penetrated by using so-called "Trojan horse" mechanisms.

[10] In 2015 in the US the total number of TB deaths was 470 which is 152 times less than in 1934. In 1910 there were even 2.4 times more TB deaths than in 1934. For cancer it is a different situation in the sense that there were 140,771 deaths in 1934 and 612,207 in 2015.

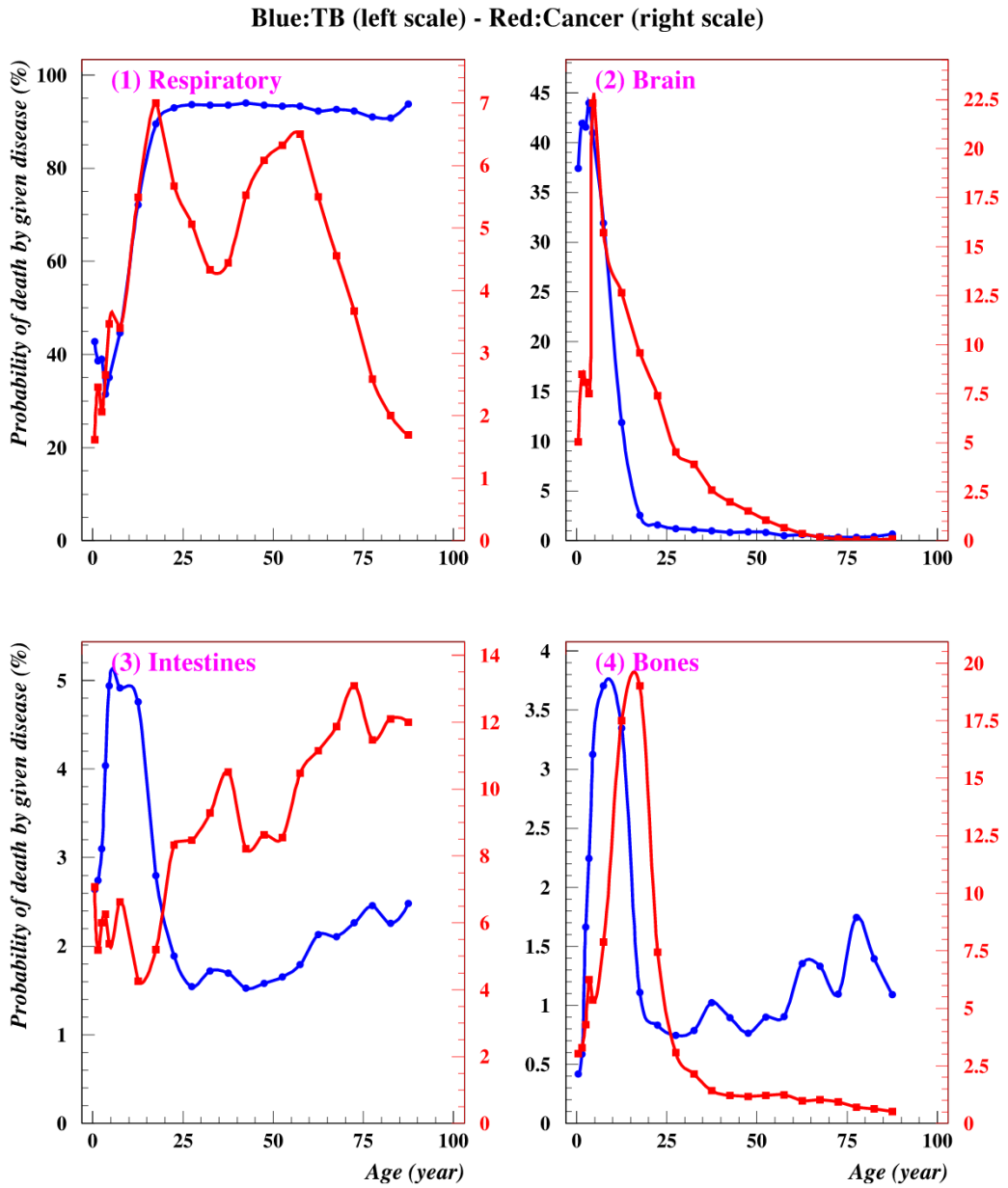

Fig. 5a. Comparison between the conditional probabilities represented by the ratios: (deaths by TB type)/(all TB deaths) (blue line with round dots) and (deaths by cancer type)/(all cancer deaths) (red line with squares), USA 1934–1943. The left-hand scale refers to TB whereas the right-hand scale refers to cancer.
Source: Bureau of the Census: Mortality Statistics 1934–1936, and Bureau of the Census: Vital Statistics of the United States, Part 1, 1937–1943.

The TB–cancer correlations show that in 5 of the 7 cases (i.e. 71%) there is a significant correlation. For these 5 cases the average correlation is: $r = 0.61 \pm 0.11$.

In addition two points should be observed.

• Even for the "intestines" and "lymphatic" cases for which there is no correlation the profiles share some common features. Thus, for "intestines" after the age of 25 the two ratios do not fall to zero (as is the case for "brain" or "bones") but increase more or less steadily (applying a smoothing moving average would almost eliminate the ups and downs of the cancer profile). Moreover, an age shift of only 10 years would bring the peaks of the two curves of the lymphatic case together.

• It must be realized that among organs the profiles are of very different shapes which makes similarities arising merely by chance fairly unlikely.

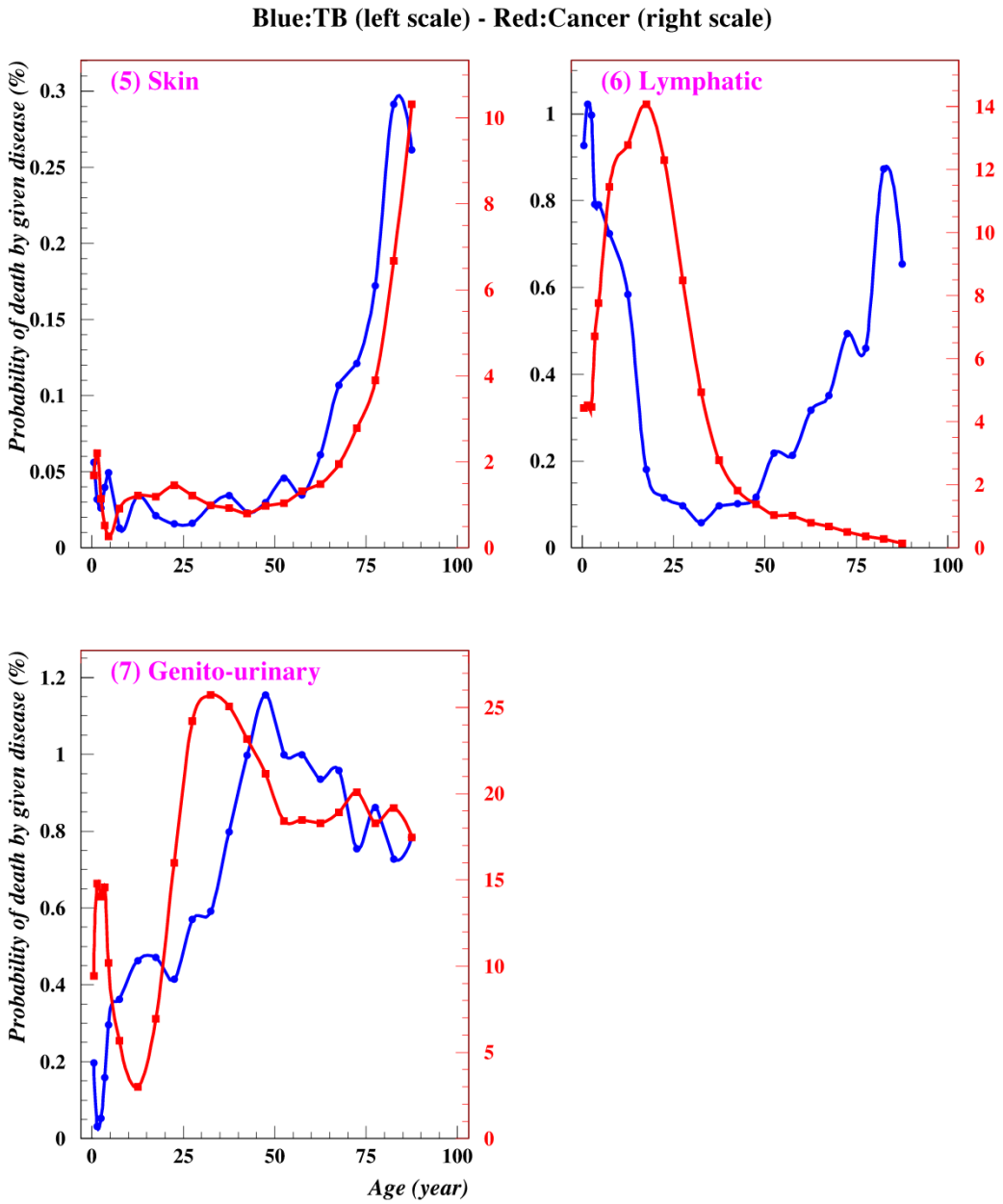

Fig. 5b (continued from Fig. 5a). Comparison between the conditional probabilities represented by the ratios: (deaths by TB type)/(all TB deaths) (blue line with round dots) and (deaths by cancer type)/(all cancer deaths) (red line with squares), USA 1934–1943. The left-hand scale refers to TB whereas the right-hand scale refers to cancer. The TB ratios represent the conditional probability of dying at a given age from a specified type of TB within the set of all people dying from TB. There is a similar definition for cancer. The 7 cases shown in Fig. 5a,b do not result from a selection; they represent *all cases* for which data are available. The correlations, confidence intervals (for a probability level of 0.95) and ICD codes are given below in the following form: cor, CI, TB/C. (1) cor = 0.55 (0.17, 0.79), 23/47; (2) cor = 0.67 (0.35, 0.85), 24/subclass of 53; (3) cor = −0.560 (−0.81, −0.24), 25/subclass of 46; (4) cor = 0.46 (0.046, 0.74), 26+27a,b/subclass of 53; (5) cor = 0.91 (0.79, 0.96), 28/52; (6) cor = 0.01 (−0.41, 0.43), 29/72b; (7) cor = 0.56 (0.18, 0.79), 30/46+51. All correlations are significant except (3) and (6). Moreover under an age shift of 10 years the two curves of (6) become correlated too.
Source: Bureau of the Census: Mortality Statistics 1934–1936, and Bureau of the Census: Vital Statistics of the United States, Part 1, 1937–1943.

4.4. Birth defects versus wear-out

The curves of Fig. 5a,b suggest that there is a connection in the way TB and cancer lesions develop in different organs. A rough distinction can be made between the lesions (e.g. 2, 4, 6) which develop mostly in young age (and are likely due to birth defects) and the lesions (e.g. 1, 3, 5, 7) which develop mostly in old age (and are likely due to a wear-out process).

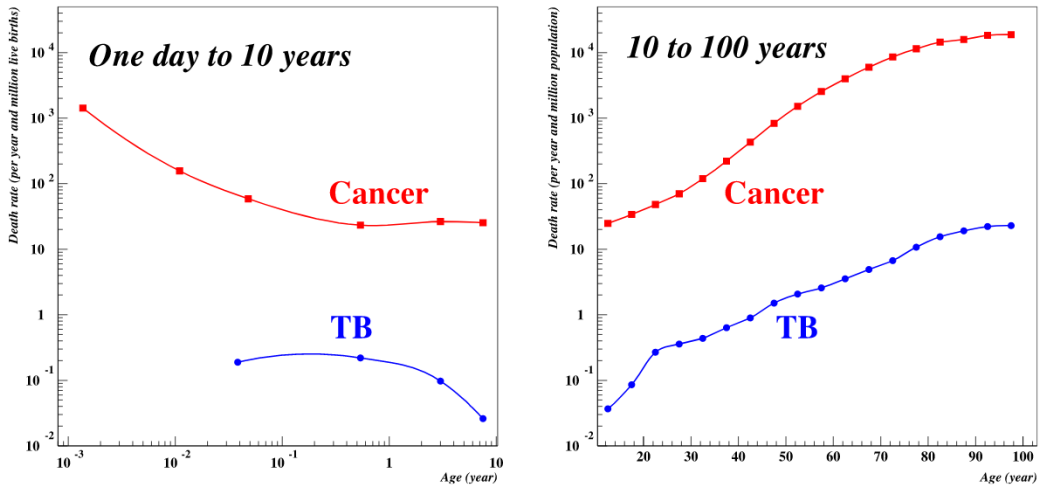

Fig. 6. Comparison between the death rates of TB and cancer, USA 1999–2015. Left: age from 1 day to 10 years, right: age over 10 years. Whereas the death levels are very different, the shapes of the age-specific death rates are fairly similar. For all causes of death, in the 0–10 year age range the death rate is an hyperbolic function of age of the form: $\mu_b \sim 1/t^{\gamma}$ [29]. For TB: $\gamma = 0.33 \pm 0.3$, for cancer: $\gamma = 0.43 \pm 0.2$. In the range 10–100 year, it is the Gompertz law which applies, that is to say an exponential increase: $\mu \sim \exp(t/\tau)$. The doubling times $T = \tau \log(2)$ expressed in years are as follows. TB: $T = 9.7 \pm 0.8$, cancer: $T = 7.9 \pm 0.7$.
Source: CDC Wonder database 1999–2015 (underlying causes of death). As of April 2017 the relevant web-address was: https://wonder.cdc.gov.

Such conclusions would have been impossible to reach by using death rates instead of death ratios. Indeed, age-specific death rate curves in the adult age-range are increasing exponential functions (as stated by Gompertz's law) a feature that would preclude any shape comparison. On the contrary, the age-profiles of the death ratios have very contrasted shapes that can be compared significantly. The aim of this article was to convey our belief that the age-profiles offer useful "signatures" of the corresponding diseases.

5. A conjecture to explain the treatment conundrum

5.1. Death rate levels versus death profiles

What is the present-day situation regarding TB and cancer? As shown in Fig. 6, roughly speaking in terms of order of magnitude TB and cancer death rates differ by a factor 100 at all ages. However, contrary to their levels, the shapes of death rate curves are not very different. The parameters of the two laws differ by 20% on average (23% for the exponent γ and 18% for the doubling time T).

5.2. Conjecture for the treatment conundrum

TB and cancer are extremely different in terms of treatment effectiveness. We have seen that in the past 100 years TB mortality was divided by 1000 whereas cancer mortality remained basically the same. This is what we call the *treatment conundrum*. How can it be explained? In the following subsection we propose a testable conjecture.

5.3. Army vs. police

In any country a clear distinction is made between army and police. The role of the army is to ward off foreign attackers and to destroy the forces who were able to penetrate on the national territory. In contrast the action of the police is directed against domestic elements who are sources of disorder or threaten the nation's security. Whereas waging foreign wars is a well defined business, fighting domestic enemies is a more murky task. The two notions tend to overlap in civil wars or guerrilla warfare. The specificity of guerrilla warfare is that the insurgents hide among the population and are therefore not easy to identify and destroy. There are no definitive victories. Once a region has been cleaned, fighting may resume elsewhere.

A similar distinction can be made for the immune system. Bacteria, viruses, fungi, parasites are foreign invaders which will be identified, targeted and destroyed by the lymphocytes (B and T cells), antibody proteins and macrophages. On the

contrary, cancer cells are domestic enemies. For the sake of brevity, the part of the immune system which fights foreign invaders will be called the *exosystem* whereas the part directed against domestic deviants will be called the *endosystem*.[11]

It may be useful to note that in fact the exo- and endosystems overlap. A clear confirmation is the fact that the BCG vaccine against tuberculosis is a remarkable booster of the immune response to bladder cancer. Since the late 1970s it is known that instillation of BCG into the bladder brings about a local immune reaction against the tumor. Moreover recurrence is prevented in up to 67% of cases.[12]

5.4. A testable explanation of the treatment conundrum

The distinction between the exo- and endosystem suggests a possible explanation.

We have observed that partisan fighters are much more difficult to identify than foreign armed forces. It is natural therefore to make the same assumption for the immune system. More precisely, we propose the following conjecture.

> *Exo-endo conjecture* For an organism which enjoys optimal living conditions, at any age the exo immune system is more effective than the endo immune system in the sense that the natural mortality rate is much higher for endo-diseases (like cancer) than for exo-diseases (like tuberculosis or measles).

This conjecture explains that the present-day death rate is 1000 times lower for TB than for cancer but it does not explain why the two rates were almost the same in the early 20th century. This feature may be explained by the fact that in the industrial cities of the 19th century human beings were far from enjoying optimal living conditions. In other words we are led to think that urbanization favored the development of infectious diseases and in particular of TB.

5.5. Possible role of urbanization

Unfortunately we do not know early prevalence levels around 1800 respectively in rural and urban places but irrespective of where it was higher the contacts between rural and urban people must have increased the number of cases especially in the cities because of a higher population density (with respect to the influence of density on epidemic propagation see [31]) and poorer living conditions. This resulted in a great TB epidemic observed in all European countries.

For the United States, the earliest data are for the end of the 19th century. Below are death rate data (expressed in deaths per 100,000) for highly urbanized states on one hand and for rural states on the other hand.

- Massachusetts (1871): 339, Massachusetts (1890): 259, New York (1900): 213, New Jersey (1900): 205.
- Michigan (1900) 106, Montana (1910): 89.

These data confirm that TB mortality was highest in cities.

For cancer on the contrary there is no correlation between the place of residence and the mortality (as cancer affects mostly elderly it is the average age of people in a given area which is the key-variable).

The fact that for the black population the rates were at least two times higher than for the general population, e.g. New Jersey (1900): 463, New York (1900): 528, also confirms the high impact of housing and working conditions. In contrast for cancer the rates are almost the same for African Americans and white people.

We are not used to view TB as an epidemic but one should remember that from infection to death or recovery the time constant of this disease is of the order of several years. For influenza it is a few weeks that is to say some 50 times less. Whereas influenza epidemics last two or three months, a TB epidemic may last 20 years.

5.6. Role of the generational selection process

The fall of TB death rates between 1850 and 1950 is often explained by better living conditions. While living conditions may have played a role, if our conjecture is correct the bulk of the decrease should be attributed to the selection process through which people whose immune system could not fight the disease were eliminated. The people who survived were those who had a natural immunity or whose immune system was able to adapt.

For such a selection to operate, the persons who have weak immunity should not be able to transmit it to their children.

This was indeed the case for TB one century ago for its peak rate occurred in the 20–30 age group (see [32]). Needless to say, for cancer the situation is very different because its death rate is very low for the 20–30 age group and becomes substantial only after the age of 60. By that time, parents have already given birth to their children transmitting them their weak endo immune system. This cycle can then repeat itself at each generation.

An objection may come to mind.

If the death rate reduction is due to a selection process why has such a selection not eradicated measles or TB in past centuries?

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[11] It would seem that the exosystem has received more attention than the endosystem. On the website of the Nobel Committee there is a fairly detailed presentation of the immune system destined to the general public. In the 5 pages there is only one line which refers to cancer cells. We are told that the killer T cells (one of the two kinds of T cells) are specialized in attacking *cells* of the body infected by viruses or bacteria as well as cancer cells.

[12] The source is: Lamm et al. [30] cited in the Wikipedia article entitled "BCG vaccine".

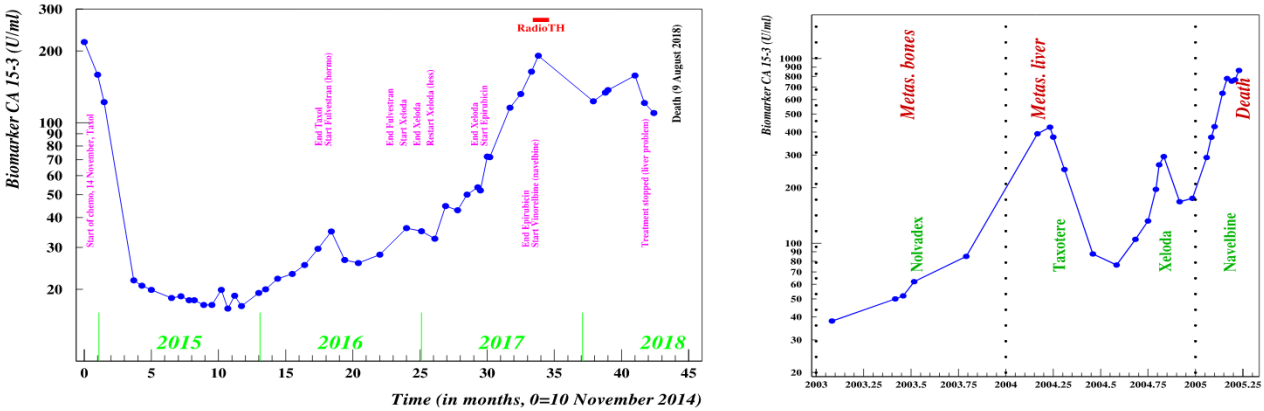

Fig. 7. Changes in tumor biomarker CA 15-3 in the last stage of cancer treatments. CA stands for cancer antigen. CA 15-3, which is particularly used for breast cancer, gives a measure of the amount and activity of cancer cells. The labels indicate the chemotherapy treatments. "RadioTH" refers to a radiotherapy treatment which lasted 5 weeks. **Left:** The graph shows that after a first treatment that was very effective, the following were on average less useful. **Right:** The cancer remained under control until late 2003. The following phase can be compared to the first graph. We see that irrespective of the specific treatments, the ascending phases in the wake of the sharp falls lasted about the same time, i.e. between 1.5 and 2 years. In a more general way, comparison of several graphs of that kind may reveal regularities which may give information about the resilience of the immune system. Such comparisons would be in line with what is done when comparing semi-replication of physical experiments.
Source: Left: Private communication; right: https://sites.google.com/site/journalduncancer/home.

There is a fairly obvious answer.

Transmission of immunity to the next generation is certainly not a 100% process which means that in successive generations immunity will gradually evaporate. Then, once immunity has been sufficiently eroded an outbreak will result in epidemics of large proportion.[13] Through such epidemics the virus will become more prevalent which in turn will lead to a situation of endemic disease which was the situation around 1850 (Fig. 2). Then the succession of phases shown in Fig. 2 may start again.

Actually, the US outbreaks of 1989–1991 are a prefiguration of what may happen on a larger scale in the future if vaccination rates continue to decline. These outbreaks (as well as the outbreak of 2001 in Japan) were made possible because of a reduced vaccination rate at levels around 80%. Contrary to the disease itself which confers life-long immunity, vaccination ensures immunity on average only over 15 years; in addition, about 5% of people who have been vaccinated fail to become immune to the disease [34].

Throughout this paper we advocated the use of comparative analysis. Apart from the TB–cancer comparison, this approach can also be applied to cancer treatments as suggested in Fig. 7 and explained in the following subsection.

5.7. The last battle of the immune system

In the present paper we used comparative analysis to estimate the effectiveness and resilience of the immune system in various situations, e.g. in our discussion of the first, second and third lines of defense. Here we wish to describe the behavior of the immune system in the last phase.

Fig. 7 shows marker levels in two cases of breast cancer. In both cases the ascending phases which eventually lead to death have similar durations of about 5 years.

In line with our TB–cancer comparison we would like to draw similar graphs for TB. For that purpose it would be necessary to find data for TB cases in the time before the introduction of antibiotics. In the late 1920s there were well-known TB markers, for instance the so-called urochromogen test or the Arneth count of leucocytes [35]. So far, however, we could not find the data that would be required.

6. Conclusion

6.1. From the perspective of patients

Presently, the majority of cancers are incurable. Moreover, all too frequently by the time of diagnosis many have progressed to a state where an operation to remove the tumor is not possible. Multiple tumors and secondaries can be present. Chemotherapy may frequently be used in an attempt to shrink tumors. However whether specific chemotherapies

[13] As Maurice Bartlett [33] has shown that a measles epidemic can develop only in a community of sufficient size (around 200,000) such an epidemic will certainly start from and develop inside cities.

will be effective, or even if they are, for how long they will be effective, seems to be very much a matter of trial and error. In some instances the patient can also be too frail for such invasive procedures. Towards the inevitable end, the patient can only hope that a good palliative care program is available.

In countries where specific palliative care units are available they are usually destined only to patients in their last days. Would it be possible to set up palliative units similar to the TB sanatorium described in Thomas Mann's novel "The magic mountain"? It may be remembered that the novel's main character, remained at the Davos sanatorium for 7 years. In other words, this kind of sanatorium would be open to patients willing to trust the capability of their immune system once the most favorable conditions have been identified and implemented.

6.2. Strong similarities between TB and cancer

The main message of this paper was to emphasize the similarities between TB and cancer. However, this left open the question of why there was a tremendous difference in the success of treatments. To explain it, we proposed what we called the exo-endo conjecture and we pointed out the key role of childbirth age with respect to median illness age.

6.3. Extension of the present study

For the purpose of this paper we had by necessity to use data from the first half of the 20th century because our main requirement was to have enough death cases in order to limit statistical fluctuations. How can we extend this analysis to a greater number of lesions?

If, instead of using death rates we could find and use incidence rates the number of cases would be multiplied by a large factor. This factor depends of course upon how lethal a lesion is; for instance lesions of the thyroid can be cured with high probability which means that the incidence rate may be 20 or 30 times higher than the death rate. This would allow an interesting extension.

TB and cancer are not the only diseases which can target different organs; syphilis, HIV or diabetes are other examples. This will provide a second extension. It will be interesting to see if there are meaningful connections between such families of diseases.

The large amount of data which have been collected in the framework of the "Global Burden of Disease" project [36] may be a good source for a subsequent study.

Appendix. Key-role of analogies in scientific progress

Readers may wonder what can be gained and learned by emphasizing analogies between TB and cancer. Perhaps the best answer is to observe that throughout the history of science analogies have permitted great progress.

The purpose of the present appendix is to make readers realize that even in physics, the most successful among all scientific fields, analogy has played a great role at some crucial junctures. In the hope that they may convince doubtful readers, we give below a few illustrations.

It is not always realized that throughout the development of physics from the 16th century up to nowadays physicists have relied on thinking by analogy. The purpose was always the same, namely to build a bridge between phenomena which were fairly well understood and others which were still mysterious. Seen in this perspective, the role of thinking by analogy is not limited to physics. In any field, when facing uncharted territory, one needs some guidance. While such guidance may come in several ways, analogy with similar but simpler cases is certainly one of them.

A.1. Role of analogy in physiology and genetics

The following examples describe cases observed in physiology and genetics.

- In William's Harvey main work published in 1628 he describes how blood is being pumped to the brain and body by the heart. Remarkably this was also the time in which great progress was achieved in pump technology. The elaborate water works built at that time in the gardens of the Versailles castle are a testimony of the fact that hydraulic systems were at the center stage of technology. This made the idea that even a small organ like the heart could pump blood in remote parts of the body much more acceptable even though the detailed mechanisms were not completely understood.
- Selective breeding was established as a scientific practice during the Agricultural Revolution of the 18th and early 19th century. Charles Darwin relied on the notion and success of selective breeding on order to build the theory of evolution that is described in his 1859 book "On the Origin of Species". As a matter of fact, its first chapter discusses selective breeding of such animals as pigeons, cats, cattle, and dogs.

The techniques of selective breeding also played a key role in Gregor Mendel's famous experiments. It is the fact that he followed the cross-breeds over several generations which gave him a new insight but the techniques used by his gardener were well known.

A.2. Role of analogy in theoretical particle physics

In the late 16th and early 17th century the question of how two masses can attract one another without apparently any contact was a key issue for astronomy as well as for the question of free fall. From Galileo to Kepler to Newton electrostatic and magnetic attraction provided welcome examples supporting the conjecture of the existence of a gravitational force. Nowadays, the mechanism of gravitational attraction explains many phenomena, from the fall of an apple, to the "fall" of the Moon toward the Earth, to the formation of black holes, to the rotation of spiral galaxies.

In the 1920s, in the discussions which led to the creation of quantum mechanics, the analogy with optics, namely geometrical optics on the one hand versus wave optics on the other hand, played a great role for it facilitated the adoption of the notion of wave–particle duality.

While the two previous examples are familiar to all physicists they are perhaps too broad and not mathematical enough to be really convincing. Taken from particle physics, the next examples show that analogies were of great help even mathematically for they helped to build an appropriate theoretical framework.

In the 1960s, in an attempt to describe strongly interacting particles, physicists created what is now called quantum chromodynamics (QCD) and for that purpose they used quantum electrodynamics (QED) as a blue print. QED was much simpler than QCD because it considered particles which have only electromagnetic interactions.

The next example is similar in the sense that it was also an extension of electromagnetism. In the 1970s and 1980s so-called Yang–Mills gauge theories took model on gauge invariance in electromagnetism in which it is recognized that there is a degree of arbitrariness in the definition of the scalar and vector potentials. Although this idea was introduced in the 1950s (see [37]) such gauge theories became commonly used in particle physics only a few decades later.

The role of analogy in the history of physics was studied and emphasized by the French physicist Pierre Duhem as attested by the following excerpt ([38], p. 140). "The history of physics shows that the search of analogies between different categories of phenomena may have been the most productive of approaches tried by theoretical physics".

It should not come as a surprise, therefore, that when they turn to the fields of biology and medicine, physicists adopt a comparative perspective with the purpose of finding parallels and common rules for apparently unrelated phenomena.

It is hoped that the macro-biological perspective that we develop in the present paper may prove of value in complement to the highly detailed descriptions permitted by the techniques of molecular biology and genetic sequencing.

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