Science: Increase in cancer cases as a consequence of eliminating febrile infectious diseases

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1. Epidemiological research into the connection between fever and protection against cancer

Hippocrates already mentioned that people who develop cancer had fever in their lives much less often than people who do not get cancer. In the 19th, 20th and 21st century reliable epidemiological studies showed that people going through several fever episodes at an early age less often got cancer at an advanced age.

Hofman [1], Engel ([2,3]), Sinek[4], Witzel[5], Remy[6], West[7], Wynder[8], and Newhouse[9] described the same association in case-control studies.

In 1998 a reliable case-control study described that, with 95% probability, going through childhood diseases with fever (Febrile Infectious Childhood Disease or FICD) results in a reduction of between 5% and 32% of all cases of cancer except breast cancer, with an average of 18%. This is very significant. For The Netherlands (2007: 87.000 new cases/year), this means more than 12.000 cases a year! (H.U. Albonico et al. *Febrile infectious childhood diseases in the history of cancer patients and matched controls* (Summary here)

Other interesting studies describe the same connection between the growing number of cancer cases and the decrease of febrile childhood diseases as a result of vaccinations (!), antibiotics and antipyretics over the last few decades (Hoption, Kato[10], Cerhan[11]).

It seems that the more acute infections with high fever, including those in adulthood, the smaller the risk of cancer. The use of antibiotics, antipyretics - i.e. paracetamol and aspirin - , antihistaminica and even decongestants (nose sprays) increases the risk of cancer. G. Mastrangelo et al., 1998 [12] described that in Italy between 1859 and 1963 every 2% decrease in mortality of an infectious disease appeared to be followed by a 2% increase in mortality as a result of cancer with an interval of 10 years.
Of course there are more factors (smoking, alcohol, pollution) contributing to the development of certain specific forms of cancer (lung, liver and cervical cancer). But that doesn't explain everything. It seems that acute febrile infectious diseases alter and enhance the immune system. Infections that have plagued humanity for millennia also seem to have their benefits (S.A. Hoption Cann PhD et al. 2006, (pubmed ID: 16490323))[13].

For more studies on this subject, please see the appendix.

The question is: does fever itself prevent cancer or is it the alert immune response with the subsequent fever episode which does the job?
It seems to be the fever itself. To understand why fever protects against cancer, it's necessary to take a closer look at the immune system.

2 Our immune system: The 3 important mechanisms

A number of facts regarding the immune system are important for this subject.
Let us look at three important reactions of the immune system to clarify our story.

2.1 Mechanism 1 – Attack via antibodies (Th2)

If specialised coordinating immune cells, the dendritic cells, decide that something is dangerous, they tell the immune system to attack. There are different kinds of attack: primarily by cells or by proteins (antibodies). An attack consists of a combination of those two, with the emphasis on one of them.

- the cellular attack is carried out by T lymphocytes.
- the antibody attack is carried out by B lymphocytes.

Lymphocytes are born with the ability to recognise a specific protein. Only the lymphocytes that cannot recognise the body's own proteins and cells are allowed to enter the bloodstream. The rest is mostly killed. This sorting out is done in the thymus for the T lymphocytes, and the bone marrow for the B lymphocytes. The selected lymphocytes go to a lymph node and wait for activation by a dendritic cell.

A dendritic cell shows characteristics of an item to the lymphocytes, together with further instructions for action. Over one hundred different characteristics of one bacterium are presented and attacked.

If the danger is IN the cells (cells infected by viruses or certain bacteria, cancer cells), a mainly cellular attack is instructed. Dendritic cells activate Th1 lymphocytes which recognise the danger, to multiply, swarm out and kill the enemy.

If the danger is OUTSIDE the cell (toxic proteins or viruses in the bloodstream, bacteria in a wound) a more protein-based attack is organised. Dendritic cells activate certain Th2 lymphocytes which instruct appropriate B cells to produce immense amounts of immune proteins, called antibodies, that bind to the problem and activate further appropriate immune reactions which go beyond the scope of this article. At the end the problem is killed, broken down and removed. During the whole infection, dendritic cells also instruct certain immune cells to act as suppressor cells. After the battle is over, these cells have their role in stopping the fight.

At birth, a baby receives a lot of Th2 cells and antibodies from the mother. The immune system of a baby is firmly Th2- and antibody-driven. Going through episodes of infection the Th1 path is stimulated and a healthy equilibrium between Th2 and Th1 will grow. This is essential to get a perfect balanced reaction to every type of pathogen without fighting too much or the wrong enemy. If that equilibrium is not created, more immune mistakes or ongoing attacks will take place, like auto-immune illnesses, chronic inflammations or allergies. Allergies are mostly Th2 reactions.

Vaccination uses the Th2 mechanism and makes the immune system react more the Th2 way. Real febrile childhood diseases make the immune system react the Th1 way. Going through these genuine childhood diseases not only ensures activation of the Th1 mechanism but also ensures that Th2 is subdued.

In animal studies this reduction of Th2 activity results in a smaller risk of allergies such as asthma and hay fever. Allergies have skyrocketed in the last few decades (asthma by more than 500%, 3 to 4 thousand hospital admissions per year in The Netherlands alone). See also the hygiene hypothesis on the NVKP site.

Most immune cells die within a few hours to days. So if the enemy is beaten and no new immune cells are created, the immune reaction subdues. This is enhanced by the Treg cells, which are also instructed by the dendritic cells. A few immune cells will survive and become memory cells (B mem, Th1 mem, Th2 mem, Treg mem etc.). After a genuine infection, memory cells against hundreds of different components of the pathogen will remain. Next time the immune system can react against the pathogen immediately.

After vaccination only a handful of different components will be remembered. So vaccination does not entirely mimic the real infection.

Animal models show that large amounts of T memory cells result in a smaller risk of auto-immune diseases (Homoeostatic Expansion of T Cells during Immune Insufficiency Generates Autoimmunity). Since the elimination of childhood diseases, auto-immune diseases, such as Crohn's disease, type 1 diabetes and multiple sclerosis have increased enormously.

2.2 Mechanism 2 – Attack via cell defence (Th1) including fever

In case of fever, large amounts of T cells are created, assembled in the thymus, checked and possibly killed. The good ones ripen, swarm out and combat the enemy. Fever shifts the immune system into a higher gear for the production and ripening of immune cells (American Scientist: Healing Heat: Harnessing Infection to Fight Cancer).

Ripened T cells are very important to fight cancer.

Childhood diseases mostly use the Th1 response which maximises the killing efficacy of the macrophages and the proliferation of T cells. It also produces opsonising antibodies which are essential to clean up the remnants of the enemy so that the immune system is not confused by rubbish, but can focus itself on the enemy.

A child needs at least 3 episodes of fever for a healthy development of the thymus and, besides the fever, also a good Th1 response, stimulating the cell defence and the killing efficacy of the macrophages. It seems that the immune system has to learn how to react. Just like learning to walk, it needs practice.

2.3 Mechanism 3 - Active tolerance

If a dendritic cell decides that the item is harmless, it will tell the immune cells to tolerate it. Specific T suppressor cells are created to suppress any aggressive immune reaction against this specific item. This is called active tolerance, which is intended to protect harmless substances like food and the body's own cells. According to health books, any self-reacting T or B cell is destroyed. New insights show that not all self-reaction immune cells are destroyed. By a still unknown mechanism, T suppressor cells are created which prevent these cells from acting and thus suppress immune attacks against self-proteins, own cells, food, pollen etc.

But active tolerance can also make sure that cancer cells cannot be cleared away. Potentially, the immune system is perfectly able to destroy a malignant tumour, even if it has already metastasised. Active tolerance is almost irreversible.

After organ transplantation, people must take medicines to improve the active tolerance in order to accept the new organ. Unfortunately this goes hand in hand with the disadvantage of a higher cancer risk caused by a suppressed immune response and a subsequently increased tolerance.

Fever does the opposite. Fever decreases the active tolerance!

2.4 Rara avis: Cured from metastasised cancer

Being cured from cancer is, as a matter of speaking, a rara avis.

In rare cases the body suddenly ‘decides’ that the cancer needs to be destroyed. If this happens, a truly sensational and miraculous process takes place. In a tearing rush the cancer, including all metastases, is destroyed and cannot return.
These cases almost always happen to have in common a combination of cancer with an infectious disease with high fever.

A sceptical reader might think that this is about anecdotal stories; nevertheless a number of these cases are described in serious medical literature. See here [14,15,16,17], for examples.

Here follows one well-known case.

Quote from article: **Acute infections as a means of cancer prevention**:

Dupuytren [18] in 1829: a woman with an extensive carcinoma of the breast who had refused surgery (which was barbaric and more killing than cancer in those days). Eighteen months later she was bedridden, cachectic and almost dying.

Then she became feverish. Her extensive tumour became inflamed and gangrenous. Within eight days the tumour had regressed by one-third. By the 4th week, the disease was no longer evident.

Nowadays spontaneous regressions occur in around 1 in 60,000; in the past, in the time before chemotherapy or antipyretics, it happened much more often (O’Regan B, Hirshberg C, *Spontaneous Remission: An Annotated Bibliography*).

The great frequency of such observations led to the development of active immunotherapy treatments for cancer in the 18th and 19th centuries[19]. We will only mention Coley's method [20,21,22] Coley created high fever, and subsequent tumour regression, by administering some special, living bacteria. His contemporaries reported encouraging successes.

3. Why acute febrile infections protect against cancer, while chronic infections don't

3.1 Why are chronic infections carcinogenic?

In case of an infection the immune system destroys the enemy. During that battle a lot of collateral tissue damage is done. This should be repaired. When the game is over, the immune cells disappear and the cells that must reconstruct the tissue take over.
During both phases macrophages are important. They are the immune cells that eat and digest everything abnormal, including microbes. During the active part of the infection, the lymphocytes tell them to secrete a lot of oxidising, toxic substances in order to free the tissue from pathogens. After the battle is over, these same macrophages stop secreting oxidising toxins, clear away the dead tissue and then disappear. Repair can start now.

If the enemy is not beaten after a certain time, the inflammation becomes chronic. The number of macrophages in the wound is not decreased but prolonged. Two actions start happening at the same time: attack and repair. Because of the damaging attack, the repair has to go on for ever. During the attack oxidative damage is done. During repair the DNA is very vulnerable for oxidative damage. In rare cases, the DNA of a body cell is so damaged that the cell transforms into a cancer cell.

Examples: chronic hepatitis B, asbestosis.

3.2 Why do immune reactions allow cancer to grow?

At the end of the nineteenth century, Klebs postulated that immune reactions enhance tumour growth (The Lancet 1868![23]). It turns out that he was right.

Tumours often develop in places with tissue damage. It was suspected that such areas were better suited for nourishing the tumour through the cells that should repair the damage (Jones and Rous[24,25,26] Haddow[27]).

Recent evidence demonstrates that tumours can even be stimulated instead of attacked by the immune system[28,29,30.]

Normally wounds trigger the release of several chemokines attracting tissue repair cells, which in turn assist in the healing process. Chemokines signalling that more oxygen and nutrition are needed for recovery are also released.
Such signals decrease as the wound is healing.
Cells involved in tissue repair are also attracted by tumours and their activity causes the tumour to grow faster. These signals continue at a larger scale and provide everything for the ever-growing need of the tumour (Rehman, 2003 [31]).
In the delicate balance between repair-driven growth stimulation and defensive tumour-decreasing regression, leukocytes determine the outcome: tumour progression or regression.
An acute infection can change the immune tolerance for the tumour into an attack. (Gabizon et al.[32]) and the activated macrophages can then be destructive for tumours (Poste[33])

3.3 Fever and the immune reaction

Fever improves the eagerness, efficiency and efficacy of the immune system. (Cancer Immunol Immunother 2006[34]). It enhances almost all functions of the immune system: intensified dendritic cell and T cell activity, more immune cells ripened and ready for battle and improved communication between immune cells. All this results in accelerated clearing of enemy cells and lower change into chronic inflammation (Cancer Immunol Immunother 2006[35])

Reduction of febrile periods through whatever method (antipyretics, antibiotics) in animals with an increased risk of cancer showed significant higher cancer mortality in animals as opposed to animals without fever suppression (Kluger, 2002 [36]). The same findings have been observed in humans (Greisman et al., 2002 [37], Keller [38]).

The use of medication that lowers or prevents fever is not without adverse effects. An alternative approach could be to stimulate the immune system, rather than suppress it.

4. Vaccination policies in the light of the fever and cancer connection

The WHO wants to create “a world in which all people at risk are protected against vaccine-preventable diseases”

The pharmaceutical industry is developing vaccine after vaccine against even harmless infections because illnesses cost working days and money.

What we now see is that teenagers and people in their twenties need new boosters against childhood diseases such as mumps, because vaccination does not guarantee lifelong immunity. The risk of complications in adults as a consequence of childhood diseases is many times greater. Man is thus becoming more and more dependent on vaccines.

Moreover, vaccines are also in preparation that should protect the immune system against diseases partly caused by the vaccines themselves (auto-immune diseases, allergies). The final result is an immune system supported by an enormous rush of new vaccines. The way back is becoming increasingly difficult. It seems that humanity in this century needs to be fully infused with vaccines in order to keep up an artificial immune system!

It seems that eliminating childhood diseases leads to many more risks, like increasing numbers of chronic diseases and perhaps also cancer, than was ever thought possible.

Consider that people in Sweden once, from 1979 until far into the 1990s, stopped vaccinating against pertussis because of the adverse effects of the vaccine, without this resulting in a higher mortality among their children. In the Netherlands, the media did not publish the risks of vaccines, so these are unknown to the masses.

Because of a higher prevalence of pertussis in Sweden, the age at which children got this disease **increased**, since mothers passed on more and more antibodies to their babies, while in the Netherlands babies are susceptible to pertussis, at a far more dangerous age!

In other words, it is never too late for a change of policy.

Before 1978, 98% of the Dutch children under 12 got measles. Almost all children recovered fully. Autism was rare, as were allergies and childhood cancer.

It is not too late for a change of policy.

The NVKP hopes that this article may initiate a public debate about the benefits and risks of vaccination.

APPENDIX

Quotes from:

Acute infections as a means of cancer prevention: Opposing effects to chronic infections?

In 1912, Levin undertook a comparative survey of cancer incidence in American Indians and the white population in the same localities[39]. He remarked that in the same geographical region, the proportion of American Indians over 50 years of age was higher than in their white neighbors, yet cancer was extremely rare in the American Indians. Smith et al[40],[41] used standardized mortality ratios to compare the rates of infectious diseases and cancer among white and Indian populations in Canada and the United States. Cancer mortality rates were significantly lower in the Indians, yet rates for infectious and parasitic diseases were six times higher. Although some of the infections considered antagonistic to cancer were generally chronic in nature, how the immune system responds to such infections may have been a key element. For example, in an autopsy study by Pearl[42] , the prevalence of active versus healed tuberculosis was compared in subjects with cancer and without cancer. He drew from an autopsy series of 6670 post mortem examinations, which included 816 cases of malignant disease. These subjects were then matched by age, sex, race and approximate time of death to 816 non-cancerous controls. Cancer prevalence was significantly lower in subjects with evidence of active versus healed tuberculosis [OR = 0.36, 95% CI 0.26–0.50]. Thus, the degree of immune activation within each individual may be a key factor with respect to cancer antagonism.

(...)

The most conclusive evidence, however, that acute infections may counter tumor growth comes from the work of William Coley, whose career spanned from 1891 to 1936. At the turn of the century Coley, a surgeon, developed a killed bacterial vaccine for cancer consisting of the gram positive Streptococcus pyogenes and gram negative Serratia marcescens. His initially encouraging results in inducing tumor regression with repeated inoculations[43] was followed by similar successes reported by contemporaries who experimented with his vaccine. It is documented that Coley's method of treatment could induce the complete regression of extensive metastatic disease[44],[45],[46] . Although there was considerable variation from one individual to the next, after many hundreds of cases, Coley confirmed his impressions that mimicking a repetitive acute febrile response was the key factor necessary to provoke and maintain tumor regression[47]. His treatment gradually fell out of favor following his death in 1936. By that time, radiation and increasingly chemotherapy had become mainstays of treatment for cancer and required less time, effort, and individualization than Coley's vaccine.

(..)

Other epidemiological studies have looked at the association between common acute infections in adults and cancer development (Table 2). These studies found that acute infections were associated with a reduced risk for glioma , meningioma[48] , melanoma[49],[50] and multiple cancers combined[51],[52],[53],[54] although of borderline significance for meningioma [OR = 0.73, 95% CI 0.54–1.00]48 and not significant for one study of multiple cancers [OR = 0.71, 95% CI 0.45–1.25]53 .

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