



Research paper

Slow infection control by vaccination: Paratuberculosis

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ABSTRACT

Classical causality models for infectious diseases have fulfilled an important role in the progress of medical sciences, however, new forms of association where weakly pathogenic agents cause widespread infections that mostly do not progress to disease, but that if they do so, cause protracted clinical courses where the host resources are exhausted fit better with the slow infection concept proposed over half a century ago. This model could show an infectious cause behind some diseases that have never fulfilled the conventional criteria. While new mechanisms of causation are defined, these diseases still need to be controlled to allow sustainable animal production. Here, I discuss the case of paratuberculosis control by vaccination as an example of the benefits of using a theoretically preventive treatment to modify the course of infection towards preventing clinical disease even though the infection itself might not be fully controlled.

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1. Introduction

Scientific knowledge has been the key factor of the biological success of the human species. Essentially all scientific knowledge comes to identifying the laws of causation of natural phenomena. Western medicine is a part of that body of knowledge and methods and is focused in identifying causes of disease and preventing or eliminating their action. This has granted humans the possibility of living long and in good enough shape as to further develop and transmit useful knowledge from generation to generation. Most of the progress of medicine has taken place in the last century and a half. The case of regional intestinal inflammatory disease is no exception and apart from isolated more or less precise descriptions, there is no full report of any pathological entity including identification of the causal agent until the Johne and Frothingham report of paratuberculosis in a cow. Even though a suggestion that a similar disease in humans could have the same cause was already made 15 years later (Dalziel, 1913), it took nearly 40 years to report a similar pathological entity in humans

for which the cause, however, still remains controversial (Simmons, 2010).

Both ruminant and human regional inflammatory diseases are characterized by a slow clinical course defined by wasting as a consequence of local inflammation progression. In the ruminant entity the presence of abundant mycobacteria in the macrophages allowed etiology attribution, but absence of those mycobacteria in the human counterpart prevented from extrapolating the animal model etiology. Even in the case of paratuberculosis, initial association of the inflammatory changes with its generally accepted microbial causing agent MAP, was purely based on the presence of the agent and not on its isolation that was not achieved until several years later (Johne and Frothingham, 1895; Twort and Ingram, 1911). It proved to be difficult to grow organism that takes several weeks to be detected by the naked eye. As the knowledge on the disease grew, it was observed that animals are exposed to their mother's often massive fecal contamination from very early in the life. However, only a fraction of them end up developing the disease (Chiodini et al., 1984). This early and generalized exposition poses a significant challenge to designing control strategies both because it makes preventive measures difficult to apply on time and also because it suggests that the infectious agent is not cause sufficient

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of the disease. In this paper, we will review how causation models fit with control strategies based in vaccination.

2. Infection causality models

In the late XIX century Louis Pasteur and Robert Koch defined the critical concepts that established biological agents as cause of disease as summarized in Koch postulates (Thrusfield, 1986). This was probably the greatest single step in medical sciences since a single concept provided a means to identify the cause of numerous diseases. Once the cause is known, it is possible to scientifically design the preventive and curative measures to fight it. Koch postulates are still valid for most infectious diseases. However, there are cases in which no compliance with any of some of those criteria is not considered a major problem in order to attribute causality and several sets of rules have been developed to refine the concepts behind Koch' postulates on the light of new technological developments in order to prove causality in infectious disease (Fredricks and Relman, 2010). For instance, Koch himself admitted that tuberculosis, salmonellosis and piroplasmosis fail to comply with the first postulate in the sense that there are asymptomatic carriers that never develop clinical disease (Gradmann, 2010). In other cases, like leprosy (Parkash and Singh, 2011) or transmissible spongiform encephalopathies (Aguzzi and Zhu, 2012), it is the second postulate that is not fulfilled since the etiologic agent cannot be isolated in pure culture (including cell cultures). Also there are numerous diseases whose acknowledged etiologic agent only cause disease when associated to other factors and thus that challenge the third postulate requiring disease causation in all experimentally infected individuals. More modern concepts as component-cause or causal-web models explain better these situations by acknowledging a more complex interaction of factors in disease causation, but on the other hand make it more difficult to attribute causality (Dohoo et al., 2003).

These causation criteria are particularly difficult to fulfill in human diseases where experimental infections are out of question. Thus, AIDS etiology generated a hot controversy and it took a relatively long time to be universally accepted that it was caused by HIV (Sepkowitz, 2001). A similar case happened with peptic ulcer that required self-inoculation and successful treatment to be accepted as a consequence of infection with *Helicobacter pylori* (Van Der Weyden et al., 2005; Wikipedia, 2010). The etiology of human and in general monogastric regional inflammatory intestinal disease is currently the subject of such a discussion (Nacy and Buckley, 2008) even though its ruminant counterpart, paratuberculosis, has longtime been recognized to be caused by MAP (Chiodini, 1989).

When causation cannot be proved by the above mentioned criteria diseases can be well described, but cannot be controlled by eliminating or mitigating the primary cause. This is common in human medicine where longevity and good general health conditions give an opportunity to a variety of chronic diseases of uncertain origin. In these cases, the problem needs to be addressed accepting ignorance of the primary causing agent and focusing research

on the host pathways to tissue damage. Human intestinal inflammatory disease is a clear case of this type of approach.

3. Slow infection model

The above mentioned controversy on AIDS etiology reminds that the first lentivirus to be described was maedi/visna virus. It was inadvertently introduced in Iceland in the thirties of last century with a long time quarantined import of healthy rams. This epidemic was studied by Bjorn Sigurdsson who defined the seminal concept of slow infection that later gave name to the lentivirus family (Sigurdsson and Palsson, 1958). According to the characteristics of the disease reported by Sigurdsson slow infection diseases could be defined as those where: (a) A low virulence agent (that could even be part of an normal ecologic balance with the host) is involved; (b) Susceptibility can be linked to individual genetic factors; (c) The inflammatory or degenerative change is frequently located in the environment-organism interphase; (d) There is a prominent macrophagic and lymphocytic inflammation (indicative of an innate local immune response); (e) The specific immune response is absent or inefficient; (f) There is a high ratio of healthy carriers to clinical cases; (g) The most frequent clinical onset occurs in early-adulthood; (h) There is a slow progressive clinical course leading to wasting to death.

The diseases caused by slow infections, thus, seem to require at least two broad groups of factors: intrinsic factors (genetic defect and organic maturity) and extrinsic ones (infectious agent exposure) that might or not trigger an specific immune response depending on the amount of external agent present in the host organism. This response calls up a fundamental mechanism of disease control as is immune rejection of the foreign but that is of no consequence since it is not directed against critical elements of the invading agent, but to trivial ones, that simply happen to be very abundant and exposed to the recognition system. This reasoning would imply that the suspected infectious agent would be just an opportunist that would take advantage of a local dysfunction to grow and further maintain the local host inflammatory response. This is essentially the predominant point of view on the role of infectious agents in human intestinal inflammatory disease where even a virus-genetic deficiency couple has been implicated (Simmons, 2010). If this model was applied to ruminant paratuberculosis, it would lead to postulate that MAP could be an epiphenomenon and not the primary etiology of ruminant intestinal inflammatory disease. MAP would just be detected associated to paratuberculosis because it yields a clear positive result in conventional microbiological, molecular, immunological or histopathological tests after colonizing an already damaged intestinal mucosa. Failures to produce experimental infections (Chávez, 1993; Pérez, 1992; Watkins et al., 2010) would then be easily explained as situations where the primary causes are not complete (Simmons, 2010) and then do not provide the grounds where MAP can proliferate and lead to the classical pathological forms of the disease.

Coincidentally, or perhaps not, the disease that accompanied maedi in its Icelandic epidemic was

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