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A Propos Time and Autoimmunity

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Abstract The integrated defense system has been shaped over eons showing noteworthy robustness by surviving a million-year prehistory, a comparatively short evolving history and current transformation. Self-identification being part of it, so are deviations manifold expressed in autoimmunity. Epidemiological incidence and intensity, both being subject of change, are focused in the light of the time factor. Furthermore, it is stressed that there is no bi-univocal mutual relationship between immunity and defense and the origins of autoimmunity still remain mysterious. We question whether the present transforming events have occurred within too short a time to be attributed to genetic predisposition exclusively.

Keywords Time · Autoimmunity · Atopy · Integrated defense system · Evolution · Prehistory · History · Globalization

Introduction

> Time heals all wounds, but it is also the great destroyer
>
> Jorge Luis Borges

In our move toward realizing alignment in space and time, the latter still belongs to the most counterintuitive, ambiguous and hard-to-define concepts. By definition, time is unidirectional and backtracking (backpedaling) is in charge of memory. In this paper, we add 'time' to Rolf Zinkernagel's list of easily misused terms. In that sense, he refers to specificity, tolerance, anergy, regulation, suppression, help, and memory as being prone to confuse beliefs and facts [1].

Recent insight has suggested diverse mechanisms as complementary to natural selection in driving evolution [2]. The remaining question is how can the integrated defense system (IDS) tackle the twists of environmental contingencies. By assuming that changes in body components will not evolve exactly in parallel, asymmetry is a factor which must be taking into account [3]. In the context, could time be playing a role comparable to an *evolutionary straightjacket*, able to outmaneuver the IDS? Even more intriguing, what is to be expected of the definitely swifter acceleration triggered by the current globalization? So far, variables cloud the tails from a normal distribution (Gaussian curve) and a precise answer is nowhere near completion. In addition, the conundrum concerning changes in autoimmune disease incidence awaits to be clarified [4–6].

Autoimmunity and Evolution

Diseases involving the autoimmune network share a lack of knowledge in what concerns both past and future. As a matter of fact, we only rely on current awareness [7]. *Homo sapiens sapiens* successfully managed to overcome a long prehistory and was also able to bridge historical challenges, nowadays facing transformation's turbulences (Fig. 1). Although data are limited, some speculations may be still in place. On the one hand, Allison et al. reported signs attributed to systemic lupus erythematosus (SLE) in a female Peruvian mummy who had been buried *circa* one

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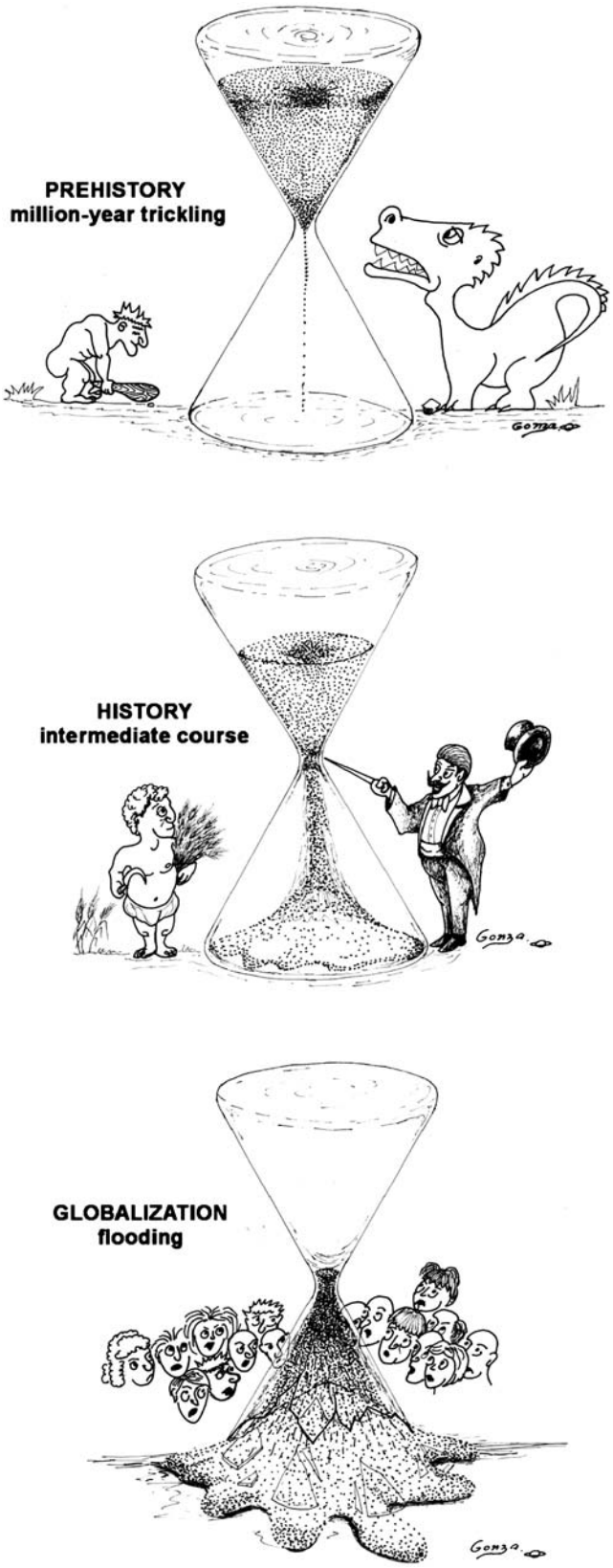

Fig. 1 Evolutionary muddle

millennium B.C. [8]. More information is available about current trends in autoimmunity [9, 10]—although data are not conclusive either [11–13].

A rising tendency of autoimmune incidence, atopic disorders in particular, has been reported during the last generation. This fact was associated with changes that, although not easy to correlate, are suspected to be involved in promoting the scourge [14–17]. For example, family size tended to shrink and, in terms of both space and hygiene, living became much more comfortable [18]. All this has to be considered in the light of population redistribution [19]. At first glance, environmental changes may be a common denominator, also implying changes in microbial exposure. On this respect, microbe–host coevolution is to be considered as a key in the puzzle and, as such, it may account for some influence on atopic disease susceptibility.

Stressing coexistence with gut microflora, Mazmanian and Kasper point to differences between atopic and nonatopic individuals [20]. It is thus understandable that, at a time when both diet and hygiene transform our immediate—almost integrated—media, an elucidation of the very nature of an autoimmune trigger means a difficult task. In fact, when and under which conditions a subject is prone to unleash autoimmune manifestations, inflammatory specially, remains to be known [21]. A relevant question is whether ignition will be only effective at certain *time* and life circumstances. Besides timing, the route of exposure is of particular interest to us. Thus we need to find out more about the ongoing transformation. The question remains whether a 'former' *herd immunity*, supposedly in support of communal defense, was in fact real. If so, an interhuman immune interaction is to be supposed and, probably, such an external access could have been the means by which the most vulnerable individuals from a group got support [4]. Be it what it may be, our new reality motivated the so-called hygiene hypothesis to explain why under certain endemic conditions, children raised on farms, familiar with pets or early attending kindergarten, are less susceptible to autoimmune disease. No doubt that the practice of hygiene has an important impact in reducing the incidence of major infectious diseases [22]. On the other hand, there is no proof so far that minor gastro-intestinal, respiratory, and/or urinary infections are declining in the developed world. Until now, hygiene habit does not translate into a significant reduction in microbial strains and numbers. The idea that exposure to invasive infection (with inherent risks) might be helpful in reducing autoimmune incidence appears to be inefficient, at least in evolutionary terms [23]. A more plausible explanation would be that customary microbial populations, which in the past achieved a sort of status quo, have been critically replaced. By changing a longstanding guard, a population with a less severe infectious mode may have become involved. It is clear that

the whole subject correlates with the time factor. Rook refers to both, the loss of 'old friends' and a less aggressive mode of pathogenic assault. He further estimates that these 'old friends' were present throughout mammalian evolution and could have had a role in the downregulation of autoimmune incidence [24, 25].

Microbial presence also includes commensal and certain environmental strains that may have given some protection to the host. It is not clear as yet, whether infectious disease in early life is associated with increased, rather than reduced, risk of autoimmune disease. As a precise role for a 'subclinical' microbial background remains to be elucidated, we ought to keep an eye on rapid growing saprophytic strains such as Mycobacteria with an *adjuvant role*. They are currently in use as therapeutic vaccine for atopic conditions, already showing promissory initial results [26]. As to whether, in fact, recent rise in atopy and perhaps other autoimmune conditions reveals an expression of disease or merely turns pre-existent latency visible, is an open question. In any case, the events took place within too short a time to be attributed to genetic predisposition exclusively. To remind is that, lately, atopic expression incidence tends to a sort of *plateau*. The panorama is thus complex being timing, in *sensu stricto*, all-pervading. Understandably, the subject is being methodically scrutinized.

People's 'In'

By relating autoimmunity and microbial activities to the time factor, it is to mention that limiting risks does not simply mean an eradication of the whole microbial population, pathogenic menace notwithstanding. It's about targeting measures in places and at times that really matter [27]. Furthermore, nonmicrobial factors like sedentarism and obesity are now being considered in relation to autoimmunity [28]. Harnessing obesity epidemic is outright fashionable; 'does it prepare us for a famine that never comes?' [29]. Our historical turning point, namely the end of undernutrition casualties' prevalence, may not be entirely fortuitous. Overweight is due to a combination of factors such as underlying genetic components in which even social life appears to be a player. The headlines nourishing *palette*, by associating an assumed autoimmune epidemic, new emerging infections and recurrence of old pathogens as well as antibiotic resistance, provide a mix that remains to be properly elucidated [30]. By 2025, over 800 million people will be over 65, thus being it a factor to consider. Obviously, age-conditioned vulnerability relates to the immune-status [31, 32]. Paradoxically, in older individuals, functional lymphocytes' fading does not prevent a rising incidence of autoreactive antibodies [33]. The still inconclusive links to autoimmunity, in fact, for long have fascinated scientists.

Timings With Respect To Autoimmunity

Inspired by "Amadeus"

'too many notes...' (variables)

This section refers to some aspects that make up human biological life experience. By lacking chronon as the time interval unit for the complex IDS function, some of the following references may be understood as such or as a result from shortcuts.

Homeostasis refers to the tendency of health to preserve its steady state, allowing it to return to a normal set point following perturbation. In consequence, rather than static, homeostasis is a dynamic process in which both immune tolerance and reaction are genuinely involved [34].

In the course of life, *tolerance*, as a main property of the IDS function, is subjected to variation. It is thus a heavily time dependent factor. As such, it is a key factor in *transplantation medicine* [35, 36] that also involves the complex question of microchimerism. In autoimmunity, tolerance cannot be dismissed either [37, 38].

It's already common place that the outcome of immune reactions heavily depends on *environmental stimuli*. Timing of exposure is significant as the impact of challenges will differ according to the maturational status of the IDS. As it was stated by Nöel Rose [39], quality as well as quantity of the immune response varies over time.

Our life evolves amidst rhythms of many frequencies and much hidden potential for autoreactivity is to be expected. The *circadian rhythm* is the best explored and adjustment of symptoms—nowadays attributed to autoimmune diseases—to it have been identified a century ago.

During pregnancy, when the offspring still is supposed to be virtually free from an influence of the mother's link with the outside world, antigenic stimuli bursting into the scene may not just be targeted specifically—rather, a response by the still immature IDS may be polyspecific, that is to say, taking additional targets in. Autoantibodies may be available, although it is not a proven fact whether such an arrangement could accomplish the means by which autoimmunity becomes triggered as a sort of bystander effect [40].[1] Also in theory, a nonspecific bystander activation, mediated by inflammatory cytokines, could be an alternative—although, its significance may be dismissed by quantitative considerations [41]. Even once the IDS matured, infection-conditioned tissue damage often relates to poorly controlled immune responses, which well could outline a framework for an autoimmune situation. Timing, it is to remind, will be

[1] Bearing in mind that, usually, a fight is not restricted to the protagonists in *sensu stricto*, innocent bystanders also are at risk.

conditioning. Delivery as a turning point does not put the foot down either, as change will not totally break off [42, 43]. Later in life, provided that the events remain inside the frame of the so-called functional window, even in the elderly, the condition of the IDS will not be marginal either. The theme cannot be omitted in any discussion about autoimmunity induction [44–46].

Among others, the time factor proves actually pivotal in the search of disease prevention. In effect, current success in experimental administration of human vaccines to diabetic prone newborn rodents starts before 2 weeks of age [47]. More about it may be found in the following examples.

Diabetes Wilkin discusses the accelerator hypothesis sustaining that type-1 and type-2 diabetes are variants of the same disease. Nevertheless, 30 years of research failed to secure the cause of type-1 diabetes, which incidence has risen threefold [48, 49]. The theory argues three processes that differentially speed up beta cell loss, namely constitution, insulin resistance as well as the immune response to it. Weight gain, and with it, insulin resistance is considered central to the rising incidence of all diabetes. Rather than an overlap between the two types of diabetes, the accelerator hypothesis envisages an overlay—one a subset of the other—only *tempo* distinguishing type 1 from type 2 [50].

Celiacs In commenting the Finnish survey of 703 celiacs with a high prevalence of autoimmune disease, Roy Jamron puts the accent on a prolonged gluten exposure in those patients in which celiac disease manifested late in life, without increasing the risk for developing autoimmune disease [51]. According to Jamron, this seems counterintuitive, but studies in the UK and Italy have shown that early manifesting celiac disease—since infancy, the critical *time* period for the development of the immune system—is accountable for the increased risk of autoimmune disease by exposure to gluten later in life. Malabsorption during infancy and early childhood can also adversely affect the crucial T cell production and repertoire. Therefore, the stage for increased risk of autoimmune disease is set early in life rather than later. In this aspect, the *timing* of gluten exposure in life seems to be more critical than the overall lifetime duration of gluten exposure.

Final Comment

Medical assistance of chronic autoimmune diseases means no less than the resolve to take responsibility for lifelong well-being. Although patients seek for immediate improvement, already their usual first question being, how long ...? discloses realism. Thus the time factor has to be accounted for [52].

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