

Review

Assessment of Causes and Potential Prevention and Therapy for Autoimmune Diseases Through Evolutionary Medicine

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Abstract

Autoimmune diseases comprise a broad group of conditions that affect virtually any organ or tissue and share mechanisms of chronic, autoimmune-based inflammation. Once rare or unknown, they have become increasingly common in recent years, affecting individuals of all ages, including the elderly, due to the growing number of older people. According to evolutionary medicine, if the frequency of a disease, or group of diseases, increases sharply over a few decades, the primary cause cannot be the effect of genetic alterations but rather the consequence of one or more alterations in the living conditions of the species. For autoimmune diseases, there is no environmental, dietary, or infectious factor that appears to correlate with their strong increased frequency. On the contrary, the epidemic of autoimmune diseases is likely correlated with serious alterations of our holobiont (i.e., our organism, the host species, plus the myriad of species coexisting with us). In particular, the critical factor appears to be the decreasing incidence of macroparasite (i.e., parasitic worm) infestations, without, however, excluding the effects of profound alterations in the bacterial ecosystems that are also part of our holobiont. The macroparasites modulate and curb the intensity of immune responses in order to survive in our bodies. In the coevolution of host organism and other species of the holobiont, a delicate balance has developed that is severely altered by the eradication of parasitic worms. Therefore, it is necessary to move beyond the concept of macroparasites as harmful species by definition and therefore to be eliminated without hesitation. Alternatively, it is essential to study our holobiont as a whole and consider the balances of its ecosystems before modern alterations. Furthermore, the evaluation of the effects of reintroducing macroparasite species with which we have coevolved into our holobiont would be enlightening or helpful to understanding autoimmune diseases and implementing effective prevention and treatment.

Keywords: evolutionary medicine; human holobiont; autoimmune diseases; helminth therapy; monoclonal antibodies



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1. Introduction

The ideas and arguments presented in this work are certainly either little-known or unusual to those familiar with the concepts and methods of current medicine. This is particularly true for the application of concepts of evolutionary medicine, when deductions drawn from known data conflict with widely accepted concepts.

As a result, what is proposed in this work may appear excessively innovative or dubious, intended to be disseminated without widespread acceptance—a consensus impossible precisely because of its innovative nature. Therefore, to avoid misunderstandings, it is appropriate to consider what is presented as hypotheses based on the concepts of evolutionary medicine and the evidence, which must be duly rejected if they (i) are not based on sufficient or clear evidence; or (ii) are based on weak or flawed arguments. In any case, they should not be accepted uncritically, but only considered worthy of evaluation if the aforementioned conditions are not met.

However, for the discussion of this work, it is useful and necessary to declare beforehand four definitions, certainly more extensively and better discussed in Ch. 1 of a recent book [1].

1.1. *Evolutionary Medicine* ([1], s. #1.1)

“Evolutionary medicine is the enterprise of using evolutionary biology to address the problems of medicine” [2], p. 417. Evolutionary medicine is the enrichment and necessary completion of current medicine with the concepts of evolutionism, which become an integral and essential part of medical knowledge for the understanding, prevention, and treatment of disease.

Paraphrasing what a famous scholar, Theodosius Dobzhansky, said about biology: “Nothing in biology makes sense, except in the light of evolution” [3], a similar concept was proposed for medicine: “Nothing in medicine makes sense, except in the light of evolution” [4].

Many other things can be said about evolutionary medicine but in order not to digress from the object of this work it is useful to refer to the detailed and extensive discussions reported in the book [1].

1.2. *Ecological Niche* ([1], s. #1.2.2)

A species, or more precisely its individuals, lives in a delimited range of conditions and relationships, which is defined as the species’ “ecological niche”. This concept includes the physical environment in which the individuals of the species live, but also the foods they eat, the characteristics of each moment and stage of life, the modes of competition with other species and within the species, how individuals attack, run away, breathe, rest, act and struggle to reproduce and survive. Furthermore, the concept of ecological niche also encompasses the countless and intricate relationships with the numberless species living on the internal and external surfaces of an individual’s body (or also within cells, or even integrated in some way with the genome), and with any species with which the individuals of the species have some relationship.

1.3. *Mismatch* ([1], s. #1.2.4)

The ecological niche of a species and the adaptation of the species to its ecological niche constitute a complex system: in the evolutionary process the genome of the species adapt to the multiple, intricate, and sometimes contradictory needs of its ecological niche. If, for whatever reason, there is a rapid change in the characteristics of the ecological niche, the most likely consequence will be a discordance or “mismatch” between the new conditions of the ecological niche and the adaptation of the species, which is a condition that may cause the onset of diseases [5,6].

1.4. *Holobiont* ([1], s. #1.2.5)

Individuals of a species were, and unfortunately still are, often considered as isolated entities struggling against the challenges posed by the environment and individuals of other species. The concept of the holobiont clearly goes beyond this vision.

The holobiont is generally understood as the whole of a main species, defined as the “host” (or “host biont”), and a large number of coexisting species (“bionts”), which are

bacteria, archaea, viruses, fungi, mycoplasma, and other species that live on its external or internal surfaces [7], including multicellular species (intestinal worms, mites, etc.) [8]. Other species coexist within the cells, often in intimate connection with our DNA, so much so that about 8% of human DNA has been estimated to be of viral origin (retroviral DNA and latent DNA virus genomes) [9]. Viruses have been found in every part of the human body [10,11], even in parts generally considered sterile such as the cerebrospinal fluid [12], circulating blood [13,14] and breast milk [15].

Our body is home to a series of complex ecosystems, including those of the intestinal, respiratory, and skin systems, and it has been estimated that the human microbiota has a total genetic information over 150 times that of the human genome [16]. These biont species and that of the host biont have a long, extraordinary, and complex coevolutionary history, and their balanced coexistence is essential for the health of the host [17].

In the past, but often even today, components of the holobiont other than the host are considered as always harmful or potentially harmful to the host, with some rare exceptions (for example, particular intestinal bacteria that synthesize vitamins beneficial to the host's health [18,19]).

The reality is much more complex, and vital interactions often occur between the host and other components of the holobiont. A striking example may be useful in this regard. Breast milk contains many special oligosaccharides (Human Milk Oligosaccharides, HMOs) which cannot be assimilated by the newborn. The number of HMOs identified was 70 in 2011 [20] and seven years later it rose to around 200 [21]. These substances serve as prebiotics for specific bacteria such as *bifidobacteria* and *lactobacilli* and perform a series of functions in which there is cooperation between these bacteria, the mother, and the newborn baby [22]. Without these beneficial actions, the existence of HMOs would be difficult to justify in evolutionary terms.

1.5. The Autoimmune Diseases

Autoimmune diseases are a broad group of disorders characterized by loss of discrimination and an attack of the immune system against the body itself. They result from an imbalance in the immune system, which abnormally attacks the body's own tissues and cells, with a loss of immune tolerance to its own antigens and impaired discrimination between self and non-self. This leads to abnormal activation of B cells, with the production of autoantibodies, T cells and immune-mediated processes that damage normal tissues. Any organ or tissue can be affected by autoimmune actions, and consequently the resulting manifestations are extremely varied [23,24]. The great variety of symptoms and the division of medicine into specialized branches, each responsible for a distinct organ or system, have hindered a common pathogenetic understanding of autoimmune diseases, favoring an illogical distinction based on the organ or system primarily involved in each disease [25].

As below expounded, another major difficulty is that many autoimmune diseases were uncommon and poorly understood even in the recent past, and that many other previously unknown autoimmune diseases are rare and, unfortunately, even less well understood. However, regardless of the causes and pathogenic mechanisms, even considering that longer life and better detection increase the number of recognized cases in modern conditions, it is accepted that "Both autoimmunity and autoimmune diseases are dramatically increasing in many parts of the world, likely as a result of changes in our exposures to environmental factors" and that the need for much greater attention to the understanding, treatment and prevention of these diseases is a priority [26].

Autoimmune diseases affect individuals of all ages, and the most severe forms are particularly dramatic in young people. However, with the increase in life expectancy and the number of elderly people, autoimmune diseases now also significantly affect older people [27,28].

In this work, for reasons that will be explained below, we will try to study autoimmune diseases, particularly their primary causes and potential prevention, from the perspective of evolutionary medicine, as already proposed in the more general context of all diseases in a recent book [1].

As stated in this book, according to the logic of evolutionary medicine, when the frequency of a disease, or a group of related diseases, starting from a low or minimal frequency, reaches significant frequencies within a few generations, and when this frequency also shows significant differences if compared across populations, it follows that:

- The primary cause, or causes, of the disease can be genetic only in a small fraction of cases, as the frequency of a harmful gene cannot significantly increase within one or few generations;
- To a large extent, the disease results from an alteration of the ecological niche to which the species is adapted. The rapidity of an alteration, on the evolutionary timescale, does not allow natural selection to spread appropriate genetic adaptations, and therefore dysfunctions or disease conditions result;

Epidemiological data allow us to attribute the primary cause to an alteration of the ecological niche but do not in themselves indicate the nature of that alteration, which requires further evidence to identify. However, epidemiological data are the essential starting point, even before knowing primary causes and pathogenic mechanisms.

2. Epidemiological Data on Autoimmune Diseases

From the perspective of evolutionary medicine, the preliminary study of the epidemiological data of the disease under examination is essential. In the first following subsection, we will report epidemiological data for a nation where autoimmune diseases are remarkably widespread and where fairly reliable epidemiological data exist. In subsequent sections, we will point out fragmented epidemiological data for populations where these diseases are rare and for modern populations where the frequency is more or less high.

Subsequent sections will focus on the increase in the frequency of autoimmune diseases in recent decades and on the different frequencies in segments of the same population with diverse lifestyles.

2.1. Autoimmune Diseases in the USA

It is first useful to describe the current prevalence of autoimmune diseases in a country with modern lifestyles, the USA, for which abundant reliable data are available.

These data are reported in Table 1, derived from an elaboration of what is in the public registry of autoimmune diseases [29].

It should be noted that the data are approximate for several reasons:

- Mild cases are not always diagnosed or reported;
- Multiple autoimmune diseases can coexist in an individual (according to the Autoimmune Association, up to 25% of individuals with autoimmune diseases have more than one such disease [30]);
- Many autoimmune diseases are rare and poorly understood. They are sometimes confused with more common and better-known diseases;
- For some of the diseases listed in Table 1, the nature of the disease, i.e., whether autoimmune or another type, is not confirmed with certainty.

Therefore, the information in Table 1 should be considered indicative and approximate and not definitive or precise.

With these caveats, the data show that, limiting ourselves to the USA and diseases with a minimum number of reported cases >10,000, we have an estimated number of recorded cases ranging from a minimum of over 31 million to a maximum of almost 44 million.

Additionally, considering diseases for which the autoimmune nature is considered probable but not yet confirmed, again only for diseases with a number of cases >10,000, we have a number of recorded cases ranging from an estimated minimum of over 52 million to a maximum of almost 177 million.

These data indicate that the problem of autoimmune diseases represents a major health issue, certainly not to be neglected or considered of secondary importance.

Table 1. List of Autoimmune Registry (data from [29]). Part A—Autoimmune diseases with pathogenic evidence (number of cases in thousands, rounded to the nearest whole number). Part B—Unconfirmed autoimmune diseases (i.e., without an accepted known cause but showing features common with autoimmune diseases, with autoimmunity proposed as a cause in at least one scientific article, or comorbid with confirmed autoimmune diseases).

Part A		
With min. Frequency >200	Level of Evidence	US Cases Min–Max
Psoriasis	T-cells	8665–12,332
Autoimmune urticaria	Autoantibodies	2666
Celiac disease	Autoantibodies	2500–3333
Graves’ disease (Autoimmune thyrotoxicosis)	Autoantibodies	2096
Crohn’s disease	T-cells	1998–2566
Autoimmune thyroiditis (Hashimoto’s thyroiditis)	Autoantibodies	1733–1933
Ulcerative colitis	Immune-mediated	1634–2100
Rheumatoid arthritis	Autoantibodies	1100–2633
Type 1 diabetes mellitus (T1D)	Autoantibodies	867–1133
Rheumatoid vasculitis	Autoantibodies	863–1107
Multiple sclerosis	Autoantibodies	799–804
Polymyalgia rheumatica	Immune-mediated	738–850
Alopecia areata	Autoantibodies	699–930
Idiopathic pulmonary fibrosis	Immune-mediated	674–1648
Sjögren’s disease	Autoantibodies	500–1433
Pediatric autoimmune neuropsychiatric disorder associated with streptococcus	Autoantibodies suspected	362
Uveitis	T-cells	344
Vitiligo	Autoantibodies	334–667
Reactive arthritis	Immune-mediated	260–354
Cutaneous lupus erythematosus	Autoantibodies	233–273
Systemic lupus erythematosus (Lupus)	Autoantibodies	218–270
With min. frequency <200 and >10		
Psoriatic arthritis	Immune-mediated	200–833
Temporal arteritis (Takayasu’s arteritis)	T-cells	182–288
Episcleritis	Autoantibodies	175
Lichen sclerosus	Immune-mediated	167
Antiphospholipid syndrome	Autoantibodies	133–167
Acute febrile mucocutaneous lymph node syndrome (Kawasaki’s disease)	Autoantibodies	116
Primary biliary cholangitis	Autoantibodies	98
Bullous pemphigoid	Autoantibodies	86
Dermatomyositis	Autoantibodies	71
SLE glomerulonephritis syndrome	Autoantibodies	70–72

Table 1. Cont.

Part A		
With min. frequency <200 and >10		
Evans syndrome	Autoantibodies	58–86
Autoimmune hepatitis	Autoantibodies	56
Urticarial vasculitis	Autoantibodies	53–720
Systemic sclerosis (Scleroderma)	Autoantibodies	50–100
Myasthenia gravis	Autoantibodies	50–67
Autoimmune disorder of inner ear (Ménière's disease)	Immune-mediated	50
Cataplexy and narcolepsy	Autoantibodies	47
Autoimmune encephalitis	Autoantibodies	46
Myositis	Autoantibodies	43–52
Warm autoimmune hemolytic anemia	Autoantibodies	37–43
Felty syndrome	Autoantibodies	33
Juvenile rheumatoid arthritis	Autoantibodies	29–37
Lupus vasculitis	Autoantibodies	26–27
Dermatitis herpetiformis	Autoantibodies	25–37
Autoimmune hemolytic anemia	Autoantibodies	20–70
Behcet's syndrome	Autoantibodies	17
Polymyositis	Autoantibodies	17–73
Pemphigus	Autoantibodies	17–18
Rheumatic fever	Autoantibodies	17
Primary sclerosing cholangitis	T-cells	16–24
Antineutrophil cytoplasmic antibody positive vasculitis	Autoantibodies	15–61
Autoimmune pancreatitis	Immune-mediated	15
Autoimmune thrombocytopenic purpura	Autoantibodies	15–32
Necrotizing vasculitis	Immune-mediated	15
Addison's disease	Autoantibodies	14–74
IgA nephropathy	Immune-mediated	10–15
TOTAL		31,372–43,739
With min. frequency < 10		
Acute disseminated encephalomyelitis (Autoantibodies); Adult onset Still's disease (Autoantibodies); Angiofollicular lymph node hyperplasia (Autoantibodies); Antisynthetase syndrome (Autoantibodies); Autoimmune angioedema (Autoantibodies suspected); Autoimmune neutropenia (Autoantibodies); Chronic inflammatory demyelinating polyradiculoneuropathy (T-cells); Cold agglutinin disease (Autoantibodies); Cryptogenic organizing pneumonia (Autoantibodies); Guillain-Barré syndrome (Autoantibodies); Immunoglobulin A vasculitis (Autoantibodies); Immunoglobulin G4 related disease (Autoantibodies); Intermediate uveitis (T-cells); Mixed collagen vascular disease (Autoantibodies); Myelin oligodendrocyte glycoprotein antibody-associated disease (Autoantibodies); Neuromyelitis optica (Autoantibodies); Paraneoplastic cerebellar degeneration (Autoantibodies); Relapsing polychondritis (Autoantibodies); Steroid-responsive encephalopathy associated with autoimmune thyroiditis (Hashimoto's encephalopathy) (Autoantibodies); * Transverse myelitis (Autoantibodies);		
With min. frequency < 1		
Acquired epidermolysis bullosa (Autoantibodies); Acquired hemophilia (Autoantibodies); Anti-glomerular basement membrane disease (Autoantibodies); Aplastic anemia (T-cells); Autoimmune encephalitis caused by N-methyl D-aspartate receptor antibody (Autoantibodies); Autoimmune Gastritis (Autoantibodies); Autoimmune lymphoproliferative syndrome (T-cells); Autoimmune oophoritis (Immune-mediated); Autoimmune orchitis (Autoantibodies); Autoimmune progesterone dermatitis (Autoantibodies suspected); Autoimmune retinopathy (Autoantibodies suspected); Autoimmune vasculitis (Autoantibodies); Balo concentric sclerosis (Autoantibodies); Benign mucous membrane pemphigoid (Autoantibodies); Cogan syndrome (Autoantibodies); Eaton-Lambert syndrome (Autoantibodies); Enthesitis (Autoantibodies); Essential mixed cryoglobulinemia (Immune-mediated); Herpes gestationis (Autoantibodies); Hypersensitivity angiitis (Autoantibodies); Infertility associated with antisperm antibodies (Autoantibodies); Linear IgA dermatosis (Autoantibodies); Microscopic polyangiitis (Autoantibodies); Myocarditis due to autoimmune disease (Autoantibodies); Neuromyotonia (Autoantibodies); Ophthalmoplegia due to graves' disease (Autoantibodies); Opsoclonus-myoclonus syndrome (Immune-mediated); Polyglandular autoimmune syndrome type 1 (Autoantibodies); Polyglandular autoimmune syndrome type 2 (Autoantibodies); Polyglandular autoimmune syndrome type 3 (Autoantibodies); Polyglandular autoimmune syndrome type 4 (Autoantibodies); Pure red cell aplasia (Autoantibodies); Rasmussen syndrome (Autoantibodies); Retinocochleocerebral vasculopathy (Autoantibodies suspected); Stiff-person syndrome (Autoantibodies); Sympathetic uveitis (Autoantibodies); Systemic sclerosis with limited cutaneous involvement (CREST syndrome) (Autoantibodies suspected); Vogt-Koyanagi-Harada disease (Autoantibodies);		

Table 1. Cont.

Part B	
With min. frequency > 200	US cases Min–Max
Chronic post-COVID 19 syndrome	16,718–16,961
* Restless legs	13,332–96,657
* Raynaud’s phenomenon	6933–29,030
Fibromyalgia	4733–6899
Epilepsy	4175–5480
Hidradenitis suppurativa	1767–2800
Lichen planus	933–1089
Ankylosing spondylitis	867
Endometriosis	788–825
Chronic fatigue syndrome	767–14,432
Microscopic colitis	343
Sarcoidosis	197–201
With min. frequency < 200 and >10	
Primary idiopathic dilated cardiomyopathy	122
Acute lichenoid pityriasis	102
Postmyocardial infarction syndrome	89
Systemic mast cell disease	86–97
Complex regional pain syndrome	69
* Undifferentiated connective tissue disease	47–467
Chronic interstitial cystitis	35–75
Eosinophilic esophagitis	33–190
Cutaneous mastocytosis	33
Pyoderma gangrenosum	19–20
Scleritis	17
TOTAL	52,205–176,865
With min. frequency < 10	
Erythema nodosum; Fasciitis with eosinophilia syndrome; Inclusion body myositis; Morphea (localized scleroderma); Subacute bacterial endocarditis	
With min. frequency < 1	
Chronic Lyme disease; Chronic multifocal osteomyelitis; Ligneous conjunctivitis; Lipomatosis dolorosa; Mooren’s ulcer; Moyamoya disease; Neuralgic amyotrophy; Palindromic rheumatism; Paroxysmal nocturnal hemoglobinuria; POEMS syndrome; Polyarteritis nodosa; Progressive hemifacial atrophy; Rheumatic chorea; Schnitzler syndrome; Tolosa-Hunt syndrome	

Notes: (1) The symbol * means that in [31] the disease was reported as “Symptoms” related to autoimmune diseases, i.e., occurring commonly among people with autoimmune diseases; (2) The column “Level of evidence”, as reported in [29], does not represent a synthetic exposition or a definitive conclusion of the pathogenic mechanism but only a hint to characteristics of the pathogenic mechanism for which there is evidence.

2.2. Rarity in Populations Following Ancestral Lifestyles or in Nations in the Early Stages of Modernization

Populations living in primitive conditions have lifestyles (notable physical activity, environment not contaminated by chemicals, no smoking, high-residue diet with reduced or absent sugar and alcohol) far from modern ones that are considered risk factors for hypertension, type 2 diabetes, smoke-related diseases, atherosclerotic diseases, and cancer. According to the logic of evolutionary medicine, a population living in ancestral conditions is adapted to conditions persistent since ancestral times and does not experience problems of “mismatch” of its adaptation with a changed ecological niche [1,32]. Consequently, if autoimmune diseases are due to some hypothetical change in the ecological niche, they should be absent or rare in ancestral conditions.

Some studies have been conducted on primitive populations living in hunter-gatherer conditions, a condition believed to be close to the ancestral one to which our species is adapted. These populations, the Yanomamo of the Amazon and the Ache of Paraguay, do not suffer from the diseases associated with the modern lifestyles (s. above), and no cases of autoimmune disease are mentioned [33,34]. However, the absence of such cases could also be explained by the small size of the populations studied and the difficulty in identifying autoimmune disease cases.

More reliable data come from studies of much larger populations, in particular African, prior to lifestyle modernization. The available data are related to specific autoimmune diseases, not to the entirety of these diseases.

Foster and Harris reported that in seventeen years, from 1952 to 1969, they had observed only two cases of multiple sclerosis in two major hospitals in Kenya [35]. They also point out that there were doubts about the occurrence of multiple sclerosis among indigenous Africans [36–39].

In 1967, Dean reported that no cases of multiple sclerosis had been observed among the 11 million Bantu people of South Africa and that the disease was uncommon among Asian and Coloured South Africans, while among white South Africans the annual incidence was 0.6 per 100,000. He also pointed out that no cases of multiple sclerosis had been reported among Australian Aborigines and that the disease was uncommon among the Maori of New Zealand [39].

In 1960, among Africans, celiac disease was reported to be extremely rare and there was no conclusive evidence of any cases of Crohn's disease [37].

In 1970, at the University Hospital of Ibadan (Nigeria), cases of Addison's disease, myxoedema, Hashimoto's thyroiditis, systemic collagen disease, and pernicious anemia were extremely unusual, and cases of thyrotoxicosis, ulcerative colitis, and myasthenia gravis were only slightly less rare [40]. In the same hospital, over a 10-year period, there were only 42 admissions for rheumatoid arthritis among 100,000 patients, and in a carefully studied population survey of 571 subjects living in nearby villages, only two subjects affected by mild polyarthritis were found [40].

In 1980, in Ethiopia, a careful study of 7966 hospital patients found that autoantibodies were uncommon. This confirmed the rarity of autoimmune diseases in clinical observation [41].

In 1996–1997, autoimmune diseases were described as uncommon in tropical rural populations of Africa [42,43].

2.3. Increase in Frequency with Modernization of Lifestyles and Within a Few Decades

Between 1985 and 2015, there was a worldwide net % increase/year incidence and prevalence of autoimmune diseases, equal to 19.1 ± 43.1 and 12.5 ± 7.9 , respectively [44].

In the period from 1960 to 1996, the incidence of type 1 diabetes (T1D), based on 37 studies conducted in 27 countries, showed an increase of 3.0% per year. The data showed that T1D incidence was increasing worldwide in both low- and high-incidence populations. The relative increase was more marked in populations with a lower incidence, but was also detected in populations with a higher incidence ($>14.6/100,000/\text{year}$) [45]. In the same work, it was predicted that by 2010, for many populations, the incidence would reach a value of over $30/100,000/\text{year}$ and that in Finland it would reach a value of $50/100,000/\text{year}$ [45]. However, in this country the incidence of T1D among subjects under 15 years of age, in the period 1980–2011 increased from 12 to 65 new cases/ $100,000/\text{year}$ [46].

In the period 1990–2011, in the UK, the incidence of celiac disease increased from 5.2 to $19.1/100,000/\text{year}$ [47].

Douglas Kerr, a faculty neurologist and neuroscientist at the Johns Hopkins Hospital in Baltimore, founder and director of the Johns Hopkins Transverse Myelitis (TM) Center, stated in 2008 that, prior to the 1950s, there were a total of only four cases of TM reported in the medical literature, while “Currently, my colleagues at the Johns Hopkins Hospital and I hear about or treat hundreds of new cases every year.” Kerr also highlights: (i) a continuous rise in the number of cases of multiple sclerosis but also of other autoimmune diseases such as systemic lupus erythematosus and T1D; and (ii) that the probability of developing a diagnosed autoimmune disorder is one in twelve Americans while the probability of developing cancer or heart disease was one in fourteen and one in twenty, respectively [48].

As reported in [49], in the period 1950–2000, a sharp increase in cases of T1D [50], Crohn’s disease [51], and multiple sclerosis [52] was observed in developed countries.

In Latvia, in the period 2010–2023, the incidence of T1D, as reported in public data, increased in 13 years from 191.4 to 271.4/100,000 (+41.8%), and new cases increased from 93 to 258 (+177%) [53].

2.4. Current Significant Frequency in Nations Other than the USA

In 1997, a review considered the frequencies of 24 autoimmune diseases as reported in U.S. and European studies covering the previous 30 years. The prevalence of these autoimmune diseases was estimated to be 3.2% [54].

In 2007, a review studying the epidemiology of 31 autoimmune diseases and based on data from the Danish national hospitalization registry reported a prevalence of 5.3% [55].

In 2015, it was observed that autoimmune diseases, although previously considered rare diseases, were now shown by rigorous epidemiological studies to affect 3–5% of the population [55]. The same study reported that the incidence of T1D was 5–10, 10–20 and <1/100,000/year in populations from Europe, the USA and China, respectively.” [56].

Improved diagnostic capabilities and greater healthcare attention in this regard certainly contribute to the reported increase in the frequency of autoimmune diseases, but this only partially could explain the increase and differences in the frequency of autoimmune diseases.

In 2009, another review [57], largely based on studies from 1989 to 2008, highlighted that for certain diseases, which in non-severe cases did not require hospital admissions (e.g., hyperthyroidism, hypothyroidism, alopecia, vitiligo, celiac disease, psoriasis), their incidence was significantly underestimated. For example, a study of 50,000 adults in the Netherlands showed that for clinically diagnosed cases the prevalence was 0.016% while for unrecognized cases it was 0.35% [58]. However, if appropriate correction factors were applied for undiagnosed and/or non-hospitalized cases, an overall prevalence for autoimmune diseases was estimated between 7.6% and 9.4%.

2.5. Difference in Frequency in Parts of Similar or Identical Populations with Different Lifestyles

Finland, inhabited by Finns, and Russian Karelia, inhabited by a mixture of ethnic Russians and minorities among which Finns and Karelians (who speak a language close to Finnish), are geographically adjacent regions with quite different lifestyles. In the Finnish part, there is less crowding in homes, better economic conditions, the water used is in excellent hygienic conditions, and there are low infection rates. In contrast, in Russian Karelia, economic conditions are mediocre, the water used from Lake Ladoga is not well sanitized, and there is frequent contact with chickens and cows. A marked difference in the incidence of celiac disease and T1D was observed between the two parts. Specifically, in the Russian part, there were one-sixth as many cases of T1D and one-fifth as many cases of celiac disease as in the Finnish part [59,60].

In Russian Karelia, where the incidence of T1D averaged 7.4/100,000, children of Karelian or Finnish ancestry showed a non-significantly lower incidence compared to children of Russian ancestry, and this difference was negligible compared to the much higher incidence observed in Finland (41.4/100,000) [59].

2.6. Sex-Related Difference in Autoimmune Disease Frequency

It is well known that females are more likely than males to be affected by autoimmune diseases [61], so much so that approximately 80% of individuals with autoimmune diseases are female [62]. The causes of the greater vulnerability of the female gender to autoimmune diseases are still unclear, even if they are probably related to hormonal differences between the two sexes [63].

In general, females exhibit stronger and faster immune responses to infections than males. A more effective immune response corresponds to a more rapid and effective resolution of infectious diseases and lower mortality, but also to a greater vulnerability to autoimmune diseases [64,65]. This greater vulnerability of females to autoimmune diseases appears to be related to a higher frequency of helminthic infections [66–68], which could be explained by a greater need to modulate and curb immune reactions.

The difference in the immune response between the two sexes may be related to pregnancy and the need for more effective fetal defense. Although it is known that there are exacerbations of autoimmune diseases during pregnancy [69], this hypothesis needs specific confirmation. However, this difference between the two sexes, although duly highlighted here, is not the subject of this review with regard to its causes and is not even relevant to the discussion that will be held below.

3. Autoimmune Diseases as a Consequence of Alterations in the Ecological Niche

A search of the scientific literature on proposed causes of autoimmune diseases reveals a large number of studies that, however, show a tendency to investigate the etiology of specific autoimmune diseases rather than the overall complex of such diseases. This fragmentation of autoimmune diseases might be correct and realistic, but it does not explain the general increase in frequency of an entire category of diseases that appear to be related in pathogenesis and biohumoral alterations. Furthermore, these studies do not explain the increased incidence of each specific disease.

One example is the case of autoimmune hepatitis, as discussed in [70]. In this work, the authors highlight correlations of the disease with certain types of antigens and gene variants, as well as other correlations with certain types of infections. However, these correlations do not justify the increased incidence of the disease, which is also paralleled by other forms of autoimmune diseases.

Another example is that of rheumatoid arthritis in the in-depth study presented by [71]. In this review, various risk factors increasing the frequency of the disease are highlighted (certain genetic characteristics, cigarette smoking, dietary factors, obesity, occupational disease, periodontal disease), but here too the increased frequency of the disease appears not justified.

A third example concerns psoriatic arthritis [72], a condition for which some correlations with gene variants and some suspected relationships with certain factors are known, but nothing is reported explaining the increased frequency of the disease.

However, an interesting general explanation regarding the origin of autoimmune diseases is constituted by a development of Strachan's Hygiene Hypothesis regarding the origin of allergic diseases as a consequence of the reduced exposure to antigens of microbial, animal and vegetal origin [73,74]. This development proposes that the primary cause of

autoimmune diseases is the absence of helminth infections with their immunoregulatory activity [75–77].

The approach of the evolutionary medicine is not limited to the case of the relationship between the absence of helminths and the onset of autoimmune diseases, but extends to all cases in which a modification of the ecological niche is related to a disease or group of diseases. In fact, the traditional approach is predominantly empirical and starts from the association between a factor X and a disease Y. For evolutionary medicine, the method has more general theoretical bases that also require empirical data for each distinct relationship between modifications of the ecological niche and the resulting diseases [1].

For the two approaches, regarding autoimmune diseases, the conclusions appear similar: (i) relationship between lower frequency of helminth infections and increased frequency of autoimmune diseases; (ii) presence of numerous co-factors, in particular genetic predisposition and environmental factors; and (iii) in presence of a strong increase in the incidence of autoimmune diseases in a few years, “since genetic basis has not undergone any major changes in such a short period of time, environmental factors are highly suspected to be responsible for this recent outbreak” [77].

In the description of evolutionary medicine, without denying the importance of individual genetic vulnerabilities or environmental factors that contribute to the onset of autoimmune diseases, the main cause (“main or primary factor” in the terminology of evolutionary medicine [1]) is indicated in the absence of helminthic infections to which our species is adapted. In this description, all the known co-factors, including the greater genetic vulnerability in some individuals, contribute to the pathogenesis, but alone are not sufficient to determine the onset, or are so only in a marginal or episodic way. Consequently, they cannot be considered as main or primary factors at the origin of autoimmune diseases.

Indeed, as stated in [77], since a significant change in gene frequency over one or a few generations seems unlikely, the sharp increase in the incidence of many autoimmune diseases is incompatible with a predominantly genetic etiology. Pisetsky discusses a combination of environmental factors and a complex genetic predisposition involving multiple genes that regulate immunity [23]. These predisposing genes necessarily act only in conjunction with environmental factors—to be defined—since epidemiological data for populations with non-modern lifestyles show that in the absence of such factors, the frequency of autoimmune diseases is much lower. Therefore, considering only these predisposing genes without first evaluating environmental factors, or rather changes in the ecological niche, appears limiting and misleading.

Let us now consider a group of diseases that: (i) appear similar in pathogenesis and biohumoral alterations; (ii) have largely increased in frequency from an ancestral or ancient condition in which they were rare or practically absent; (iii) with increases in frequency not compatible with an effect of pathological genes that should have had an improbable parallel increase in frequency within a few generations; (iv) with markedly different frequencies among various populations; and (v) with different frequencies in parts of the same population with different lifestyles.

Evolutionary medicine proposes a rapid change in the ecological niche as the only plausible explanation for the pathogenesis of such a group of diseases. As the species is not adapted to such different conditions, by definition because change is rapid on the evolutionary timescale, disease conditions arise from this “mismatch” between the species’ adaptation and ecological niche change.

Compatible with this explanation is the possibility that a portion of these diseases are due to genetic variants, but the frequency of such cases with genetic origin should be small and correspond to the low incidence observed in ancestral conditions to which the species is considered well adapted.

If, therefore, autoimmune diseases have their primary cause in alterations of the ecological niche to which we are adapted, the question immediately arises as to what these alterations are.

As discussed extensively in [1], ecological niche alterations can be of two general types: (i) alterations not regarding the holobiont"; (ii) alterations regarding the holobiont. As suggested below, alterations of the second type are the likely primary cause of autoimmune diseases.

3.1. Autoimmune Diseases as Caused by Alterations of the Ecological Niche Not Regarding the Holobiont

Alterations of the first type may involve, among other things, dietary alterations; exposure to harmful substances; multiple carcinogenic factors; altered social interactions; infectious epidemics; etc. Among the factors that have been considered for their possible role in the pathogenesis of autoimmune diseases, we have infectious processes, components of the diet, microbiota, tobacco smoke, hormones, pharmaceutical agents, ultraviolet light, heavy metals, silica solvents, vaccines and collagen or silicone implants [78–80]. However, for autoimmunity "there are very few agents [among environmental factors] that clearly have a role and identification of generic risk factors remains elusive" [55].

3.2. Autoimmune Diseases as Caused by Alterations of the Ecological Niche Regarding the Holobiont

Alterations of the second type concern alterations of the holobiont, that is, the set of innumerable species that make up the human holobiont, and the even more numerous interrelationships between holobiont species, and in particular between the host and other species of the human holobiont.

Regarding the genesis of autoimmune diseases starting from alterations of the holobiont, some facts and considerations must be highlighted:

- (A) In the 1970s, when studying the frequency of autoimmune diseases as a cause of hospitalization in Nigeria, diseases such as Addison's disease, Hashimoto's thyroiditis, thyrotoxicosis myxedema, ulcerative colitis, systemic collagen diseases, rheumatoid arthritis, pernicious anemia, and myasthenia gravis were found to be rare. However, a high percentage of rheumatoid factor positivity was observed in the served populations without apparent disease conditions. It was also observed that in many parts of tropical Africa there was a high prevalence of parasitic infestations correlated with immunological changes and that in the same areas autoimmune diseases were rare. From this it could be deduced, as a plausible hypothesis, that the interaction between host and parasite somehow curbed the abnormal immunological mechanisms involved in the pathogenesis of autoimmune diseases [40,81].
- (B) Before the 1940s, a large portion of the US population, both among adults and children, carried helminths. This condition was even more common among the poor in major cities and in rural areas of the South [82] and, subsequently, in disadvantaged populations such as those of Indian reservations [83]. By 1990, both in the US and Europe, the presence of helminths had dramatically declined, while it was still found in immigrants from developing countries [84].
- (C) As discussed in [85], populations and groups with a higher prevalence of helminth infections show a low risk for inflammatory bowel disease (IBD). Modern hygiene practices lead to a lack of exposure to helminths and this appears to be a major contributing factor to the onset of IBD. Furthermore, there is an inverse correlation between Crohn's disease (CD) and helminth colonization. In the US and Europe, this disease is more common in urban versus rural populations, and in northern versus southern regions. A similar correlation is observed when comparing developed versus

less developed countries. For all these correlations regarding CD, the opposite is observed for the presence of helminths. Until modern times, the presence of intestinal helminths in both children and adults was the norm. Helminths and the human immune system have coevolved in close proximity since time immemorial. Helminths modulates the host's immune system to prevent excessive reactions that would block their persistence in the host [74,77].

- (D) Subjects with helminthic presence show reduced immunological responses to unrelated concomitant antigenic exposures. This suggests that helminth eradication is a risk factor for autoimmune diseases [82,86,87]. The interaction between helminths and their hosts is the result of a long co-evolution that has led to complex and multifaceted characteristics that allow for benign coexistence. Helminths activate Th2 responses, which help limit worm numbers in the host, and stimulate the production of potent immunomodulatory molecules such as IL-10 and TGF- β , and the proliferation of regulatory T cells [88].
- (E) It has been emphasized that the relationships between host and parasitic worms have persisted for many millions of years. In this coevolution of host and parasites, the worms attempt to slow down and circumvent the host's defenses while the host tries to avoid the excessive presence of parasites. This ancestral balance has certainly profoundly shaped the human immune system, and it is likely that the presence of parasitic worms is necessary to preserve our immunological health [89].
- (F) There are significant epidemiological data and numerous animal studies supporting the hypothesis that helminths immunomodulation lowers for the host the risk of autoimmune diseases and allergies. For example, the presence of helminths is correlated with high serum levels of IL-10, which can be protective against atopy [90]. Stimulation of the production of substances such as IL-4, IL-10, TGF- β , and the multiplication of regulatory T cells, induced by the presence of helminths, can be a protective factor against the development of IBD and other immunological diseases [85].
- (G) In rats, infection with *Schistosoma mansoni* significantly attenuates colitis induced by 2,4,6-Trinitrobenzene sulphonic acid [91].
- (H) In a study on rhesus macaques (*Macaca mulatta*) about a form of alopecia that shows chronic inflammatory infiltrates of the dermis and is analogous to human disorders belonging to the category of autoimmune diseases, animals born and raised in captivity were compared with animals born in the wild that, unlike those in captivity, were infected with lung mites. This second group of animals, in comparison with the former, showed reduced inflammation and cellular infiltrates of the dermis and a significant lower incidence of alopecia [92].
- (I) Domesticated animals (dogs, cats, horses) and animals kept in captivity in zoos (baboons, chimpanzees, rhesus monkeys, gorillas, cotton-top tamarins) are routinely subjected to pharmacological interventions to eliminate worms. This is done with the intent of improving their health, but they suffer from allergic and autoimmune diseases that appear similar to those of humans (many examples and an extensive discussion are reported in [93], pp. 299–302).
- (J) Epidemiological data and animal studies indicate that helminth eradication is certainly contributing to the increased incidence of autoimmune and immune-mediated diseases among populations with improved sanitation. These diseases include Crohn's disease, ulcerative colitis, multiple sclerosis, T1D, rheumatoid arthritis, food allergy, and asthma [94]. For example, it has been highlighted that (i) the increasing incidence of T1D cannot be exclusively explained by genetic factors; and (ii) the ability of helminth infection to influence the onset and progression of T1D is important for possible therapeutic applications [95].

4. Treatment of Autoimmune Diseases

Measures to combat autoimmune diseases in general fall into two categories.

4.1. Measures That Address the Symptoms and Pathogenic Mechanisms of Autoimmune Diseases

In earlier years, autoimmune diseases were rare disorders considered as distinct and unrelated troubles with unknown etiology. Consequently, their treatment was only symptomatic, and the drugs used, particularly Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) and corticosteroids, aimed to combat the manifestations and consequences of inflammation. Later, with the growing awareness that autoimmune diseases were the manifestation of unexplained attacks by the immune defenses against parts of the body itself, immunosuppressive drugs began to be used (e.g., methotrexate, ciclosporin). These drugs acted with varying degrees of success on the pathogenic mechanism, but they had various and serious drawbacks. Subsequently, seeking therapeutic methods with more selective mechanisms and more reliable efficacy, along with fewer deplorable side effects, starting in the early 2000s, specific monoclonal antibodies and biological agents began to be adopted for the treatment of autoimmune diseases [96].

The monoclonal antibody adalimumab was approved by the FDA in 2002 for the treatment of rheumatoid arthritis. Since then, the same antibody has been approved for various other autoimmune diseases [97], and other monoclonal antibodies have been added over the years for the treatment of many autoimmune diseases, as shown in Table 2.

Table 2. Autoimmune diseases treated with monoclonal antibodies.

multiple sclerosis	[98]
autoimmune hemolytic anemia	[99]
primary Sjögren's syndrome	[100]
rheumatoid arthritis	[101]
immune thrombocytopenia	[102,103]
thyroid-associated ophthalmopathy	[104]
uveitis	[105]
myasthenia gravis	[106,107]
T1D	[108]
ankylosing spondylitis	[109]
autoimmune encephalitis	[110,111]
systemic lupus erythematosus	[112,113]
neuromyelitis optica spectrum disorder	[114]
chronic autoimmune demyelinating neuropathies	[115]
pemphigus vulgaris	[116]
antiphospholipid syndrome	[117]
autoimmune diseases of the skin ("pemphigus vulgaris, cutaneous lupus erythematosus, dermatomyositis, systemic sclerosis, thyroid dermopathy, autoimmune pemphigoid diseases, and cutaneous vasculitis diseases.")	[118]
inflammatory skin diseases ("bullous autoimmune diseases, eczema, prurigo, alopecia areata, chronic spontaneous urticaria, Netherton syndrome and a variety of other chronic inflammatory skin diseases.")	[119]

The costs of treating autoimmune diseases are significant and growing strongly. The Autoimmune Association reports that, even considering that "Currently, there are few

effective treatments for the more than 150 chronic conditions classified as autoimmune diseases”, in 2025, the economic burden for 29 autoimmune diseases in the US is estimated at around \$180 billion, and that without new and more affordable treatments, this figure could double within 15 years [120].

Monoclonal antibodies, and other biological agents with analogous effects, are certainly a common type of therapy for autoimmune diseases and are often highly effective in their treatment (and also for other types of diseases, such as cancer [97]). However, for the treatment of autoimmune diseases, there are two fundamental objections to them.

- The first is their high cost as: “they are some of the most expensive treatments, resulting in a degree of hesitancy to introduce new monoclonal antibody agents.” [121]. As an example of costs, in 2016, the additional costs of one year of treatment for juvenile idiopathic arthritis with two monoclonal antibodies (adalimumab or tocilizumab) or two biologic agents (etanercept or abatacept) compared to methotrexate therapy have been estimated at £38,127, £38,656, £32,526, and £39,536, respectively [122]. If these figures are multiplied by the number of subjects treated, or even more so by the number of subjects who should be treated for autoimmune diseases, the possible amount reached are hardly sustainable for rich nations and completely unaffordable for economically poor or low-income nations.
- The second objection is that monoclonal antibodies or other biologic agents are a therapeutic tool, with limited effects over time. They do not permanently eliminate the disease and, moreover, have no preventative value. Or rather, if they did have preventative value, their widespread use, even for asymptomatic individuals, is not feasible, both because of the resulting astronomical cost and the potential side effects in asymptomatic individuals. It should also be emphasized that while diseases such as cancer result in either recovery or death, both of which lead to the end of therapy, autoimmune diseases in general are not resolved with monoclonal antibodies and can persist for a lifetime.

Furthermore:

- (i) Not all autoimmune diseases can be effectively treated with monoclonal antibodies or other biological agents. For example, for three liver and biliary tract diseases (autoimmune hepatitis, primary sclerosing cholangitis, and primary biliary cholangitis), which are certainly autoimmune diseases, there are no specific monoclonal antibodies or biologic agents available that can offer effective specific treatment [123].
- (ii) their efficacy is partial and not always sufficient. In the treatment of moderately to severely active ulcerative colitis, the use of one of several monoclonal antibodies or other biological agents showed significant efficacy compared to placebo, but the efficacy was partial and no treatment was always effective [124].
- (iii) there are side effects that limit their use. For example, in the treatment of inflammatory bowel disease, the use of tumor necrosis factor α (TNF α) antagonists (some monoclonal antibodies, biological agents, and small-molecule inhibitors/modulators) increases the risk of serious infections because the treatment reduces the body’s defenses against infections [125], a risk confirmed in the treatment of ulcerative colitis in the aforementioned study [124]. As another example, in the comparison between the use of adalimumab and ten other monoclonal antibodies or other agents with biological effects in the treatment of psoriasis, adalimumab, the reference treatment, showed a frequency for all adverse events of 614/1000 patient-years, while the other antibodies and drugs had an incidence that was sometimes lower and sometimes higher, but never negligible, even for the incidence of malignant neoplasms [126].

A different approach is to develop and use substances that mimic those produced by helminths to slow down the immune defenses and consequently to prevent or slow down the onset and course of autoimmune diseases. Particularly interesting and well-documented is the use of phosphorylcholinated peptides, such as tuftsin-phosphorylcholine, already being tested for various autoimmune diseases and with stimulating prospects [127–130]. The potential advantage of this approach is that of being able to take advantage of the immunomodulatory effects of the helminths without their reintroduction in the organism.

Another example of this approach is the use of SjDX5-53, a small 3 kDa peptide obtained from egg extracts of schistosome, which promoted the production of regulatory T cells that can slow down the development of autoimmune diseases [131].

Other types of therapy for autoimmune diseases, currently in the experimental phase, propose the use of Janus kinase inhibitors [132] or CAR T cells [133,134].

A more drastic approach is the use of hematopoietic stem cell transplantation to achieve the reset of immunological memory and its profound renewal [135]. This type of therapy is increasingly used for severe cases of autoimmune diseases that do not respond to other therapies, but here too there are the problems of costs and risks intrinsic to this radical therapeutic approach [136].

Personalization of treatment is essential, whether conventional drugs, monoclonal antibodies or other therapies are used. Unfortunately, there is no definitive solution, as many variables (e.g., sex/gender, previous drug treatments, comorbidities and polypharmacy) play an important role and are often interrelated. Several biomarkers are now available, such as autoantibodies, which can be monitored to help prevent treatment failure and guide the clinician when a change in therapy is necessary, and pharmacogenetic analysis based on the identification of genetic polymorphisms that can affect both the efficacy and safety of drugs [137]. The personalization of treatment can be of great help in identifying patients at high risk of treatment failure and in choosing the treatment that is expected to have the highest probability of success, while also having a significant impact in terms of containing healthcare expenditure.

However, to summarize the current state of insufficient treatment of autoimmune diseases, it is useful to recall what was highlighted in two authoritative reviews: “In general, current immune-modulatory drugs used in the treatment of autoimmune diseases are broadly acting, non-disease specific, and, consequently, associated with side effects such as infection and malignant disease. Furthermore, it is clear that the majority of patients are not responding optimally, if at all, to these therapies” [138]; “Current approved therapeutic interventions for autoimmune diseases are mainly non-specific immunomodulators and may cause broad immunosuppression that leads to serious adverse effects.” [139].

4.2. Measures Aimed at Preventing the Onset and Worsening of Autoimmune Diseases

Epidemiological data suggest that multiple sclerosis and other autoimmune and immune-mediated diseases are significantly less common in subjects that are helminth carriers. In murine models of colitis, multiple sclerosis, T1D, and asthma, mice with helminth infection show protection from these diseases, likely due to the down-modulation of inflammatory responses induced by the presence of helminths. This evidence has sparked interest in investigating the therapeutic potential of helminth infections induced under controlled conditions for the treatment of patients with autoimmune diseases [140].

So, there are increasing efforts to combat autoimmune diseases by using non-stable helminth infections (helminth therapy) [141–145].

This approach is currently based on several assumptions that are not necessarily correct; i.e., (i) helminth infection is always something with negative health consequences; (ii) consequently, the use of helminths must be transitory and the helminths used must be of

species that cannot permanently establish themselves in treated individuals; (iii) helminthic therapy is acceptable in subjects with full-blown disease and therefore with symptoms that justify its use and the risks of the first assumption. Furthermore, in compliance with the last criterion, therapy is generally delayed. These limitations explain, at least in part, the results that are not always positive or clear.

Another approach is to delve deeper into the biochemical mechanisms by which helminths can slow down and modulate host immunological reactions [146] and from this knowledge to obtain drugs that have similar effects. This different approach allows us to overcome resistance arising from the use of macroparasites, as they are widely considered merely harmful species. However, there are other difficulties:

- it is necessary to develop drugs that are currently unavailable;
- it is necessary to determine to what extent they reproduce the beneficial immunotolerance effects naturally induced by macroparasites;
- it may be difficult to faithfully mimic the immunomodulatory effects of the natural infection by macroparasites;
- the tolerability and possible side effects of such drugs must also be assessed;
- lastly, and not least, the costs associated with their development and large-scale use must also be assessed.

Another argument that could easily lend itself to contradictory evaluations is that the development and use of this category of drugs, precisely because they require high costs for development and use, would stimulate significant investment by the pharmaceutical industry and also scientific research and employment in this field. However, the main objection is that this category of drugs does not address the root cause of autoimmune diseases, namely the absence of macroparasites with their beneficial effects in suppressing and modulating the immune system.

For helminthic therapy, some concepts, which are a direct derivation from what was discussed before, should be considered:

- (1) An autoimmune disease is not a disease without a cause. Evidence suggests that autoimmune diseases have, in most cases, as primary cause the eradication of macroparasites, which is part of a severe alteration of the human holobiont;
- (2) Therefore, it is rational to prevent the alteration of the holobiont by avoiding the eradication of the macroparasites or by a new infection with macroparasites;
- (3) If the eradication of the macroparasites has already taken place, the alteration of the holobiont must be corrected as best and soon as possible by reinserting the helminths;
- (4) This should be achieved by reintroducing macroparasites to which our species has long adapted (e.g., *Enterobius vermicularis*, pinworm; *Ascaris lumbricoides*, roundworm). It should not be attempted using parasites for which adaptation is nonexistent or incomplete (e.g., parasites adapted to other species—as *Thichuris suis*, the pig whipworm, and *Hymenolepis diminuta*, the rat tapeworm cysticerci—or parasites common in tropical environments for which populations living for millennia in other habitats have little or no evolutionary experience—as *Necator americanus*). Reinfection with macroparasites does not exclude the possibility that, if necessary, e.g., because they are poorly tolerated or cause problems, they can be limited in their proliferation or eradicated through the use of dewormers;
- (5) Reintegration of macroparasites should occur as early as possible in life when the immune system is developing. Contacts between host and parasites occur under evolutionarily “natural” conditions at an early age, and it is by no means guaranteed that contact at later (not “normal”) ages will lead to a complete correction of the possible abnormal development of the immune system.

The methods for combating or preventing autoimmune diseases, both the methods already available and used, and those potential or to be developed, are summarized in Figure 1. The methods under heading (3) include merely symptomatic therapies (and—not reported—palliative measures). The methods summarized under headings (2) and (2') include therapies—already available or to be developed/expanded—that act on the pathogenic mechanisms. Finally, the methods under heading (1) appear to be the only ones that can effectively prevent autoimmune diseases by applying a simple and banal rule of evolutionary medicine: if a disease is caused by an alteration of the ecological niche, the restoration of the original ecological niche is the priority. This prevents the onset of the disease and, if more or less irreversible alterations have not occurred, can also contribute significantly to a better course or even to the cure of the disease.

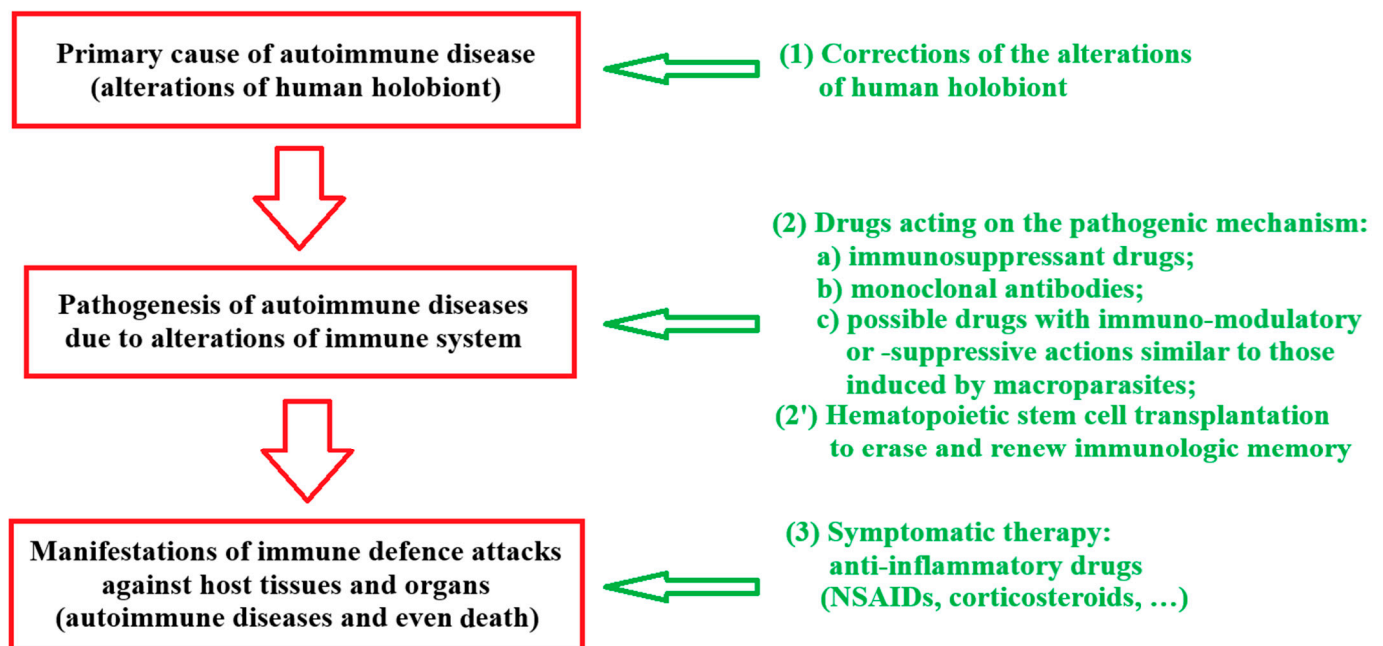


Figure 1. The three categories of measures to combat autoimmune diseases: (1) Correction of the ecological niche alteration that causes the disease. This type of measures can also be useful for slowing or curing the full-blown disease; (2) and (2') Some therapies acting on the pathogenic mechanism; (3) Symptomatic therapies.

5. Conclusions

The category of diseases described by the term autoimmune diseases has a high and growing impact due to the number of patients affected, the severity of many of these diseases, and the growing economic and social costs.

Currently, the therapeutic measures available and adopted curb this growing burden only partially. Considering the economic cost alone, the related economic burden appears growing and increasingly unsustainable, even for developed economies.

Therefore, it seems useful to move from the current strategy of treating cases with clinical evidence to a more rational strategy for preventing these diseases.

As evidence indicates that the primary cause is an alteration of the ecological niche to which we are adapted, a rational approach is to correct the alteration at the root of this category of diseases.

However, a radical shift in how we conceive of our biological nature and, consequently, the strategic directions of medicine is essential, moving from current medicine, which is in general pre-Darwinian, to a medicine that takes due account of the principles of natural evolution [1].

Two concepts become indispensable for this radical shift.

The first is that each human being is not an isolated biological entity but merely the main component of a complex ecosystem, the holobiont, which includes a large number of species, including macroparasites.

The second concept is that diseases, whether mild or even serious and fatal, can result from alterations of our holobiont. Treating only the manifestations of these diseases is an irrational and often unhelpful approach to addressing them. A rational approach to the prevention and even treatment of these diseases must focus on restoring our holobiont to its original state.

The organisms that constitute our holobiont, which have coexisted and coevolved with our species since long before the very birth of our species, must be recognized as cohabitants that, in some cases, can cause disease, but are often benevolent cohabitants or even necessary components for our health. If we have full knowledge and awareness of this reality, we will be able to rationally and effectively address the pathological conditions that arise from alterations to our holobiont.

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