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## The autoimmunologist: geoepidemiology, a new center of gravity, and prime time for autoimmunity

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### ABSTRACT

There are currently over 100 human diseases that are considered to be autoimmune or chronic inflammatory affecting 5–10% of the world population and spanning through all medical specialties. As a result, health care costs are enormous and the clinical management is often challenging, particularly considering the comorbidity rates and the multi-organ involvement of each condition. We herein propose the creation of a new specialist, coined the autoimmunologist, to overcome the current limitations in the diagnostic process and clinical follow-up of patients with autoimmune diseases. More importantly, we also propose the creation of regional centers of excellence in autoimmunity where clinical research and management, as well as basic research may be united and interact in ideal synergy to ultimately create real translational research and provide better health care.

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There are over 10 textbooks of physiology published since 2005 and currently in use in medical schools throughout Europe and North America and there are probably a similar number used in Asia and South America. Indeed, physiology is the breathe of medicine and is as much a requirement in the curricula of medical schools in 2008 as it was in 1908. All these texts include chapters on the circulatory, respiratory, and nervous systems, along with the latest advances in cell biology, yet there is not a single chapter on the immune system in any of them, with the possible exception of descriptions of the lymphatic organs. Quite strikingly, if one reviews any of the several dozens of textbooks of medicine, whether in family practice, surgery, orthopedics, or internal medicine, the term “immunology” is found throughout multiple areas of these specialties.

The history of immunology as a discipline per se can be traced back to the spectrum of infectious diseases and allergy. It was not until later that the conceptual revolution began in defining the nature of tolerance and the distinction between self and non-self thanks to the Nobel laureate Paul Ehrlich. Ehrlich became famous not so much for his contributions in autoimmunity, but rather because he coined “The Horror Autotoxicus” stating that an immune

response against one’s own body elements would necessarily lead to death; the concept of autoimmunity can be traced back to these years [1,2]. Following the 1947 discovery of LE cells and later of serum antinuclear antibodies (ANA), it became clear that there are not only multiple autoimmune diseases, but also that autoantibodies are more numerous than autoimmune diseases. Our knowledge on autoimmunity has paralleled the fast pace of discovery for new diagnostic tools [3] and we are currently in the era of microarrays to diagnose and ideally predict autoimmunity [4,5].

For several decades now the rheumatologist and clinical immunologist were the only clinicians to follow patients with autoimmune diseases, which were often lumped under the vague term of ‘collagen vascular pathology’. In earlier years, autoimmune diseases were considered rare and the appearance of autoantibodies was often considered pathognomonic until the dissection of serum ANA drastically changed the scenario. The increased serological sophistication demonstrated that autoantibodies were detected also in a fraction of otherwise healthy subjects without developing clinically overt autoimmunity during follow-up [6,7] and in some cases autoreactivities occurred naturally [8,9]. In this latter case, autoantibodies may further provide new links to unsuspected comorbidities [10]. Similarly, it became clear that ANA subtypes provided clues not only to clinical correlations but also to the etiology of autoimmunity.

Autoimmune diseases are believed to cumulatively affect 5–10% of the general population and are a significant cause of morbidity and mortality worldwide. The classification of a clinical condition

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**Table 1**  
The geoepidemiology and pathogenesis of human autoimmune diseases

	Autoimmune pathogenesis	Tissue specific/systemic	Autoantigen(s)	Age of onset	Prevalence	Yearly incidence	Male/female ratio	Monozygotic twin concordance	Geoepidemiology/ethnicity	Reference
Acute disseminated encephalomyelitis	Accepted	Myelin	Myelin-basic protein	Prepuberal (>3)	–	0.4/10 <sup>5</sup> (in <20 yo)	1/1	–	Unknown	[53]
Addison's disease	Accepted	Adrenocortical gland	21-Hydroxylase (CYP21)	15–45	1–14/10 <sup>5</sup>	0.6–4/10 <sup>5</sup>	1/0.8–2.4	Discordant pair	Unknown	[54]
Ankylosing spondylitis	Accepted	Spine	Collagen type II, proteoglycan	<30	1–14/10 <sup>5</sup>	0.5–14/10 <sup>5</sup>	2/1	0.65	↑ Northern countries	[55]
Antiphospholipid antibody syndrome	Accepted	Platelets	Cardiolipin, β2-glycoprotein I (B2-GPI)	30–40	1% (aPL)	0.4% (thrombosis in aPL+)	1/5	Clinically discordant pair	↑ Middle-Eastern Africa	[56]
Autoimmune hemolytic anemia	Accepted	Red blood cells	Rh antigens	>50	–	1–3/10 <sup>5</sup>	–	–	Unknown	[57]
Autoimmune chronic hepatitis	Accepted	Liver	Actin, asialoglycoprotein receptor, cytochrome P450 2D6 (CYP2D6), F-actin	<40 (T1, T3), 2–14 (T2)	0.4/10 <sup>5</sup>	0.7/10 <sup>5</sup>	1/7	–	= Worldwide	[58]
Bullous pemphigoid	Accepted	Derma	BP180, BP230	60–80	–	0.1–4.3/10 <sup>5</sup>	1/1	–	↑ Mediterranean, Jewish	[59]
Celiac disease	Accepted	Small bowel	Tissue transglutaminase	Childhood	0.3–5%	4–15/10 <sup>5</sup>	1/1	0.75–0.83	↑ North Africa, Middle East	[60]
Crohn's disease	Suspected	Bowel	Desmin, <i>Saccharomyces cerevisiae</i> , tubulin β isoform 5?	15–30, 60–80	8–200/10 <sup>5</sup>	2–10/10 <sup>5</sup>	1.2/1	0.04	↑ Northern countries	[61]
Giant cell arteritis	Accepted	Large arteries	Endothelial cells	>50	1.5/10 <sup>5</sup>	15–35/10 <sup>5</sup>	1/2.5	Concordant pair	↑ Northern Europe	[62]
Goodpasture's syndrome	Accepted	Kidney and lung	Collagen type IV-α3-chain	45	0.1/10 <sup>5</sup>	–	–	–	Unknown	[63]
Graves' disease	Accepted	Thyroid	Thyrotropin receptor, sodium iodide symporter	40–60	1.1%	14/10 <sup>5</sup>	1/7	0.17–0.60	Iodine-related	[64]
Guillain-Barre' syndrome	Accepted	Myelin	GM gangliosides	–	–	1.5/10 <sup>5</sup>	1.25/1	–	↓ Arabs	[65]
Hashimoto's disease	Accepted	Thyroid	Thyroid peroxidase, thyroglobulin	50–60	3–4%	22/10 <sup>5</sup>	1/5–18	0.55	Unknown	[66]
Idiopathic thrombocytopenic purpura	Accepted	Platelets	Glycoprotein IIb/IIIg and Ib/IX	–	1.6–6.6/10 <sup>5</sup>	–	1/3	–	Unknown	[67]
Multiple sclerosis	Accepted	CNS	Myelin-basic protein, myelin oligodendrocyte glycoprotein (MOG)	25–45	58/10 <sup>5</sup>	3/10 <sup>5</sup>	1/2	0.25–0.31	↑ Northern Europe, ↓ Asia	[68]
Myasthenia gravis	Accepted	Neuromuscular plaque	Acetylcholine receptor	<40, 50–60	5–20/10 <sup>5</sup>	0.4/10 <sup>5</sup>	1/3	44%	↑ Western countries	[65]
Myositis	Accepted	Derma and muscle	DNA-dependent nucleoside-stimulated ATPase, aminoacyl-tRNA synthetase, signal recognition protein (SRP54)	5–15, 45–65	0.5–5/10 <sup>5</sup>	1–2/10 <sup>5</sup>	1/2	Concordant pair	↑ Western Australia	[65]
Pemphigus vulgaris	Accepted	Derma	Desmoglein 3	40–60	–	0.1/10 <sup>5</sup>	1/1	–	↑ Northern Africa	[59]
Pernicious anemia	Accepted	Gastric mucosa	Intrinsic factor type 1	60–70	151/10 <sup>5</sup>	–	1/2	–	↑ African-Americans, Latin-Americans	[69]
Polymyalgia rheumatica	Suspected	Musculoskeletal	Unknown	>50	751/10 <sup>5</sup>	13–110/10 <sup>5</sup>	1/1.7	–	↑ Northern Europe	[70]
Primary biliary cirrhosis	Accepted	Bile ducts	Pyruvate dehydrogenase complex-E2 (PDC-E2)	50–60	40/10 <sup>5</sup>	1–49/10 <sup>5</sup>	1/10	0.63	↑ Northern Europe, Northern US	[71]
Primary sclerosing cholangitis	Suspected	Bile ducts	Tubulin β isoform 5	40	3.9–10/10 <sup>5</sup>	0.4/10 <sup>5</sup>	1.5/1	Concordant pair	↑ Northern Europe	[72]
Primary systemic vasculitis	Accepted	Small and medium vessels	Proteinase-3, myeloperoxidase	45–55 (F), 55–65 (M)	10–53/10 <sup>5</sup>	1–10/10 <sup>5</sup>	1/1	–	↑ Rural areas	[62]
Rheumatoid arthritis	Accepted	Articulation	Rheumatoid factor, keratin, CCP, collagen, fibronectin	45–55	1%	41/10 <sup>5</sup>	1/2	0.12–0.20	↑ Native Americans	[73]

Rheumatic fever	Accepted	Joints, endocardium	Cardiac myosin	5–18	0.1–2%	8–51/10 <sup>5</sup>	1/1	-	1 Developing countries	[74]
Sarcoidosis	Suspected	Systemic	Unknown persistent antigen	20–50	10–64/10 <sup>5</sup>	1/10 <sup>5</sup>	1/1–2	0.15	↑ African-Americans	[75]
Sjogren's syndrome	Accepted	Salivary and lacrimal glands	La phosphoprotein (La 55-B), golgin (95, 97, 160, 180)	40–50	0.1–3%	4/10 <sup>5</sup>	1/9	Concordant pair	Unknown	[76]
Systemic lupus erythematosus	Accepted	Systemic	Cardiolipin, carbonic anhydrase II, collagen, RNA polymerase I–III (RNP), fibronectin, golgin (95, 97, 160, 180), C1q, histone	30–50	6–24/10 <sup>5</sup>	4–7/10 <sup>5</sup>	1/9	0.24	↑ Africa, Caribbean, Far East	[77]
Systemic sclerosis	Accepted	Systemic	H2A–H2B-DNA RNA polymerase I–III (RNP), fibrillarlin, topoisomerase-1 (Sci-70)	35–56	4–12/10 <sup>5</sup>	0.2–12/10 <sup>5</sup>	1/5	0.04	↑ African-Americans	[78]
Type I diabetes mellitus	Accepted	Pancreas β-islets	Insulin receptor, glutamate decarboxylase (GAD65), IA-2 (ICA512), insulin	6–13	192/10 <sup>5</sup>	12/10 <sup>5</sup>	1/1	0.20–0.70	↑ Northern Europe, ↓ Asia, African-Americans, Hispanic-Americans	[79]
Ulcerative colitis	Accepted	Colon	Desmin, <i>Sarcditaromyces cerevisiae</i> , tubulin β isoform 5?	15–30, 60–80	2–10/10 <sup>5</sup>	21–240/10 <sup>5</sup>	1/1	0	↑ Northern countries	[61]
Vitiligo	Suspected	Melanocytes	SOX-10, tyrosinase	60	0.1–2%	0.1–8.8%	1/1	0.23	↑ Asia	[59]

For a wide series of conditions available data are illustrated for age of onset, prevalence/incidence rates, sex ratios, and monozygotic twin concordance rates. Furthermore, we report the evidence suggested in the literature for epidemiological or ethnic differences in disease susceptibility or incidence; these may support the existence of genetic or environmental bases. Please note that multiple sources were used to complete this overview but one representative citation is included for each condition.

as autoimmune poses several dilemmas. As a result, over 100 proposed conditions can be coined as putatively autoimmune or chronic inflammatory, as illustrated in Table 1; their incidence and prevalence rates vary widely while a genetic component [11] and the presence of a sex imbalance [12,13] are among factors characterizing several conditions. The economic burden of autoimmune diseases is enormous, particularly based on their geographical pattern of incidence (i.e. geoepidemiology). The National Institutes of Health estimate that over 23 million US residents have an autoimmune disease accounting for yearly direct costs of approximately \$100 billion. As a comparison, we should note that direct costs related to cancer and vascular diseases are \$57 and \$200 billion, respectively. Estimated costs for each patient and extrapolations of total yearly costs in the United States are of several billions, as illustrated in Table 2. These high costs have several causes, including the prevalence comparable to heart diseases, the frequent multi-organ involvement and resulting disability, the high comorbidity rate [14], and the increasing costs of medical treatments. Overall expenditure on medications for arthritis has more than doubled just in the last years (between 1998 and 2003) [15] while even out-of-pocket medical care expenses for these patients increased by over 50% during the same time period [16]. We should also note that costs indirectly caused by autoimmune diseases, as in the case of reproductive [17,18] or psychological [19,20] issues, cannot be accounted for in current estimates. Indeed, the emergence during the past decade of biologics and hematopoietic stem cell transplants has dramatically changed the clinical picture of autoimmune diseases [21,22] and future developments are expected with new treatments based on T regulatory cells [23,24] or gene manipulation [25,26]. In the case of biologics, data supporting their use in autoimmune diseases provided the proof of principle that biologics could target specific molecules, as well represented by anti-CD20 [27–29]. The advent of biologics demonstrated that different autoimmune or chronic inflammatory diseases may share pathogenetic pathways [30,31], as in the case of antagonizing tumor necrosis factor (TNF- $\alpha$ ) [32] in Crohn's disease and rheumatoid arthritis [33,34]. The growing spectrum of conditions that can be treated with biologics has rapidly made these molecules the latest blockbusters in the pharmaceutical industry. The use of biologics requires special expertise in their administration for the possibility of short-and long-term adverse events [35] and additional issues such as dose escalation regimens [36]. In a complementary fashion, more accurate diagnostic measures (i.e. imaging facilities, autoantibodies) have recently become available for routine use [3]. Despite constituting a short-term economical challenge for their high costs, these new options share the potential to provide enormous long-term benefits particularly in younger patients for which an early diagnosis [7] or an effective treatment is now at hand [37].

With the increasing concerns on health care costs and the worldwide implementation of managed care systems, economic issues cannot be overlooked by health care providers (Table 2). It has been suggested that public and private health care providers should carefully evaluate the economic implications of coverage decisions [38]. Numerous studies [39] investigated the cost effectiveness of biologic agents in autoimmune disease and demonstrated that their prescription accounts for the largest proportion (54%) of the cumulative costs of autoimmunity therapies [38] while, when used as indicated, manifests a good cost effectiveness [40]. We are convinced that the economic scenario of new treatments will also be rapidly changing in the near future with the advent of other approaches [41].

Based on these observations, it should be now clear that the rheumatologist is no longer the only clinician treating patients with an autoimmune disease. Despite the current terms of

**Table 2**  
Annual direct costs per patient and estimated total costs in the United States for common autoimmune disorders

	Cost/patient/year (US\$)	Total costs/year (US\$ billions)	Reference
Rheumatoid arthritis	3600–13 300	22.15	[80]
Sjogren's syndrome	4250	10.3	[81]
Type 1 diabetes mellitus	12 140	7.1	[82]
Multiple sclerosis	14 810	5.4	[83]
Ulcerative colitis	13 260	3.2	[84]
Crohn's disease	19 740	3.2	[84,85]
Systemic lupus erythematosus	11 040–21 710	2.5	[86,87]
Psoriasis	1090	1.8	[88]
Ankylosing spondylitis	2540	1.2	[89]
Systemic vasculitis	13 090	1.0	[90]
Systemic sclerosis	8080	0.9	[91]
Guillain-Barre' syndrome	36 360	0.2	[92]

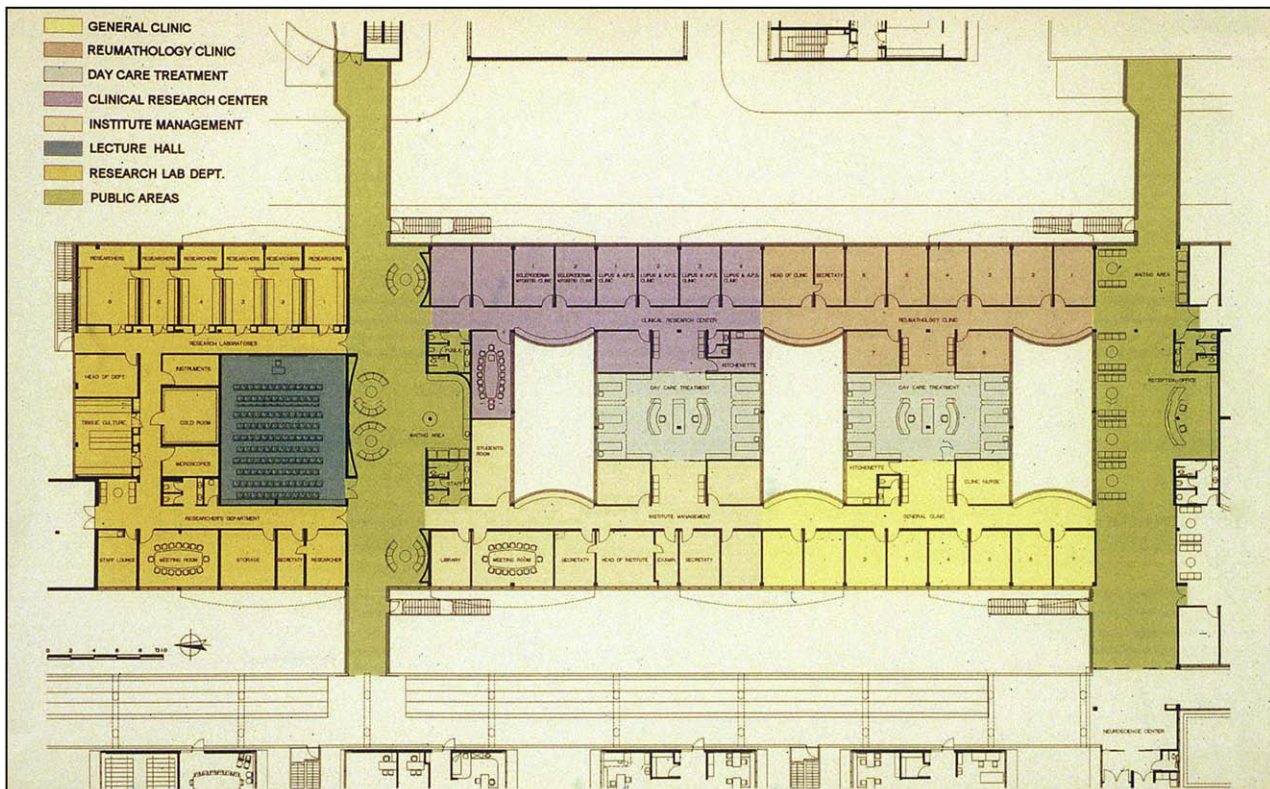
Amounts were adjusted by the Medical Care 2008 consumer price index and range midpoints were used for total costs' calculations.

“allergic and immunological diseases,” the allergist primarily follows patients with type I hypersensitivity disorders. The combination of clinical immunology and allergy is artificial in most countries with differences between the two specialties outnumbering similarities and physicians focusing on either specialty in their daily practice. This division is well represented at scientific meetings and in the literature where one can surmise that specific autoimmune or chronic inflammatory diseases (such as type I diabetes, multiple sclerosis, or inflammatory bowel diseases) are not being treated by allergists but rather by specialists trained in clinical immunology. We are convinced that this predominance of specialty crossovers represents the need, if not the existence de facto, of a new professional figure of specialist, perhaps better coined as *the autoimmunologist*. The autoimmunologist will have clinical training in one of the clinical subspecialties dealing with

autoimmunity (including, but not limited to rheumatology, allergy, neurology, hematology, hepatology, or endocrinology) but, more importantly, will also have spent a significant part of her/his training in basic or clinical immunologic research. Accordingly, the autoimmunologist will not only have spent 3 or more years in internal medicine or pediatric training, but preferably also 3 or more years in a subspecialty field, including a minimum of 1 year in autoimmune diseases.

Is there a need for one more specialty now that others tend to be joined, as in the case of hepatology and gastroenterology? We are convinced that there is a significant justification for introducing autoimmunology as a new specialization. Our knowledge on the etiopathogenesis of autoimmune diseases [42] supports the view that common features of different clinical entities outnumber their differences [43,44]. This is ideally represented during the past 5–10 years by the redefined cases of apoptosis [45], innate immunity involvement [46], B-cell abnormalities [47], or mother–fetus interactions [48]. As a consequence, the therapeutic approaches to different diseases are becoming increasingly similar, despite specific variations and regimen tailoring, as well represented by B-cell targeting [49,50].

We may expect that the specialists from the different disciplines involved in this thesis will object to our proposal being afraid that their ‘territory’ may diminish considerably. We are already witnessing the buds of neurologic sub-specialization with the creation of centers of expertise in multiple sclerosis. To overcome the potential limitations we are also proposing the creation of Centers of Excellence in Autoimmunity. In our view, these Centers will be regional and will include medical staff from diverse disciplines that will treat patients with any autoimmune or chronic inflammatory disease from multiple sclerosis to uveitis and inflammatory bowel disease. Ideally, the Center will include both clinical and basic science components (as illustrated in the blueprint in Fig. 1). The



**Fig. 1.** A blueprint proposal for a comprehensive Autoimmune Center. The building is composed of multi-disciplinary physician's rooms, two admitting units (one dedicated to therapies with biologics or other treatments, one to clinical evaluations of novel approaches), research and service laboratories.

clinical part will have two components, one being dedicated to the diagnosis and care of patients and including paramedical and nursing personnel with expertise in these fields to monitor treatment adverse effects. The second subunit will be devoted to clinical trials on new biological and non-biological therapies. This clinical subunit will be connected to the other components of the Center and will acquire experience in assessing the efficacy of the drugs, as well as in the identification of early and late adverse effects. A clinical service laboratory will perform all the necessary diagnostic analyses and we can foresee that in the near future this will be based on multiplex assays, thus justifying the use of a Center-dedicated serology service. A basic science unit will also be included in the Center and will be designed to allow physicians and basic researchers involved in laboratory activities to interact with the clinical component. We are convinced that the co-existence of these three units will provide the ideal milieu for an optimal quality of care for all autoimmune diseases and for a close link between the bench and the bedside.

We believe that the introduction of autoimmunologists heading multi-disciplinary teams within Centers of Excellence will lower the overall economic burden due to autoimmune diseases [44]. Indeed, patients will be diagnosed at early stages, thus enabling effective therapies to be initiated earlier in the course of the disease with expected better outcomes and tolerability [51]. As health care costs are considerably higher compared to primary care, governments worldwide encourage to shift care from hospitals to community-based services in all fields of medicine [52]. For this reason, the majority of patients attending the proposed Center of Excellence will utilize day care units thus minimizing the need for hospitalization.

Thanks to the contribution of extraordinary immunologists over the past decades, we have come a long way since Paul Ehrlich. The recent solution to some of the enigmas of autoimmunity has enabled us to see the common pathways of different diseases leading to a better understanding of their clinical expression and treatment. We submit that this knowledge should now lead to the novel establishment of a specialization and dedicated Centers of Excellence to provide cutting-edge research, care, and teaching within the wider scope of autoimmune diseases.

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