Published in final edited form as:
J Autoimmun. 2012 December ; 39(4): 253–258. doi:10.1016/j.jaut.2012.05.001.

Criteria for Environmentally Associated Autoimmune Diseases

Frederick W. Miller[a], **K. Michael Pollard**[b], **Christine G. Parks**[c], **Dori R. Germolec**[d], **Patrick S.C. Leung**[e], **Carlo Selmi**[e,f], **Michael C. Humble**[g], and **Noel R. Rose**[h]

Frederick W. Miller: millerf@mail.nih.gov

[a]Environmental Autoimmunity Group, National Institute of Environmental Health. Sciences (NIEHS), National Institutes of Health Clinical Research Center, NIH 10, Room 4-2352, 10 Center Drive, MSC 1301, Bethesda, MD 20892-1301, Phone: 301-451-6273, Fax: 301-451-5585

[b]Department of Molecular and Experimental Medicine, The Scripps Research Institute, La Jolla, CA

[c]Epidemiology Branch, NIEHS, Research Triangle Park, NC

[d]National Toxicology Program, NIEHS, Morrisville, NC

[e]Division of Rheumatology, Allergy, and Clinical Immunology, University of California, Davis, CA

[f]Autoimmunity and Metabolism Unit, IRCCS Istituto Clinico Humanitas, Milan, Italy

[g]Division of Extramural Research & Training, NIEHS, Research Triangle Park, NC

[h]John Hopkins Center for Autoimmune Disease Research, Bloomberg School of Public Health, Baltimore, MD

Abstract

Increasing evidence supports a role for the environment in the development of autoimmune diseases, as reviewed in the accompanying three papers from the National Institute of Environmental Health Sciences Expert Panel Workshop. An important unresolved issue, however, is the development of criteria for identifying autoimmune disease phenotypes for which the environment plays a causative role, herein referred to as environmentally associated autoimmune diseases. There are several different areas in which such criteria need to be developed, including: 1) identifying the necessary and sufficient data to define environmental risk factors for autoimmune diseases meeting current classification criteria; 2) establishing the existence of and criteria for new environmentally associated autoimmune disorders that do not meet current disease classification criteria; and 3) identifying in clinical practice specific environmental agents that induce autoimmune disease in individual patients. Here we discuss approaches that could be useful for developing criteria in these three areas, as well as factors that should be considered in evaluating the evidence for criteria that can distinguish individuals with such disorders from individuals without such disorders with high sensitivity and specificity. Current studies suggest that multiple lines of complementary evidence will be important and that in many cases there will be clinical, serologic, genetic, epigenetic, and/or other laboratory features that could be incorporated as criteria for environmentally associated autoimmune diseases to improve diagnosis and treatment and possibly allow for preventative strategies in the future.

Correspondence to: Frederick W. Miller, millerf@mail.nih.gov.

Keywords

autoimmune disease; environmental risk factors; criteria

1. Introduction

Autoimmune diseases (AID), which result from an individual's immune system attacking self-tissues, are relatively common diseases in the U.S., affecting 7–10% of the population [1]. Although there is some debate as to the definition of AID, the frequent presence of autoantibodies or specific criteria – including direct evidence from transfer of pathogenic antibodies or pathogenic T cells; indirect evidence based on reproduction of AID in experimental animals; and circumstantial evidence from clinical clues [2]–are often useful to identify these disorders. AID are complex disorders in which many independent lines of investigation suggest that the environment, acting on genetically susceptible individuals, plays a causative role [3]. Although there are at least 80 different diseases considered to have autoimmune etiologies, the bulk of research has focused primarily on a smaller group of the more common illnesses, and even fewer autoimmune conditions have been carefully studied with regards to environmental causes. Based on current knowledge and our limited capacity to phenotype AID, it appears that the same agent can induce very different autoimmune disorders, possibly due to different genetic backgrounds (i.e., silica associated rheumatoid arthritis, systemic sclerosis and systemic lupus erythematosus), and that multiple agents can produce a very similar clinical picture (i.e., different drugs leading to similar lupus-like syndromes) [4].

Classic examples of environmentally associated autoimmune diseases include medication-induced syndromes [5] and diseases such as the toxic oil syndrome [6] and the eosinophilia myalgia syndrome [7]. Nonetheless, important unresolved issues for developing classification criteria for identifying autoimmune diseases for which the environment plays a causative role, herein referred to as environmentally associated autoimmune diseases, include the extent and type of data needed to define these diseases. These questions apply to several different scenarios with varying requirements and implications: 1) identifying the necessary and sufficient data to define environmental risk factors for autoimmune diseases meeting current classification criteria; 2) criteria for identifying and defining new environmentally associated autoimmune diseases that do not meet current clinical classification criteria; and 3) guidelines for identifying specific environmental agents that induce autoimmune disease in individuals, typically in a clinical setting.

2. Identifying the necessary and sufficient data to define environmentally associated autoimmune diseases meeting current classification criteria

Defining the role of environmental exposures as risk factors for the development of autoimmune disease meeting current classification criteria has primarily relied on epidemiologic comparisons of disease incidence or prevalence in exposed and unexposed cohorts (see Miller et al., accompanying paper). Other approaches, however, including immunologic studies (see Selmi et al., accompanying paper) and investigations of animal models (see Briwa et al., accompanying paper), have added considerable supporting evidence for the role of the environment in the pathogenesis of autoimmune diseases. A challenge for this field has been to clarify how much evidence is required to define a given exposure as a risk factor for the development of disease. Traditional epidemiologic approaches have relied on a number of features of associations that were initially outlined by Hill in 1965 [8]. These include the strength of the association, consistency of findings among multiple studies, specificity, temporality, a biological gradient or dose-response

relationship, plausibility, coherence with current principles of biology and medicine, experiments showing that elimination of the suspect agent results in decreased disease incidence in the population, and analogy to similar conditions (Table 1).

Different levels of confidence can be considered in these assessments, following the Vallombrosa guidelines (http://www.healthandenvironment.org/infertility/vallombrosa_documents), as were applied in the accompanying paper on epidemiologic assessments (see Miller et al.). The specific exposure-disease associations were classified in the categories “confident,” “likely,” or “unlikely” regarding the contribution of the agent to the development of the disease using the Hill criteria and these guidelines, through which assessments were made in the “confident”, “likely” and “unlikely” categories. The “confident” category includes exposure-disease associations in which support came from several studies from different populations using different designs (e.g., cohort, case-control), relatively robust evidence of an overall association as identified by high-magnitude risks or the use of high-quality or established exposure assessment methods, evidence of an exposure-response gradient, and/or evidence of effect modification by disease subtype or genetic factors that supports biologic plausibility. The “likely” category includes collections of research studies: (a) similar to those in the “confident” category but missing important elements, such as clarification of the temporal association between exposure and onset of an autoimmune disease; (b) that contain more conflicting results; or (c) that were based on fewer studies. Associations were considered “unlikely” when a number of well-performed studies showed a convincing lack of association. Associations were considered to have insufficient supporting data when no studies were reported or when those reported were too limited in design or power to allow conclusions to be drawn. Although this may be a useful provisional approach, further experience with these and other approaches is needed to reach full consensus on guidelines in this area.

Generally, the success of any approach will depend on the inclusion of rigorous validated exposure assessment tools across studies in different populations and using different designs. While such assessment tools often exist, they have yet to become widely available to researchers. Methods may be further improved in the future using new data mining and other technologies to collect and integrate personal, commercial, health care, social science or geographical exposure data, and integrated with knowledge of relevant exposure pathways and modeling the biology of exposure-response mechanisms.

3. Identifying new environmentally associated autoimmune diseases that do not meet current classification criteria

A second scenario is the epidemic appearance of a new disease in association with an environmental exposure that had not been previously recognized. For example, the toxic oil syndrome occurred after 1,2-di-oleyl ester (DEPAP) and oleic anilide were added to rapeseed oil [6], and the eosinophilia myalgia syndrome occurred after ingestion of certain lots of L-tryptophan that were produced after a change in the manufacturing processes [9]. To facilitate the identification and description of new environmentally associated autoimmune diseases like those, an expert group has come to the consensus that a combination of primary and secondary elements (Table 2) that include many of the criteria listed above could be useful to define environmentally associated autoimmune diseases [10]. They also suggest a four-stage process, with appropriate nomenclature, including: (1) proposing the association; (2) testing the association; (3) defining specific criteria for the disorder; and (4) redefining the specific criteria for the disorder as additional information becomes available (Table 3).

4. Identifying specific environmental agents that induce autoimmune disease in individuals

Another situation involves the clinical evaluation of individual patients with apparent autoimmune diseases, including those meeting standard classification criteria or showing evidence of a known or new environmentally associated autoimmune syndrome. The reporting of individuals who developed an autoimmune disease after a specific exposure (challenge), which resolved after removal of that exposure (dechallenge), and recurred after reintroduction of the exposure (rechallenge) has added a large literature on the role of many agents, especially therapeutic drugs and biologics, in the induction of autoimmune diseases [11–13]. The classic example is those disorders where autoimmunity develops as a side-effect of medication use, for example drug-induced lupus [5]. These disorders, by definition, often do not meet standard classification criteria for idiopathic autoimmune diseases, which typically rule out medication-induced syndromes.

In this situation each clinician must make an individual judgment, based on many factors involved in the patient's case, as to whether an environmental agent might have caused the clinical syndrome in the patient and if the evidence and severity of the disease warrant discontinuation of the agent, and even reinstitution of the agent at a later time. Clinicians often conclude for individual patients that for a given drug a positive challenge (development of disease after exposure), followed by a dechallenge (improvement of disease after removing the agent), and then followed by rechallenge (redevelopment of the same disease after re-exposure), if it is appropriate to readminister the drug, is adequate evidence to define that agent as a causative one for the development of that specific autoimmune disease in that person [14]. One approach to defining these types of exposure-related diseases could be to consider challenge alone as fulfilling "possible" evidence, challenge followed by dechallenge as "probable" evidence, and the full trio of challenge, dechallenge, and rechallenge as providing "definitive" evidence for that specific environmentally associated autoimmune disease in that individual patient (Table 4).

In many patients with diseases induced by environmental factors, however, the agent cannot be removed or its effects may be long lasting or permanent, and so the dechallenge model is less relevant in identifying the "causal" environmental agent. Examples include exposures such as smoking or occupational exposure to silica dust. Smoking, for example, may contribute to an ongoing cycle of inflammation and self-reactivity initiated by citrullination [15], while silica effects may persist due to the body's inability to destroy or clear silica from the lung, associated lymph nodes, or other organs [16]. Literature on the role of ongoing exposures and associated autoimmune diseases is not well developed, but in many cases it seems reasonable for patients and clinicians to explore whether exposures can be avoided or reduced to ameliorate symptoms and prevent exacerbations. In certain settings this also could have legal implications, for example, with compensation for autoimmune diseases due to occupational exposures. The criteria for causation in such medical-legal scenarios follow a different standard [17] and are outside the scope of the present document, which applies to the medical and scientific approaches to developing classification criteria for environmentally associated autoimmune diseases.

Other than the established dechallenge/rechallenge model for identifying drug-induced autoimmune disorders, we see a need to develop and disseminate resources to guide the collection and interpretation of environmental and occupational data in clinical settings, to aid in evaluating potential environmental causes of autoimmune disease in a given patient. At best, clinical questions typically include smoking history and current occupation. Specific validated questionnaires are needed to target lifetime exposures to specific agents (e.g.,

silica), keeping in mind that exposures may occur across a wide variety of industries and occupations [18].

6. Overview and future approaches

Although many environmental agents have been associated with a variety of autoimmune diseases, there are no accepted criteria for diagnosis or classification that can distinguish the environmentally associated cases from other types of autoimmune disease. Beyond the difficulties in assessing environmental exposures, the rarity of many autoimmune diseases, the possible long latency of the effects of exposures on individual diseases, and their phenotypic heterogeneity have resulted in few defined environmentally associated autoimmune diseases to date. Furthermore, there has been a lack of consensus about how to best define these entities and what specific criteria are necessary and sufficient. Given the growing number of environmental agents of concern that might cause autoimmune diseases, the medical and legal implications of many of these diseases, and the potential to prevent some of these diseases if strong risk factors are identified, further work and consensus building are needed to develop criteria for defining and diagnosing environmentally associated autoimmune diseases.

To develop such criteria it will likely be optimal to use both epidemiologic, clinical and laboratory studies, including data on biomarkers of exposure [19] to test the hypothesis that an environmental exposure is associated with an autoimmune disorder [10]. At present there is a dearth of laboratory tools for identifying environmentally induced autoimmunity, largely due to the lack of studies linking biomarkers (biological response markers) specific for a particular environmental exposure to the expression of autoimmunity. This paucity of biomarkers stands in stark contrast to the relationship between clinical therapeutics and autoimmunity, where drugs have been linked to systemic autoimmunity through clinical features [20] and autoantibody specificity [21]. A significant factor in such success is the easy identification of drug-exposed patient populations.

Given the prevalence data for autoimmune diseases [1], the development of classification criteria could require large cohort studies and it will be difficult to perform population-based studies in this area. Biomarker approaches used in drug discovery and development [22] and toxicity profiling [23] may prove useful for formulating high-throughput screens for markers of exposure. Although the use of these technologies to identify biomarkers related to environmental exposure is a relatively new field of study, several avenues have been discussed [23–25]. Application of high-throughput assays to biomarker discovery in environmentally associated autoimmunity will require analysis of both cellular and humoral immune parameters. For example, autoantibodies are a hallmark of idiopathic autoimmune diseases, and specific autoantibodies are associated with specific phenoytpes [26]. Autoantibody profiles, i.e., combinations of autoantibodies, have also been used to characterize particular diseases [26], including drug-induced lupus [27]. Existing multiplex autoantibody arrays that employ large numbers of autoantigens [28–30] will be useful to determine whether specific environmental exposures are associated with particular autoantibody profiles.

Other high-throughput arrays exist to determine: profiles of blood cells and their secreted products [31]; cytokines, intracellular molecules, and cell surface markers [32]; and pathways of signal transduction [33]. Such a combination of assays would require only a small blood sample but could provide considerable coverage of the innate and adaptive immune responses in individuals with suspected environmentally induced autoimmunity. These assays, together with in vitro studies, could further define the cellular players and the possible mechanisms of the suspected environmental agents involved in the induction or

perpetuation of the autoimmune response. Environmental exposures can exacerbate underlying idiopathic autoimmunity and/or elicit an autoimmune response specific to a particular exposure [12,20]. Identifying different disease mechanisms might enable us to discriminate between exacerbation of idiopathic disease versus a response induced solely by exposure. This possibility can be explored using animal models susceptible to a particular disease (e.g., systemic lupus erythematosus) compared to related healthy strains [34]. Carefully planned animal studies should yield information on disease mechanisms and potential biomarkers for use in subsequent human surveillance studies.

As noted above, environmental factors may cause classically defined autoimmune diseases that cannot now be distinguished from currently defined “idiopathic autoimmune disease”. These, however, may be distinct and able to be distinguished by use of specific novel exposure-related or disease-related tools for assessing exposures and by applying new technologies relating to our increased understanding of mechanisms. For example, while silica-associated autoimmune diseases have not typically been distinguished from idiopathic forms of these diseases, a strong exposure history might help to distinguish a case of silica-associated disease. In other instances the clinical presentation and autoantibodies appear to differ in the environmentally associated cases compared to the current idiopathic cases. For example, common clinical features of drug-induced lupus include relatively mild myalgias and arthralgias, serositis, and other constitutional symptoms, with less frequent renal or central nervous system involvement than seen in idiopathic lupus [5]. Other commonly reported features of drug-induced lupus include a lower incidence in females, a higher incidence in older patients, the presence of IgG antibodies directed against the H2A.H2B-DNA subnucleosome complex, and less frequent anti-double-stranded DNA autoantibodies than seen in idiopathic lupus [35].

It is possible that factors in addition to the detailed clinical manifestations and autoantibodies, such as the dose and duration of exposure to the environmental agent, gender, concurrent illnesses, other concomitant exposures, or polymorphisms in the genes responsible for the metabolism or immune response to the agent [36] are important in determining whether an individual will develop disease [14,37], and a combination of these and other data may be useful to develop new criteria for autoimmune diseases, whether related to the environment or not (Table 5). This concept is an extension of the “pattern-based” approach, in which data from several separate sources were used by a committee of experts to develop and validate new reproducible and clinically sensible diagnostic criteria for the eosinophilia myalgia syndrome [38].

In the case of smoking-associated rheumatoid arthritis (RA), very strong associations have been reported for specific combinations of autoantibody type (particularly anti-citrullinated protein antibodies) and genotypes [39]. At the same time, most smokers do not develop RA and so more information is needed in susceptible subgroups–for example, family members of RA patients–to determine whether certain additional genotypes are associated with an increased susceptibility to developing smoking-related RA. In order to identify genetic susceptibility factors for environmentally associated autoimmune diseases, more studies are needed with sufficient statistical power (i.e., a large number of exposed patients), although the analysis of specific subphenotypes may allow for an improved ability to define genes from large genome-wide association studies. Most genetic differences reported to date are not substantial enough to be used to predict who will or will not develop disease after a given exposure. Nonetheless, future investigations should include large cohorts of subjects with environmentally associated autoimmune diseases to determine whether combinations of clinical features, autoantibodies, genetics, epigenetics, pathology, or other factors could be used together, to diagnose and eventually prevent environmentally associated autoimmune disease [14].

In summary, we have reviewed approaches for defining environmentally associated autoimmune diseases in three contexts: 1) identifying the necessary and sufficient data to define environmental risk factors for autoimmune diseases meeting current classification criteria; 2) establishing the existence of and criteria for new environmentally associated autoimmune disorders that do not meet current disease classification criteria; and 3) identifying specific environmental agents that induce autoimmune disease in individuals, typically in a clinical setting. We realize that additional efforts in all these areas are needed to achieve true consensus in this relatively undeveloped field and to define classification criteria that can distinguish environmentally associated autoimmune disease cases from others with high sensitivity and specificity. Although the focus of this paper is on autoimmune diseases, it is possible that similar approaches may be useful in developing criteria for many forms of environmentally associated disorders.

Acknowledgments

The authors gratefully acknowledge the expertise and input from Dr. Glinda Cooper. We also appreciate the useful discussions and suggestions and the critical comments of Drs. Mark Gourley and Ejaz Shamim.

This review was prepared in conjunction with the NIEHS Environmental Autoimmunity Conference, Durham, NC, September 7–8, 2010.

Support was provided in part by the intramural and extramural programs of the National Institute of Environmental Health Sciences, NIH.

Reference List

1. Cooper GS, Bynum ML, Somers EC. Recent insights in the epidemiology of autoimmune diseases: improved prevalence estimates and understanding of clustering of diseases. J Autoimmun. 2009; 33:197–207. [PubMed: 19819109]
2. Rose NR, Bona C. Defining criteria for autoimmune diseases (Witebsky's postulates revisited). Immunol Today. 1993; 14:426–30. [PubMed: 8216719]
3. Cooper, GS.; Miller, FW. Environmental influences on autoimmunity and autoimmune diseases. In: Luebke, R., editor. Immunotoxicology and Immunopharmacology. New York: CRC Press; 2007. p. 437-54.
4. WHO Task Group on Environmental Health Criteria. Principles and Methods forAssessing Autoimmunity Associated with Exposure to Chemicals. WHO; 2006. Environmental Health Criteria; p. 236p. 1-324.
5. Chang C, Gershwin ME. Drug-induced lupus erythematosus: incidence, management and prevention. Drug Saf. 2011; 34:357–74. [PubMed: 21513360]
6. Gelpi E, de la Paz MP, Terracini B, et al. The Spanish toxic oil syndrome 20 years after its onset: a multidisciplinary review of scientific knowledge. Environ Health Perspect. 2002; 110:457–64. [PubMed: 12003748]
7. Hertzman PA, Clauw DJ, Kaufman LD, et al. The eosinophilia-myalgia syndrome: status of 205 patients and results of treatment 2 years after onset. Ann Intern Med. 1995; 122:851–5. [PubMed: 7741371]
8. Hill AB. The environment and disease: Association or causation? Proc R Soc Med. 1965; 58:295–300. [PubMed: 14283879]
9. Kaufman, LD.; Gleich, GJ. Eosinophilia Myalgia Syndrome. In: Kaufman, LD.; Varga, J., editors. Rheumatic Diseases and the Environment. Arnold: 1999. p. 55-73.
10. Miller FW, Hess EV, Clauw DJ, et al. Approaches for identifying and defining environmentally associated rheumatic disorders. Arthritis Rheum. 2000; 43:243–9. [PubMed: 10693862]
11. Bannwarth B. Drug-induced musculoskeletal disorders. Drug Saf. 2007; 30:27–46. [PubMed: 17194169]
12. Pollard KM, Hultman P, Kono DH. Toxicology of Autoimmune Diseases. Chem Res Toxicol. 2010

13. Scherer K, Spoerl D, Bircher AJ. Adverse drug reactions to biological response modifiers. J Dtsch Dermatol Ges. 2010
14. Miller FW. Environmental agents and autoimmune diseases. Adv Exp Med Biol. 2011; 711:61–81. [PubMed: 21627043]
15. Klareskog L, Padyukov L, Alfredsson L. Smoking as a trigger for inflammatory rheumatic diseases. Curr Opin Rheumatol. 2007; 19:49–54. [PubMed: 17143096]
16. Otsuki T, Maeda M, Murakami S, et al. Immunological effects of silica and asbestos. Cell Mol Immunol. 2007; 4:261–8. [PubMed: 17764616]
17. Price JM, Gates GS. “Junk science” in the courtroom. Causes and effects ASAIO J. 1995; 41:139–42.
18. Parks CG, Cooper GS. Occupational exposures and risk of systemic lupus erythematosus. Autoimmunity. 2005; 38:497–506. [PubMed: 16373255]
19. Jayapal M, Bhattacharjee RN, Melendez AJ, et al. Environmental toxicogenomics: a post-genomic approach to analysing biological responses to environmental toxins. Int J Biochem Cell Biol. 2010; 42:230–40. [PubMed: 19836462]
20. Rubin RL. Drug-induced lupus. Toxicology. 2005; 209:135–47. [PubMed: 15767026]
21. Burlingame RW, Rubin RL. Drug-induced anti-histone autoantibodies display two patterns of reactivity with substructures of chromatin. J Clin Invest. 1991; 88:680–90. [PubMed: 1864977]
22. Bakhtiar R. Biomarkers in drug discovery and development. J Pharmacol Toxicol Methods. 2008; 57:85–91. [PubMed: 18024093]
23. Mahadevan B, Snyder RD, Waters MD, et al. Genetic toxicology in the 21st century: reflections and future directions. Environ Mol Mutagen. 2011; 52:339–54. [PubMed: 21538556]
24. Duramad P, Holland NT. Biomarkers of immunotoxicity for environmental and public health research. Int J Environ Res Public Health. 2011; 8:1388–401. [PubMed: 21655126]
25. Wetmore BA, Wambaugh JF, Ferguson SS, et al. Integration of Dosimetry, Exposure and High-Throughput Screening Data in Chemical Toxicity Assessment. Toxicol Sci. 2011
26. Tan EM. Antinuclear antibodies: diagnostic markers for autoimmune diseases and probes for cell biology. Adv Immunol. 1989; 44:93–151. [PubMed: 2646863]
27. Rubin RL, Burlingame RW, Arnott JE, et al. IgG but not other classes of anti-[(H2A-H2B)-DNA] is an early sign of procainamide-induced lupus. J Immunol. 1995; 154:2483–93. [PubMed: 7868914]
28. Balboni I, Limb C, Tenenbaum JD, et al. Evaluation of microarray surfaces and arraying parameters for autoantibody profiling. Proteomics. 2008; 8:3443–9. [PubMed: 18752214]
29. Graham KL, Robinson WH, Steinman L, et al. High-throughput methods for measuring autoantibodies in systemic lupus erythematosus and other autoimmune diseases. Autoimmunity. 2004; 37:269–72. [PubMed: 15518040]
30. Tabakman SM, Lau L, Robinson JT, et al. Plasmonic substrates for multiplexed protein microarrays with femtomolar sensitivity and broad dynamic range. Nat Commun. 2011; 2:466. [PubMed: 21915108]
31. Utz PJ. Protein arrays for studying blood cells and their secreted products. Immunol Rev. 2005; 204:264–82. [PubMed: 15790364]
32. Kattah MG, Coller J, Cheung RK, et al. HIT: a versatile proteomics platform for multianalyte phenotyping of cytokines, intracellular proteins and surface molecules. Nat Med. 2008; 14:1284–9. [PubMed: 18849997]
33. Chan SM, Ermann J, Su L, et al. Protein microarrays for multiplex analysis of signal transduction pathways. Nat Med. 2004; 10:1390–6. [PubMed: 15558056]
34. Pollard KM, Pearson DL, Hultman P, et al. Lupus-prone mice as models to study xenobiotic-induced acceleration of systemic autoimmunity. Environ Health Perspect. 1999; 107 (Suppl 5): 729–35. [PubMed: 10502538]
35. Chang C, Gershwin ME. Drugs and autoimmunity--a contemporary review and mechanistic approach. J Autoimmun. 2010; 34:J266–J275. [PubMed: 20015613]
36. Okada S, Kamb ML, Pandey JP, et al. Immunogenetic risk and protective factors for L-tryptophan associated eosinophilia-myalgia syndrome. arth and rheum. 2009 in press.

37. Miller, FW. Genetics of environmentally-associated rheumatic disease. In: Kaufman, LD.; Varga, J., editors. Rheumatic Diseases and the Environment. London: Arnold Publishers; 1999. p. 33-45.
38. Hertzman PA, Clauw DJ, Duffy J, et al. Rigorous new approach to constructing a gold standard for validating new diagnostic criteria, as exemplified by the eosinophilia-myalgia syndrome. Arch Intern Med. 2001; 161:2301–6. [PubMed: 11606145]
39. Kallberg H, Ding B, Padyukov L, et al. Smoking is a major preventable risk factor for rheumatoid arthritis: estimations of risks after various exposures to cigarette smoke. Ann Rheum Dis. 2011; 70:508–11. [PubMed: 21149499]
40. Portanova JP, Arndt RE, Tan EM, et al. Anti-histone antibodies in idiopathic and drug-induced lupus recognize distinct intrahistone regions. J Immunol. 1987; 138:446–51. [PubMed: 2432124]
41. Strickland FM, Richardson BC. Epigenetics in human autoimmunity. Epigenetics in autoimmunity-DNA methylation in systemic lupus erythematosus and beyond. Autoimmunity 2008. May 15.2012 41:278–86.

Research highlights

- We discuss criteria for environmentally associated autoimmune diseases in 3 areas
- One area is autoimmune diseases meeting current classification criteria
- Another area is establishing the existence of and criteria for new disorders
- A third area is criteria for individual patients in clinical practice

Table 1

Epidemiologic Approaches for the Identification of Environmental Exposures and Development of Autoimmune Diseases Meeting Current Classification Criteria[a]

Approach	Elements to Consider	Comments
Defining risk factors for autoimmune diseases meeting current classification criteria through epidemiology	Strength of association – Is the level of difference noted between risk of disease in exposed and unexposed populations strong?	Consensus on the number and types of the elements needed for confident, likely or unlikely associations is yet to be determined
	Consistency – How similar are results from multiple studies?	
	Specificity – How unique is the given association?	
	Temporality – Does the exposure precede the disease?	
	Biological gradient – Is there a dose-response relationship?	
	Plausibility – Is there a biologic rationale?	
	Coherence – Are the findings consistent with current principles of biology and medicine?	
	Experiment – Does elimination of the suspect agent result in decreased disease in the population?	
	Analogy – Are there similar findings in related areas?	

[a]Modified from [8]

Table 2

Approaches for the Identification of Environmental Exposures and Development of New Autoimmune Diseases not Meeting Current Classification Criteria[a]

Approach	Elements to Consider	Comments
Primary elements	Temporal association – Did the exposure precede the disease?	A consensus of the authors was that to publish findings of a possible causal relationship between an environmental exposure and a new clinical syndrome, at least 4 of all 8 attribution elements and at least 3 of the 5 primary elements should be present. The 3 primary attribution elements should include temporal association, lack of likely alternative explanations, and at least 1 of the other primary elements—evidence for dechallenge, rechallenge, or biologic plau sibility
	Lack of likely alternative explanations – Have all other explanations been explored and eliminated?	
	Dechallenge – Did the defining aspects of the disorder disappear or improve when the exposure and all of its effects were removed?	
	Rechallenge – Did the disorder reappear or worsen when the exposure was reintroduced?	
	Biologic plausibility – Is the disorder plausible based upon the known in vivo and/or in vitro effects of the exposure?	
Secondary elements	Analogy – Are there prior published or unpublished reports of a similar disorder developing after the exposure in question or after a similar exposure?	
	Dose responsiveness – Is there any evidence that the dose or extent of the exposure is related to the likelihood of developing the disorder or to the disorder's severity?	
	Specificity – Are the defining symptoms, signs, and laboratory features of the disorder the same as those seen in previous cases after exposure to the same environmental agent	

[a]Modified from [10]

Table 3

Proposed Stages for Identifying and Defining New Environmentally Associated Autoimmune Diseases[a]

Stage	Description	Proposed Nomenclature for the Syndrome (Example)
Stage 1 – Proposing the association	Case reports, defined by adequate criteria, propose a possible association of a specific clinical syndrome with a given exposure	Syndrome following exposure (rheumatoid arthritis following hepatitis B vaccination)
Stage 2 – Testing the association	After a number of such cases are reported, surveillance criteria are proposed and epidemiologic and laboratory studies test that hypothesis	Cardinal signs, symptoms, and labs but without knowing the putative exposure (eosinophilia myalgia syndrome)
Stage 3 – Defining criteria for the condition	If studies support the association, then specific preliminary classification and other criteria are defined for that specific environmental disease	Exposure-associated disorder (L-tryptophan-associated eosinophilia myalgia syndrome)
Stage 4 – Refining criteria for the condition	Criteria are reassessed and refined as necessary as additional data are obtained about the disease to confirm the association	Exposure-induced disorder (hydralazine-induced lupus-like disorder)

[a]Modified from [10] and [14]

Table 4

Approaches for the Identification of Environmental Exposures and Development of Autoimmune Disease in an Individual Patient[a]

Approach	Elements to Consider	Comments
Defining an environmental trigger for an autoimmune disease in an individual through clinical assessment	Challenge – Did the disorder appear in an appropriate timeframe after exposure and without likely alternative explanations?	No consensus on criteria, but "challenge" alone could be consider as possible criteria; "challenge and dechallenge" together could be considered criteria for a probable association; if "rechallenge" is also present this could be considered a definite association.
	Dechallenge – Did the defining aspects of the disorder disappear or improve when the exposure and all of its effects were removed?	
	Rechallenge – Did the disorder reappear or worsen when the exposure was reintroduced?	
	Assessing environmental/occupational exposures – what past exposures might have contributed to disease risk and what current or ongoing exposures may have been associated with disease risk or exacerbation?	Limitations are that the effects of many exposures cannot be removed, so in these cases dechallenge is not possible, and rechallenge may not be clinically appropriate.

[a] Adapted from [14]

Table 5

Examples of Possible Elements Important in Developing Specific Criteria for Environmentally Associated Autoimmune Diseases

Element	Description	Example [Reference]
Clinical features	Specific signs and symptoms that may differ in frequency in the environmental disease	Less frequent renal or central nervous system involvement in drug-induced lupus [5]
Laboratory findings	Routine laboratory testing, autoantibodies, or pathology that may differ in frequency in the environmental disease	Anti-histone autoantibodies are more frequent in drug-induced lupus [40]
Genetics and genomics	Different frequencies of polymorphisms in metabolizing enzymes and immune response genes in the environmental disease	HLA genes are risk or protective factors for development of L-tryptophan- associated eosinophiliamyalgia syndrome [36,37]
Epigenetics	Different modifications of genes in the environmental disease	Altered DNA methylation in drug-induced lupus [41]
Others - the dose and duration of exposure, gender, concurrent illnesses, other exposures, gene expression arrays, proteomic evaluations, cytokine arrays, etc.	Multiple variables should be studied and combined in novel ways to develop criteria that can distinguish with high sensitivity and specificity individuals likely to develop disease after a given exposure	Higher dose and older age were risk factors for development of eosinophilia myalgia syndrome after L- tryptophan [36]