

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/survophthal

History of ophthalmology

Autoimmune disease: Conceptual history and contributions of ocular immunology



Curtis E. Margo, MD, MPH^{a,b,*}, Lynn E. Harman, MD^b

^a Department of Pathology and Cell Biology, Morsani College of Medicine, University of South Florida, Tampa, Florida, USA

^b Department of Ophthalmology, Morsani College of Medicine, University of South Florida, Tampa, Florida, USA

ARTICLE INFO

Article history:

Received 7 December 2015

Received in revised form 13 April 2016

Accepted 21 April 2016

Available online 27 April 2016

Michael F. Marmor, Editor

Keywords:

autoimmune disease

autoimmunity

endophthalmitis phacoanaphylactica

immune privilege

immune tolerance

lens-induced uveitis

phacoanaphylaxis

sympathetic ophthalmia

ABSTRACT

Medical historians identify the mid-20th century as the time when the scientific and medical communities acknowledged the existence of autoimmune disease. Several conditions including sympathetic ophthalmia and endophthalmitis phacoanaphylactica, however, were proposed as autoimmune disorders much earlier. During the first half of the century, autoimmune disease was viewed as biologically implausible. Paul Ehrlich coined the term horror autotoxicus to emphasize that autoimmunity would contradict nature's aversion to self-injury. The discoveries of allergy and anaphylaxis were the first clues that the immune system was capable of self-harm. A major obstacle to comprehending the pathogenesis of autoimmunity was how the immune system distinguishes foreign from self, a process eventually understood in the context of immune tolerance. Investigators of sympathetic ophthalmia and endophthalmitis phacoanaphylactica were positioned to invalidate horror autotoxicus but lacked sufficiently convincing experimental and clinical evidence to accomplish the task. Seminal studies of chronic thyroiditis and a series of clinical laboratory breakthroughs led to the general acceptance of autoimmune disease in the 1950s. The travails encountered by ophthalmic investigators offer insights into the how medical ideas take shape. We review the contributions of ocular immunology to the conceptual development of autoimmune disease and explore the reasons why the concept caught on slowly.

© 2016 Elsevier Inc. All rights reserved.

"Currently the word 'allergy' does not have precise meaning. In fact it has so little meaning that it has been debauched to the point where it is used equally in referring to sensitivity to strawberries or mother-in-laws!" -In, *Fundamental of Immunology for Students of Medicine and Related Sciences*.^{95p153}

"The number of human diseases believed to be of autoimmune origin increased almost daily." -Noel R. Rose.⁶⁹

1. Introduction

For physicians trained within the last half century, the idea of autoimmune disease is as comfortable as infectious disease, but for clinicians and scientists before that time the notion that the immune system could without provocation inflict primary injury on its host was controversial. The vast majority of diseases now known to be autoimmune have existed since

Presented at the 29th Cogan Ophthalmic History Society Meeting, St. Louis, April 15–17, 2016.

* Corresponding author: Dr. Curtis E. Margo, MD, MPH, Department of Ophthalmology, University of South Florida, 12901 Bruce B. Downs Blvd., Box 21, Tampa, FL, USA.

E-mail address: cmargo@health.usf.edu (C.E. Margo).

0039-6257/\$ – see front matter © 2016 Elsevier Inc. All rights reserved.

<http://dx.doi.org/10.1016/j.survophthal.2016.04.006>

antiquity, but their pathogeneses have only recently rested on sound scientific footing.^{73,87} When initial observations at the turn of the 20th century suggested that the immune system might under certain circumstances react against “self” antigens, the idea of autoimmune disease was either rejected or ignored. It took another 50 years for the concept to gain general clinical recognition. This sluggish pace of development has been commented on by others but eludes simple explanation.^{11,49,69,80,82}

A comprehensive understanding of autoimmunity had to wait for knowledge of how immunologic discrimination of self is acquired, a process referred to as immune tolerance. Natural immune tolerance represents the normal state of immune unresponsiveness to self. By definition, manifest failure of this physiologic process results in autoimmune disease. Autoimmune disease encompasses a heterogeneous group of disorders that circumvent natural immune self-tolerance. The disorders invoke a variety of dysfunctional interactions that involve class I major histocompatibility complex molecules and their allelic variations, antigenic mimicry, abnormalities of immunoregulatory T cells, T cell-receptor genes, and idiotypic networks.^{46,72,86,87} Although the multiple pathways to autoimmune disease may seem overwhelming, the unifying feature is a gaffe somewhere within the system of immune homeostasis called immune tolerance.

Matters of autoimmunity are pervasive in ophthalmology. Ocular manifestations are common and often severe in many of the multisystem and organ-specific autoimmune diseases (Table 1).^{26,43,72} The eye can also be the primary target of the immune system (Table 2).^{29,30,33,61,77} We examine the conceptual evolution of autoimmunity, while focusing on the role that ocular immunology played in shaping that progression.

2. Era of uncertainty

2.1. *Horror autotoxicus*

The discoveries of immune hemolysis in 1898 and complement fixation in 1901 allowed a variety of fundamental hypotheses about the immune system to be tested in the laboratory. On hearing of these innovations, Paul Ehrlich (1854–1915) devised experimental studies with Julius Morgenroth (1871–1924) to determine how animals reacted to red blood cells of unrelated species and to their own. A key finding was that animals developed antibodies to the blood of other members of their species (isoantibodies) yet failed to develop antibodies to their own red blood cells.²⁰ The results confirmed Ehrlich’s belief that the purpose of the immune system was to defend the body from external threats. Ehrlich labeled the improbability of the immune system reacting to self-antigens as “horror autotoxicus,” a theory that would take on considerable authority in the ensuing decades.^{20,70,80,82}

Several years later, Julius Donath (1870–1950) and Karl Landsteiner (1868–1943) demonstrated a “lytic substance” in the blood of 3 patients with paroxysmal cold hemoglobinuria.¹⁶ When laboratory findings were examined in clinical context, paroxysmal cold hemoglobinuria had all the features of an autoimmune disease.⁸¹ Donath and

Landsteiner, however, did not fully grasp the implications of their discovery. They choose to refer to the lytic substance as a toxin or hemolysin—not an antibody and never promoted the condition as autoimmune.^{28,81,82}

By 1903, the stage was set for a battle of competing paradigms. Was autoimmunity biologically feasible or was it an improbable pathway for human disease? With increasing numbers of medical scientists trained in chemistry and immunology, the conflict could have been swift and decisive. It was anything but.^{49,69,71}

2.2. *The eclipsing concept of allergy*

The belief that the immune system could not react against self-antigens was so entrenched that scientists and clinicians essentially shunned terms such as autoimmunity or autoimmune disease until the middle of the 20th century (see Section 6.3). Yet by the 1920s, immunologists knew that the immune system had a dark side. It could inflict injury on its host in the form of allergy, the modern concept of which was introduced in 1906 by Clemens von Pirquet (1874–1929) based on research with Bela Schick (1877–1967) on serum sickness.^{35,67} The most cataclysmic expression of self-inflicted immune injury was called anaphylaxis by its discoverers Charles Richet (1850–1935) and Paul Portier (1866–1962).^{67,68,82} For nearly 4 decades, the basic premise of autoimmunity was expressed and often disguised in the language of allergy.

2.3. *Exploratory doldrums*

Scientists may have been reluctant to invest much time exploring the idea of autoimmunity given its doubtful existence. Relatively few laboratories maintained active research in the area.⁴⁹ Hashimoto described lymphocytic thyroiditis in 1912, but as with paroxysmal cold hemoglobinuria, this did not result in any sustained research into autoimmune mechanisms until midcentury.^{18,69} In retrospect, some basic science research during the first half of the century dealt with autoimmune processes, but was not reported in those terms, nor did they ignite much clinical interest. Using laboratory animals, for example, investigators were able to generate autoantibodies to spermatozoa and kidney proteins, and induce allergic encephalitis, but these laboratory models had no known human counterparts at the time and seemed to have limited clinical relevancy.^{44,49,82}

3. Suspicious ocular inflammations

Sympathetic ophthalmia and endophthalmitis phacoanaphylactica both generated considerable enthusiasm as possible autoimmune responses to ocular antigens at a time when medical immunology had little interest in the subject. (Although the term endophthalmitis phacoanaphylactica is presently disfavored, the name will be retained in this discussion for historical purposes.)

Download English Version:

<https://daneshyari.com/en/article/4032401>

Download Persian Version:

<https://daneshyari.com/article/4032401>

[Daneshyari.com](https://daneshyari.com)