The Geoepidemiology of Autoimmunity: Capsules from the 7th International Congress on Autoimmunity, Ljubljana, Slovenia, May 2010

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Between May 5 and 9, 2010 the 7th International Congress on Autoimmunity was held in Ljubljana, Slovenia, presided over by Prof. Yehuda Shoenfeld of Israel. The congress and the participants were honored by the attendance at the opening session of the president of Slovenia, Dr. Danilo Türk. The *Journal of Autoimmunity* issued a special edition of the main topics presented at the meeting. Many of the presentations focused on the geoepidemiological aspects of autoimmune conditions. In this report we underline some of the interesting topics that were covered at the congress.

DEFINING AND ANALYZING GEOEPIDEMIOLOGY AND HUMAN AUTOIMMUNITY [1,2]

This review examines the prevalence and incidence of type 1 diabetes mellitus, multiple sclerosis, autoimmune thyroid disease and inflammatory bowel disease around the world and tries to match them with geographic location, ethnic and lifestyle differences, genetics data and environmental influences. The authors showed that both genetics and environment are major factors in determining the risk of autoimmune diseases. While the industrial regions of North America and Northern Europe are associated with a high prevalence and incidence of these disorders, it has also been reported that the rates of these disorders are rising also in urban residential areas in Africa, Asia, Southern and Eastern Europe and Latin America. Evidence suggests that environmental factors such as smoking, infections, exposure to sunlight (ultraviolet radiation), Western nutritional habits, xenobiotics, as well as physical and psychological stress are playing an increasing role in the pathogenesis of these diseases.

EPIGENETICS AND AUTOIMMUNITY [1]

Epigenetics is the control of gene packing and expression independent of alterations in the DNA sequence. The epigenetic state changes with age and becomes disrupted by environmental influences, providing an explanation for the link tying aging and environmental factors to autoimmunity. The review by Brooks et al. [3] describes biochemical mechanisms of epigenetic changes, the differences between patients with autoimmune diseases and healthy subjects, and the differences appearing in various autoimmune disorders. These changes are often attributed to medications that evoke similar symptoms of autoimmune rheumatic conditions. This association may also be elucidated via the effects of these drugs on epigenetic mechanisms. As we learn more about epigenetics and its mechanisms it is very likely that these phases will be considered as potential targets for new therapies.

LIGHT, INCLUDING ULTRAVIOLET [2]

Ultraviolet light can ignite pathogenic inflammatory pathways and at the same time be used to suppress pathological cutaneous immune responses such as psoriasis. In their review Maverakis and co-authors [4] expand on the kinds of ultraviolet light and the damage that this light may cause to DNA, which ends in apoptosis and exposure of nuclear antigens to the immune system. At the same time, ultraviolet light induces the secretion of cytokines and chemokines from keratinocytes. It also has a role in photoallergic and phototoxic reactions.

EFFECTS OF TOBACCO SMOKE ON IMMUNITY, INFLAMMATION AND AUTOIMMUNITY [3]

Smoking is a known contributor to many pathological conditions. However, its influence on innate and adoptive immune response is less acknowledged. In their review Arnson et al. [5] discuss the role of smoking in the ignition of immune responses by augmenting the production of pro-inflammatory cytokines and the suppression of anti-inflammatory cytokines such as interleukin-10. In addition, smoking has been shown to activate macrophages and dendritic cells and to elevate immunoglobulin E concentrations, resulting in the development of asthma and atopic diseases. By inducing autoantibodies smoking may have a role in the pathogenesis and exacerbation of autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus and others.

THE IMPLICATIONS OF AUTOIMMUNITY AND PREGNANCY [4]

Although the treatment and management of autoimmune diseases in pregnant women has improved the prognosis for both mother and child, pregnancy in most of these conditions is still classified as high risk with a potential for significant and sometimes life-threatening complications for mother and child alike.

Both hormonal and immunological changes during pregnancy have numerous effects on the course of autoimmune diseases as well as on the progression of pregnancy and fetal outcome; they also have a direct impact on women's future fertility. Borchers and co-researchers [6] describe the effects of autoimmune diseases (like antiphospholipid syndrome, SLE, rheumatoid arthritis, and type 1 diabetes) on pregnancy and fetal outcomes. The authors also discuss the clinical and immunomodulating effect that pregnancy has on the course of autoimmune conditions. The complex interaction of pregnancy and modern therapeutic modalities is also discussed.

TRAVEL AND TRAVAILS OF AUTOIMMUNITY: A HISTORIC JOURNEY FROM DISCOVERY TO REDISCOVERY [5]

The history of autoimmunity is reviewed here, starting a few years after the discovery of antibodies by Bordet in 1898, and continuing through the discovery of their role in the immune response by Erlich in 1901 and the first report of autoantibodies by Donath and Landsteiner in 1904. The authors describe the 30 years of eclipse between 1915 and 1945 when almost nothing was done, and the rediscovery of this field in 1945 when speculation of an autoimmune etiology for the blackwater fever in South Africa was raised, followed by the discovery of serum antibodies to erythrocytes by Coombs in 1946, the lupus erythematosus cells and the rheumatoid factor later on. The review ends with the recognition of autoimmunity in 1965 when a conference on autoimmunity was convened followed by the publication of two volumes on autoimmunity, which led to consensus on the centrality of this field.

NUTRITION, GEOEPIDEMIOLOGY, AND AUTOIMMUNITY [6,7]

Over the past years multiple lines of evidence have indicated that the variation in the prevalence of autoimmune diseases in different regions of the world stems from different patterns of food consumption, sanitation, probiotics and the content of seminal nutrients such as vitamin D, vitamin A, selenium, zinc, omega-3 fatty acids, probiotics, and flavanols. It is believed that these nutrients play a role in determining immune responses in infections, allergies and autoimmune diseases.

The authors conclude that some of the geoepidmiological differences may be attributed to dietary habits around the world, but clinical studies are warranted to establish this association.

SLE = systemic lupus erythematosus

STRESS AND AUTOIMMUNITY [8]

Stress may affect the immune system either directly or indirectly through the nervous and endocrine systems. Interdisciplinary psychoneuro-immunological research increasingly demonstrates clinically relevant interrelations between psychological stressors and the onset and progression of chronic diseases. Additionally, subsequent studies indicate that stress may induce acute-phase responses and inflammation [9,10]. The activation of the stress-response system influences the hypothalamic-pituitary-adrenal axis, the sympathetic nervous system and the immune system. Several studies have shown that social factors are useful prognostic factors in patients with autoimmune rheumatic diseases.

Patients with SLE, RA and primary antiphospholipid syndrome were asked to complete a questionnaire on various stressors that preceded the onset or exacerbation of their disease. Patients stated that sickness or death in the family, financial problems, loss of a job, and the unstable political situation caused them considerable prolonged anxiety. One or several factors outside of a person's control, many of them persisting for long periods, were reported to cause stress. SLE patients selected stress in 75.8% of the cases, far more often than other known triggers such as smoking (46.8%) and family history (21.3%). A significant percentage of patients with primary antiphospholipid syndrome (44.8%) considered prolonged stress to be the main cause of their disease, as did a similar number of RA patients (42.5%).

Mizokami et al. [11] provided valid circumstantial evidence for the effect of stress on autoimmune thyroid disease and particularly the onset of Graves' hyperthyroidism following major stress. There is also some data suggesting an association between stressful life events and an increased risk for multiple sclerosis exacerbations. Several factors, including duration, frequency, severity and the type of stress, as well as the patient's optimism, perceived social support, and coping strategies have been related to the disease course [12]. Nevertheless, solid evidence linking stress and autoimmune diseases is still lacking and the data remain circumstantial. Mechanisms by which stress affects autoimmune disease are not fully understood and need to be elucidated.

MULTIPLE SCLEROSIS: GEOEPIDEMIOLOGY, GENETICS AND THE ENVIRONMENT [13]

Of all autoimmune related conditions it seems that multiple sclerosis is the most clearly related to geographic distribution. The total number of people living with MS worldwide is estimated to be 2–2.5 million. The disease is unevenly distributed around the world: its prevalence varies between < 5 cases per 100,000 people in tropical areas or Asia and > 100–200 cases per 100,000 in temperate areas, especially those with

RA = rheumatoid arthritis
MS = multiple sclerosis

large populations of Northern European origin, including the United States, Canada, New Zealand and parts of Australia. It is a widely held notion that MS frequency increases progressively with geographic latitude. Nonetheless, there are pockets of high MS frequency such as Sardinia in the warm, south Mediterranean region, while among Inuit people living in Canada's cold far north MS frequency is low, contrary to what would be predicted from a simple ambient temperature/latitudinal geographic model of MS distribution.

The large range of incidence and prevalence seen in different regions in some countries does not necessarily follow latitudinal or other geographic gradient and implies that environmental and genetic factors participate in the disease pathogenesis. Genetic susceptibility could not explain changes in the incidence of MS in immigrant populations. These changes have occurred over periods too short (one generation) to be explained by genetic factors alone and strongly implicate the influence of environmental factors, as expressed in the two following examples. In Israel the frequency of MS among the native-born Israelis of African/Asian origin approximates the higher rate among Israelis of European/American origin rather than reflecting the lower rate of MS among their immigrant forebears [14].

Analysis of the immigration to Australia with regard to the risk of developing MS was presented, showing that MS prevalence increased with latitude south of the equator. The relationship persisted in studies done 20 years apart and thus appeared stable. The prevalence of MS in the migrant population from the United Kingdom and Ireland to Australia as well as in the native-born (non-aboriginal) population also showed a correlation with latitude. Although there was a gradient in prevalence with latitude, the measured prevalence of MS among these immigrants was less than in their country of origin. In the Australian study, unlike other epidemiological reports, there was no significant difference in MS frequency between those who immigrated before or after age 15 years.

One of the strongest correlations of latitude is sunlight intensity and ultraviolet radiation. In Tasmania 136 cases with MS were compared with 272 controls. Higher exposure to sunlight when aged 6–15 years was associated with a decreased risk of MS. Probability of MS with high vs. low exposure to sunlight was 0.31 (95% confidence interval 0.16–0.59). Goldacre and co-authors [15] reported that skin cancers related to exposure to sunlight were significantly less common in patients with MS than in matched controls, implying that greater exposure was protective against MS.

Another pillar to the belief that latitude may affect MS development originates from the understanding that vitamin D may provide the link to these observations. A correlation study between the levels of $25(OH)D_3$ in the blood and the risk of MS was conducted among U.S. military personnel. The serum samples used were stored in the Department of Defense Serum Repository of 257 confirmed MS patients and 514 matched controls. The risk for MS was 51% lower among individuals with levels of $25(OH)D_3 > 100$ nmol/L before the onset of the disease, as compared to those with less than 75 nmol/L [16]. If vitamin D plays a role in preventing MS, it, rather than ultraviolet radiation alone, may be the more relevant factor that mediates MS frequency in different regions.

THE GEOEPIDEMIOLOGY OF SLE [17]

Prevalence studies of SLE have several flaws: many of the existing studies were based on small-source populations and cases were ascertained in the absence of standardized diagnostic criteria. Some of the more recent studies are based on self-report or on health system databases.

Overall incidence rates (per 100,000) range from 1.0 in Denmark to 8.7 in Brazil, while prevalence rates vary from 28.3 in Denmark to an estimated 149.5 in an analysis of hospitalization data in Pennsylvania, USA, which adjusted for the hospitalization rate for SLE. To what extent these figures reflect true geographic differences in lupus occurrence is difficult to determine since methodological issues are likely to account for a major part of the variation.

Several high-quality databases pointed out that the overall incidence rates of SLE range from $1.0/10^5$ in Denmark, 2.6 and $3.0/10^5$ in two areas in Norway, $4.8/10^5$ in Sweden, to $4.7/10^5$ in Martinique. Incidence rates in the USA, Canada, the UK and other countries generally also fall into the range between 2 and $4.7/10^5$. Data from several regions in the USA indicated that the incidence of SLE increased three- to sevenfold in the decades between 1950 and 1992 [18]. This was probably at least partially attributable to the availability of better diagnostic tests, increasing awareness of the disease, and the establishment of standardized diagnostic criteria during this period, with some of these advances resulting in increased identification of milder cases. Increases in SLE incidence during the 1970s and 1980s were also reported from Denmark and Iceland, but were not observed in Sweden.

A more recent study using not only American College of Rheumatology criteria, but also three independent sources and the capture-recapture method confirmed a 2.5-fold higher incidence among African Americans compared to European Americans from Allegheny County, Pennsylvania. Prevalence rates (per 100,000) in various ethnic groups in Hawaii in 1970–75 differed even more substantially, being 5.8 among European Americans, 24.1 among Chinese, 20.4 among part-Hawaiian, 19.9 among Filipino, and 18.2 among Japanese [19]. Up to eightfold higher incidence and prevalence rates in Afro-Caribbean and Asian compared to European subjects have also been reported from the UK [20]. An older study found the rates among Puerto Ricans in New York to be intermediate between those of European Americans and African Americans. A recent study from the island of Puerto Rico reported a prevalence esti-

mate of 159/10^5 (277/10^5 for women) based on an analysis of claims submitted to a health insurance company. This is the highest overall prevalence rate reported to date, though it is similar to the prevalence estimate of 149.5/10^5 for all races in Pennsylvania, USA, which was based on hospitalization data [21].

Limited data are available on indigenous populations, but they also strongly suggest that SLE is more common among Native American Indians in Canada, Maori and Pacific people in New Zealand, and Aborigines in Australia compared to the respective European populations. Together, these results strongly suggest that Europeans and their descendants in various parts of the world have the lowest SLE incidence rates of all ethnic groups.

In marked contrast to the high prevalence rates reported for people of African descent living in Europe or North America, the prevalence of SLE in western Africa, the region from which most slaves originated, is reported to be very low. The rates in the Caribbean appear to be intermediate. This paradox has given rise to the "prevalence gradient hypothesis," which postulates that the prevalence of SLE increases as one goes from Africa to either North America or Europe. A possible explanation for the low prevalence in Africa could be that malaria and parasitic infections alter the immune response in such a way as to provide protection from autoimmunity, thereby keeping the incidence of lupus low. Another explanation may be the decreased exposure to sun and reduced levels of vitamin D in dark-colored populations. If such a gradient really existed, it might provide important insights into the environmental factors that contribute to, or prevent, the development of SLE. However, while there is some support for this hypothesis, it must be emphasized that there are no actual reliable prevalence data from West Africa. More recent findings from sub-Saharan Africa indicate that lupus may not be as rare as had long been thought. Several studies from the UK found high SLE prevalence rates among recent immigrants from West Africa, a vast majority of whom had developed the disease before their immigration to the UK. This does not support the gradient hypothesis, but rather suggests that the prevalence rates in the UK might be inflated by people who emigrated from poor countries in search of better health care. In addition, the similarly high prevalence rates in recent black African immigrants and second-generation Afro-Caribbeans in the UK who have not shared a common environment for at least 200 years suggest that genetic predisposition plays a major role in the increased incidence (and prevalence) of SLE among people of African descent.

THE ENVIRONMENT, GEOEPIDMIOLOGY AND AUTOIMMUNE DISEASE: RHEUMATOID ARTHRITIS [22]

Rheumatoid arthritis is a chronic inflammatory joint disease characterized by a distinctive pattern of bone and joint destruction. RA is also a systemic disease, and several patient subsets can be distinguished based on the presence of extra-articular manifestations.

Studies in North America and Northern Europe have shown prevalences of 0.5–1.1%, while in Southern Europe, lower prevalences of 0.3–0.7% have been reported. The few prevalence studies performed in developing countries based on the 1987 American College of Rheumatology criteria suggest significantly lower prevalences than in Northern Europe and North America, namely about 0.1–0.5%. Although this finding may indicate that RA is less common in developing countries, it may also reflect age distribution differences and underdeveloped health care systems.

In some geographic areas, the prevalence and incidence of RA vary across ethnic groups. For example, the prevalence of RA is high among Pima Indians. Recent data indicate that within ethnic groups the incidence and prevalence of RA vary according to the latitude and geographic area of residence [23]. Vieira et al. [24] examined spatial variation using home addresses. They reported a statistically significant area of increased RA risk in the northeast United States ($P = 0.034$). These results may indicate that sunlight exposure and vitamin D may have a potential role in the development of RA.

GEOEPIDEMIOLOGY: THE ENVIRONMENT AND SPONDYLOARTHROPATHIES [25]

Spondyloarthropathies are a group of common inflammatory rheumatic disorders characterized by axial and/or peripheral arthritis, associated with enthesitis, dactylitis and potential extra-articular manifestations such as uveitis and skin rash. The diseases that comprise the group share a common genetic predisposition, the HLA-B27 gene; however, this association varies markedly among the various spondyloarthropathies and among different ethnic groups.

Many studies have attempted to assess the estimates of the incidence and prevalence of ankylosing spondylitis and spondyloarthropathies in various populations using different methods. Using a 50-year period hospital attendance in Rochester, USA, the incidence of ankylosing spondylitis was found to be approximately 1 per 10,000 males per year and one-third of that in females. Similar findings were found in both a Norwegian and a Finish population over a 10-year period. Thus, these rather almost identical findings indicate the constancy in the epidemiological characteristics of ankylosing spondylitis in these countries. However, in countries like Japan or Greece, the incidence as well as the prevalence of ankylosing spondylitis were found to be much lower. Ankylosing spondylitis is rare in Africa, though when it does occur it is still associated with HLA-B27.

There seems to be a clear correlation between the prevalence of HLA-B27 and the prevalence of ankylosing spondylitis in any given population around the world. HLA-B27 positivity varies around the world with a wide ethnic and geographic variation. The estimated prevalence of ankylosing spondylitis in Caucasians ranges from 0.1 to 1.4%. A definite exception to

this range is its prevalence in Haida and Bella Indians, which is extremely high, reaching 6.1%. Recent studies from Germany, the USA, France and Lithuania suggest that spondyloarthropathies are among the most frequent rheumatic diseases, and probably at least as common as rheumatoid arthritis.

The first and most frequently documented genetic factor identified was the tissue antigen HLA-B27. In most ethnic groups, HLA-B27 is present in approximately 90–95% of patients with ankylosing spondylitis. In the general population ankylosing spondylitis is likely to develop in up to 6% of HLA-B27-positive adults. Approximately 4–8% of the healthy population is positive for HLA-B27. Family studies have shown that first-, second- and third-degree relatives of patients with ankylosing spondylitis have a significantly increased risk of developing the disease (relative risk of 94, 25 and 3.5, respectively). Sixty percent of psoriatic patients with spondylitis and inflammatory bowel disease-associated spondylitis were positive for HLA-B27.

GEOEPIDEMIOLOGY OF SYSTEMIC SCLEROSIS [26]

Systemic sclerosis is a rare and potentially severe connective tissue disease, characterized by skin fibrosis and involvement of internal organs. Because of its rarity and heterogeneous clinical presentation, reliable epidemiological studies are lacking.

SSc prevalence is estimated at between 3 and 24 per 100,000 population and appears to be higher in North America and Australia as compared to Europe and Japan. Incidence estimates increased significantly between the 1950s and the 1980s, but this could be due to greater physician awareness of the disease. Risk factors for SSc include female gender and African origin. Reports of sporadic clusters of higher prevalence also suggest environmental risk factors. In particular, exposure to silica and solvents has been associated with SSc by several rigorous case-control studies.

A geographic clustering of a disease is a non-random spatial distribution of cases, with greater-than-expected occurrence in a geographically defined region. Silman and collaborators [27] reported a high prevalence of SSc in three areas close to the two major airports near London (Heathrow and Gatwick). A prevalence of 150/million was calculated based on 52 cases in population groups living near these airports, as compared to 31/million in other locations, but the difference was not statistically significant.

Valesini and team [28] reported a prevalence of 3497/million in a small province of Rome, based on two previously diagnosed CREST syndromes. One of the most convincing clusters was reported by Arnett et al. [29] and concerned Choctaws Indians, a Native American tribe in Oklahoma. A very high prevalence of SSc was estimated (4690/million) based on 14 cases found in full-blood Choctaws during the years 1990–1994. This prevalence was significantly higher than the prevalence calculated in non-full blood Choctaws (310/million) (odds ratio 15.4, CI 4.9–49.8) and this latter was higher than the one estimated in non-Choctaw Native Americans in Oklahoma (95/million) (OR 6.95, CI 3.3–13.7). Englert and colleagues [30] reported a prevalence of 610/million in Edenhope, South Australia in 1991, which is 10 times the size of the Sydney region. Since the SSc cases were mainly male farm workers, the role of dust storm-related silica was discussed.

Several studies in the USA have shown that black subjects have a higher age-specific incidence rate and more severe disease than white subjects [31,32]. Diffuse forms accounted for 60% versus 27% of the cases in black versus white women with SSc. Noteworthy is that no difference in incidence according to race was noted for men. Most studies in the USA also observed that black patients had an earlier age of onset than white patients. In Australia, the prevalence of SSc was significantly higher among continental European born males, presumably because of the higher silicate exposure in this population. In France, the prevalence of SSc was 140/million (CI 122–170) in European versus 210 (CI 128–293) non-European (Northern and sub-Saharan Africans, Asians and Caribbeans).

NEW UNDERSTATING OF THE EPIDEMIOLOGY OF GRAVES' DISEASE

Hemminki et al. [34] describe the familial risk for Graves' disease in addition to the familial association of Graves' disease with 33 other autoimmune and related conditions. A total of 431,763 cases were extracted from several Swedish national registers; of these, 15,743 were diagnosed with Graves' disease. Among all Graves' disease patients 3.6% were familial (including spouses). The standardized incidence ratio was 5.04 for an individual with one affected sibling to develop the disease but 310 when two or more affected siblings were identified. The SIR for offspring increased from 6.22 to 30.2 when parental age was limited to 50 or 20 years respectively. The SIR for twins was 16.45. Remarkably, a high concordance of 2.75 was found among spouses, which suggests that environmental factors are also involved in the pathogenesis of Graves' disease. Association between Graves' disease and 11 other autoimmune diseases such as Addison's disease, type 1 diabetes, Hashimoto thyroiditis, and pernicious anemia were recorded. The authors concluded that there is a genetic and environmental risk for Graves' disease, and that counseling and prevention plans should be considered in selected high-risk patients.

GEOEPIDEMIOLOGY AND ENVIRONMENTAL FACTORS OF PSORIASIS AND PSORIATIC ARTHRITIS [33]

The prevalence and incidence of psoriasis and psoriatic arthritis show an ethnic predilection and geographic variations with higher prevalence and incidence of the disease in Europe, North

SSC = systemic sclerosis

CI = confidence interval
OR = odds ratio
SIR = standardized incidence ratio

America, Australian Caucasians, and East Africa, whereas lower rates were noted in South American natives, African Americans, and the populations of China, Taiwan and West Africa. Hemminki et al. [34] also discuss the role of genetics and environmental factors behind the polygenic pattern of the expression of psoriasis in these subjects. Other factors such as infections, humidity, stressful life events, trauma, smoking, cold weather, nutrition, obesity, and certain medications are mentioned as risk factors for the disease.

HEPATITIS C AND INTERFERON-INDUCED THYROIDITIS [34]

The environmental factors postulated to precipitate autoimmune thyroid disease include iodine, medications, infection, smoking and possibly stress. This review mentions two well-documented triggers contributing to autoimmune thyroid disease: hepatitis C virus and interferon-alpha treatment. IFNα therapy for chronic HCV infection is associated with clinical and subclinical thyroiditis in up to 40% of treated subjects. Both the epidemiology and proposed mechanism of action are presented in this review, and the relation to genetic predisposition is also noted. The authors conclude that since thyroiditis is very common in HCV patients, all patients on IFNα treatment should undergo routine thyroid screening. Hopefully, in the future pharmacogenomic approaches will be used to identify patients in advance.

GEOEPIDEMIOLOGY OF COPD AND IDIOPATHIC PULMONARY FIBROSIS [35]

Chronic obstructive pulmonary disease and idiopathic pulmonary fibrosis differ in their geoepidemiology and immunopathogenesis. The European Community Respiratory Health Survey (ECRHS), the Chronic Obstructive Pulmonary Disease in five Latin American cities (PLATINO) Study, and the International Variation in the Prevalence of COPD (BOLD) Study together collected worldwide prevalence data on more than 32,000 COPD subjects from 27 nations on 6 continents. ECRHS examined the worldwide patterns of COPD according to the World Health Organization-National Institutes of Health GOLD stages in 16 countries, enrolling 18,000 participants aged 22 to 44 years. The overall prevalence was 11.8% for stage 0, 2.5% for stage I, and 1.1% for stages II–III. Multivariate modeling from this database confirms the fact that exposure to "dusty jobs" increases the risk of developing COPD, independent of smoking. PLATINO described the epidemiology of COPD in five large Latin American cities. The prevalence of COPD in 5315 adults 40 years or older ranged from 7.8% to 19.7%, signifying that COPD is a greater burden than previously thought. Although these countries have high rates of tobacco smoking, after adjusting for confounders the authors concluded that altitude may explain part of the difference in prevalence.

The BOLD study is a pioneering geoepidemiological research of COPD prevalence utilizing rigorous epidemiological methodologies. This study reported the worldwide prevalence of COPD and its risk factors in adults aged 40 years and older across countries by age, gender and smoking status. The study population comprised 9425 adults. The results of BOLD confirmed that tobacco smoking and occupational dust exposures were more common worldwide in men and correlated with a higher prevalence of COPD. Overall, the estimated prevalence rate of clinically significant stage II COPD or higher was 11.8% for men and 8.5% for women. These rates are higher than those of 26 other published studies, particularly for stage II COPD and more clinically significant forms of COPD. The prevalence of COPD GOLD stage II and higher increased steadily with age for men and women in every site. The prevalence of stage II or higher COPD exceeded 20% in 9 countries (China, Austria, South Africa, Iceland, Poland, Norway, Canada, Philippines, and Australia) for men and 7 countries (China, Austria, South Africa, Canada, USA, Philippines, and Australia) for women and individuals aged 70 years or older.

The worldwide geoepidemiology of idiopathic pulmonary fibrosis is not precisely known. Prior estimates of incidence range from 3–6 cases per 100,000 person-years in the USA population, to 16–18 per 100,000 person-years in Finland. Data originating from the United Kingdom showed an incidence of 4.6 per 100,000 person-years, which increased progressively between 1991 and 2003. These rates were higher in northern England and Scotland. No large observational studies have directly addressed ethnicity in idiopathic pulmonary fibrosis. When informally comparing the epidemiological data from Europe, the USA and Japan, the prevalence rates are similar. Most of these studies, however, did not take racial differences into account. Although "idiopathic" by definition, potential etiological factors have been implicated and include, in particular, exposure to metal dust and heavy smoking. In this interesting review evidence for autoimmune elements in the pathogenesis of these diseases is discussed.

NUCLEIC ACID-ASSOCIATED AUTOANTIGENS: PATHOGENIC AND THERAPEUTIC POTENTIALS [36]

Autoimmunity to macromolecular nucleic acid-protein complexes such as nucleosome or the spliceosome is a characteristic feature of systemic autoimmune diseases. This review elaborates on the structure and biological function of nucleic acid-associated autoantigens. The authors underline the role of nucleic acid-associated autoantigens as diagnostic markers and drivers of potentially pathogenic autoimmune responses. The role of nucleic acids as co-stimulators or activators of Toll-like receptors in antigen-presenting cells is also discussed. The authors note that inappropriate stimulation of nucleic acid-sensing receptors may lead to the loss of tolerance to auto-activation of T cells, which also enhances the synthesis of antibodies. Recent advances in

IFNα = interferon-alpha
HCV = hepatitis C virus
COPD = chronic obstructive pulmonary disease

immunotherapy such as antigens specific to nucleic acid-binding antigens and other novel roads are also discussed.

DRUGS AND AUTOIMMUNITY: A CONTEMPORARY REVIEW AND MECHANISTIC APPROACH [37]

Although many drugs have been reported to induce autoantibodies, only a few reports have indicated definitive associations between a specific drug and the development of a certain type of autoimmune disease following its administration. Drugs like hydralazine, procainamide, minocycline, d-penicillamine and anti-tumor necrosis factor agents are mentioned in this review. A variety of mechanisms that may result in autoimmune symptoms, including molecular mimicry, abrogation of tolerance, inhibition of DNA methylation and induced apoptosis, are also described. In conclusion, in order to provide an accurate diagnosis and treatment we have to understand the mechanism by which each drug modulates the immune response.

THE COMPLEMENT SYSTEM IN SYSTEMIC AUTOIMMUNE DISEASE [38]

The complement system plays a major role in the pathogenesis of many systemic autoimmune diseases. This review describes the three significant pathways of activation of the complement system and the role of each one of them in the development of autoimmune diseases such as vasculitis, SLE, antiphospholipid syndrome, systemic sclerosis, Sjogren's syndrome, dermatomyositis and rheumatoid arthritis. The authors conclude that because the complement system is such a major player in autoimmune mediated organ damage, insight into the various pathways of complement opens up new directions for treatment.

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