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SYSTEMIC LUPUS ERYTHEMATOSUS IN MANITOBA ABORIGINALS

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Systemic Lupus Erythematosus in Manitoba Aboriginals

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Abstract:

Background: For many years there have been sporadic studies describing excessive or unusual rheumatic diseases in North American Indians and Eskimos. There are marked differences amongst the various Aboriginal groups in prevalence, incidence, and manifestations of rheumatic diseases, which are unrelated to climate and geography. It seems clear that the epidemiology of rheumatic disease in Native North Americans as a whole is quite different from that described for the remainder of the North American as well as the European population. Native North Americans are a large and heterogeneous group, comprising almost 3 million people spread out over the continent, from Alaska and the Northwest Territories to Mexico in the south. There is a disproportionate burden of rheumatic disease in this population.

Systemic lupus erythematosus (SLE) is a chronic, potentially fatal, multisystem inflammatory disease of unknown etiology that primarily strikes young women. It is characterised by prominent immune aberrations giving rise to excessive autoantibody production, causing cytotoxic damage and immune inflammation. It is recognised worldwide, with wide variations in the reported incidence and prevalence. There is no Canadian data for the overall prevalence and incidence, but studies from the United States report a prevalence ranging from 14.6 to 50.8 cases per 100,000 persons. European studies show similar results, with reported prevalence rates from 12 to 39 per 100,000. Annual incidence rates in the United States have been estimated at between 1.8-7.6 cases/100,000 persons per year, with similar figures from Europe.

The prevalence of SLE is known to vary among different ethnic groups, but North American Indians have been little studied in this regard. Morton et al found an incidence of hospitalised SLE of 27.1/100,000 in the Crow Indians, 24.3/100,000 in the Arapahoe, and 16.6/100,000 in the Sioux, compared to seventy-two other tribes who had an incidence and prevalence similar to that of the Caucasian population. The Tlingit, Haida, and Tsimshian Indians, of the Southeast coast of Alaska, also had a higher than expected number of cases of SLE with a prevalence rate estimated at 91.7/100,000. The Nootka natives of the Pacific Northwest were found to have an extraordinarily high prevalence of SLE at 300-500/100,000. The only study including data on disease severity and clinical manifestations of SLE in North American Aboriginals found only mild SLE, without renal or neurological involvement.

Objectives: The prevalence of systemic lupus erythematosus (SLE) in Manitoba North American Indians (NAI) is hypothesized to be increased above that of Caucasians (CAUC), but little studied. To evaluate this we studied the prevalence rate of SLE in a population of 1.1 million.

Methods: The provincial arthritis center database and the medical records of all rheumatologists, hematologists, nephrologists, and general internists with $\geq$1 SLE patients were searched for cases of SLE diagnosed between 1980 and 1996. A subset of 175 medical records was reviewed for demographics, SLEDAI scores, SLICC/ACR damage indices, clinical manifestations and therapy. A random survey of 15% of family physicians serving this population suggested that >85% of all SLE cases were identified.

Results: A total of 257 cases diagnosed between 1980 and 1996 and meeting the ACR criteria for SLE were found. There were 49 NAI cases, most of whom were Cree, resulting in a prevalence of 42.2/100,000 compared to a prevalence of 21.6/100,000 for the remainder of the population ($p < 0.001$). NAI patients were younger at diagnosis (NAI = 31 yrs, CAUC = 37 yrs; p =. 01), had more active disease at diagnosis (SLEDAI score: NAI = 11.8, CAUC = 9.7; $p = 0.05$), and had more frequent renal involvement (NAI = 60%, CAUC = 32%; $p = 0.00$). There were no treatment differences at diagnosis and 2 years, but NAI patients were significantly more likely to require treatment with prednisone or immunosuppressives at the last clinic visit. The NAI patients had similar damage scores at diagnosis, but significantly higher scores at 2 years (SLICC/ACR damage index: NAI = 0.74, CAUC = 0.30 $p = 0.02$), and at the last clinic visit (SLICC/ACR damage index: NAI = 1.63, CAUC = 0.81; $p = 0.03$). NAI ethnicity increased the likelihood of death more than fourfold (OR 4.6, 95% CI 1.3-16.5).

Conclusions: The prevalence of SLE was increased twofold in this NAI population. NAI patients had higher SLEDAI scores at diagnosis, more frequent vasculitis and renal involvement, required more treatment later in the disease course, accumulated more damage following diagnosis, and increased fatality.

Résumé:

Contexte: Au fil des années, plusieurs études isolées ont décrit des maladies rhumatismales peu communes ou excessives chez les Amérindiens et les Inuit. La prévalence, l'incidence et les manifestations des maladies rhumatismales varient sensiblement entre les divers peuples autochtones. Ces différences ne sont pas liées au climat, ni à la géographie. Il semble évident que l'épidémiologie de la maladie rhumatismale chez les autochtones nord-américains dans l'ensemble se distingue d'une façon marquée de celle caractérisant les autres personnes nord- américaines et la population européenne. Les Autochtones nord-américains, un grand groupe hétérogène, comptent presque 3 millions de personnes, dispersées à travers le continent, de l'Alaska et des Territoires du Nord-Ouest jusqu'au Mexique. Les maladies rhumatismales ont un impact disproportionné chez cette population.

Le Lupus Erythémateux Disséminé (LED) est une maladie inflammatoire chronique et potentiellement fatale, d'étiologie inconnue, qui frappe principalement les femmes jeunes. Elle se caractérise par des anomalies graves du système immunitaire, qui causent une production excessive d'autoanticorps, engendrant des dommages cytotoxiques et de l'inflammation immunitaire. On retrouve le LED partout à travers le monde, mais l'incidence et la prévalence varient grandement. Il existe peu de données canadiennes décrivant la prévalence et l'incidence du LED, toutefois, des études américaines décrivent une prévalence entre 14,6 et 50,8 cas par 100 000 personnes. Les études européennes ont obtenu des résultats semblables, avec des taux de prévalence entre 12 et 39 cas par 100 000 personnes. Aux États-Unis, les taux d'incidence ont été estimés entre 1,8 et 7,6 cas / 100 000 personnes par an, et les taux européens sont semblables.

Il est bien connu que la prévalence du LED varie parmi différents groupes ethniques, mais le cas des Amérindiens a été peu étudié. Morton et al ont trouvé un taux de LED hospitalisé de 27,1 par 100 000 chez le peuple Crow, 24,3/100 000 chez les Arapahoe, et 16,6/100 000 chez les Sioux, comparé à 72 autres tribus dont l'incidence et la prévalence étaient semblables à celles de la population caucasienne. Les Indiens Tlingit, Haida et Tsimshian de la côte sud-ouest de l'Alaska, avaient, eux aussi, un taux augmenté de LED, avec une prévalence estimée à 91,7/100 000. Chez le peuple Nootka du Nord-Ouest pacifique, la prévalence était extraordinairement élevée, à 300-500/100 000. Quant à la gravité et aux manifestations cliniques du LED, la seule étude qui comprend des donnés relatives aux Autochtones nord-américains n'a trouvé qu'un LED peu sévère, sans implication rénale, ni neurologique.

Objectifs: Nous avons posé comme hypothèse que le taux du LED est plus élevé chez les Amérindiens du Manitoba (AM) que dans la population caucasienne, mais il a été peu étudié. Pour évaluer ceci, nous avons examiné le taux de prévalence du LED chez une population de 1,1 millions.

Méthodes: La banque de données du centre provincial de l'arthrite et les dossiers médicaux de tous les rhumatologues, hématologues, néphrologues et internistes ayant $\geq$ 1 patient avec le LED, ont été examinés pour trouver les cas de LED diagnostiqués entre 1980 et 1986. Un échantillon de 175 dossiers médicaux a été examiné pour obtenir des données démographiques, les résultats de SLEDAI, les indices de dommage du SLICC/ACR, les manifestations cliniques et le traitement. Un sondage, prélevé au hasard, de 15 % des médecins de famille desservant cette population, a démontré que plus de 85% de tous les cas de LED ont été identifiés.

Résultats: 257 cas diagnostiqués entre 1980 et 1986, répondant aux critères du ACR ont été identifiés. Il y avait 49 cas chez les AM, dont la plupart étaient Cris, ce qui se traduit en une prévalence de 42,2 /100 000, comparée à 21,8 pour le restant de la population ($p < 0,001$). Les patients AM étaient plus jeunes au moment du diagnostique (AM = 31 ans, CAUC = 37 ans; $p = 0,01$), avaient une maladie plus active au moment du diagnostique (résultats du SLEDAI: AM =11,8, CAUC = 9,7; $p = 0,05$), et démontraient une implication rénale plus fréquente (AM= 60%, CAUC = 32%; $p = 0,00$). Il n'y avait pas de différence au niveau du traitment lors du diagnostique, ni 2 ans plus tard, mais les patients AM étaient plus susceptibles à d'avoir eu besoin de prednisone ou d'agents immunosuppresseurs lors de leur dernière visite médicale. Les patients AM avaient des indices de dommage semblables au moment du diagnotique, mais leurs indices étaient considérablement plus élevés 2 ans plus tard (indices de dommage SLICC/ACR: AM = 0,74, CAUC = 0,30; $p = 0,02$), et lors de la dernière visite médicale (indices de dommage SLICC/ACR: AM = 1,63, CAUC = 0,81; $p = 0,03$). La probabilité de décès était considérablement plus élevée chez les malades AM (OR 4.6, 95%CI 1.3-16.5).

Conclusions: La prévalence du LED était deux fois plus élevée chez cette population autochtone. Les malades AM avaient des résultats de SLEDAI plus élevés au moment du diagnostique, une implication rénale plus fréquente, un plus grand besoin de traitement tard dans le cours de la maladie, ils accumulaient plus de dommage après diagnostique, et leur taux de mortalité était plus élevé.

Introduction

It is well known that the epidemiology of many of the rheumatic diseases differs markedly between ethnic groups. Such differences have important implications for clinicians caring for people with rheumatic diseases, as well as for individuals involved in planning health care resources. The majority of the published rheumatology literature pertains to the Caucasian population, with the result that information on prevalence, incidence, prognosis, and management may be less than optimal when applied to non-Caucasians.

Indigenous North Americans are a growing segment of the population whose health care needs must be addressed. In order to plan and improve care for this population, the epidemiology of rheumatic diseases specific to this population must be described. Where unusual or excessive disease appears to exist, the optimal management must be determined.

Central Canada has a very large Aboriginal population. In the province of Manitoba, roughly 10% of the total 1.1 million population is Aboriginal. Clinicians working in this province almost universally report the clinical impression of frequent, severe rheumatic disease, including systemic lupus erythematosus, in the Aboriginal population, but there have been very few studies addressing rheumatic diseases in this population. In order to improve health care for the regional Aboriginal population, studies are needed to confirm the clinical impression of more frequent disease, to examine differences in disease course and outcome, and to determine the most appropriate therapy.

Rheumatic Diseases in North Americas Indigenous Peoples

Abstract:

Objective: There are at least 3 million North American Indians and Eskimos in North America. The epidemiology of rheumatic diseases in Native North Americans differs from that described for the remainder of the North American population. An enhanced understanding of rheumatic diseases in North American Indians and Eskimos may provide valuable clues to the etiology of these diseases and improve rheumatologic care for this group of people.

Methods: The world literature was searched for all reports of rheumatic diseases in North American Indians and Eskimos. The reports were reviewed and the findings summarized by disease process.

Results: Many Native American groups have high prevalence rates of rheumatoid arthritis, (RA) systemic lupus erythematosus, connective tissue diseases, and spondyloarthropathies. There appears to be a correlation between the pattern of rheumatic diseases in Native North Americans and the patterns of migration and ancestry. In general, Amerind Indians have high rates of rheumatoid arthritis and connective tissue disease, while Na-Dene Indians and Eskimos have high rates of spondyloarthropathies. The RA seen in Native Americans is generally severe, seropositive, with an early age of onset, and frequent extraarticular manifestations. Many Native American groups have very high frequencies of the RA shared epitope. The majority of Native American and Eskimo groups also have high frequencies of HLA-B27, and some of the world's highest prevalence rates of spondyloarthropathies are described in these groups. While some groups show a marked tendency to develop either Reiter's syndrome or Ankylosing spondylitis, psoriatic and enteropathic arthritis appear to be rare.

Conclusion: The excess rheumatic disease seen in this population is most likely genetic in origin. Because of the combination of high rates of rheumatic disease and relative genetic homogeneity, Native North Americans represent a singular opportunity to study genetic contributions to rheumatic disease. For clinicians, the index of suspicion for rheumatic diseases in North American Indians and Eskimos should be high, and the severe disease and sometimes atypical presentations of rheumatic disease in this population should be kept in mind.

A number of studies have described excessive or unusual rheumatic diseases in North American Indians and Eskimos, a heterogeneous group, comprising almost 3 million people (1,2) spread out over the continent, from Alaska and the Northwest Territories to Mexico. The marked differences in prevalence, incidence, and manifestations of rheumatic diseases amongst the various indigenous groups are unrelated to climate or geography. The epidemiology of rheumatic disease in Native North Americans as a whole is clearly different from that described for the remainder of the North American as well as the European population (3-22). An improved understanding of rheumatic diseases in North American Indians and Eskimos can provide insights into the etiology of the diseases and identify needs for improved rheumatologic care for this group of people.

The ancestors of Native Americans, all of whom appear to have originated in northeastern Asia (23), crossed the Bering land strait to America in three distinct waves. This conclusion was arrived at independently by a variety of anthropological disciplines, including linguistic anthropologists (24,25), anthropologists using dental and serological evidence (23,25), and later by geneticists (26-28). A small group of people known as the Amerind, or Paleo-Indians, were the first arrivals, arriving as early as 30-40,000 years ago (26,27). Finding the continent unpopulated, they rapidly spread out and diversified. The Amerinds now make up all of the Central and South American Indians, as well as most of the North American Indians. They are the most populous and diverse Native Americans. Seven to 12,000 years ago, the second group known as the Na-Dene arrived (26,27). Finding the Americas already populated, this group, for the most part, stayed in the Northwest corner of North America, with some groups eventually migrating to western interior Canada, Washington, Oregon, and the Southwestern United States (24). The Eskimo-Aleuts arrived last, but possibly not long after the Na-Dene (24), and stayed in the far North.

This pattern of migration may have some bearing on rheumatologic disease, since disease susceptibility seems to follow a similar pattern. Most of the tribal groups with an increased prevalence of rheumatoid arthritis (RA) are Amerinds, as are most of the populations with increased prevalence rates of systemic lupus erythematosus (SLE) and other connective tissue diseases. The HLA-B27 antigen appears to be present in relatively high frequencies in all

North American Native populations, but there is a clustering of the highest frequencies in the Na-Dene and Eskimo-Aleuts (29). Consequently, while spondyloarthropathies are found at high rates in Native groups throughout North America, some of the highest prevalence rates have been found in Na-Dene and Eskimo-Aleut groups (9,15,20).

Rheumatoid arthritis

Recent evidence suggests that RA originated in a small, localized group of Native American Indians in the New World, and then was spread to the remainder of the world by the European conquest of North America (30). In contrast to the well-documented antiquity of osteoarthritis, gout, and spondyloarthritis in the Old World (31), RA was not recognized as a separate clinical entity in the medical literature of the Old World prior to 1800 (31). Repeated attempts using extensive collections of Old World skeletal remains have also failed to provide any evidence of RA (30). However, Rothschild and colleagues have been able to document RA in multiple pre-Columbian New World populations (30,32-34). It appears that 4000-6500 years ago, RA was localized to Archaic and Mississippian Indians in the area immediately surrounding the west branch of the Tennessee River, where documentation of this disease in skeletal remains persists up to about 450 years ago. Eleven to twelve hundred years ago, RA then spread into Ohio through southern Illinois and Indiana, to affect the Woodland Indians in Ohio. European contact with this area did not occur until 1750. The first unequivocal case reported in the Old World medical literature had its onset in 1785 (31,35). The brief interval between European exposure to the New World Natives affected by RA in Ohio and the first Old World description of RA clearly precludes a purely genetic explanation. This sequence of events, with initial evidence of localization to an isolated geographic area, followed by spread within the New World, and finally documentation of RA in the Old World shortly after European contact is highly suggestive of a vector-transmitted disease (30).

It is equally interesting that the prevalence of RA in Archaic Indians from the eight sites known to have RA ranged from 2.2-5.2% (30,32-34), similar to that reported for some contemporary Native American Indians (see below), and considerably higher than all reports of prevalence in North American and European Caucasians (36-39). Although the specific

relationship of these pre-Columbian Indians to present-day tribal groups is unknown, it is almost certain that they belonged to the Amerind wave of migration. The Na-Dene Indians are not known to have migrated into those areas where the skeletal remains were found, and those Na-Dene migrations that did take place may have been as recent as 1000 years ago (25). The Eskimo-Aleut group has not migrated out of the far north (25).

Rothschild and colleagues suggest that interdisciplinary analysis of the timing of the geographic spread of RA may allow identification of the responsible pathogen or allergen (30). In addition, further study of the manifestations of this disease, and the genetic and environmental factors leading to it in present day American Indians can, perhaps, be viewed as studying the 'original' form of the disease. This concept may be particularly relevant in view of some of the apparently unique features of RA found in some North American Indian tribal groups (see below), and offers considerable potential to better our understanding of RA.

Prevalence and Incidence: Some of the highest known prevalence rates for RA worldwide have been reported in Native American populations (Table 1). The Chippewa (4), and the Blackfeet (40) Indians appear to have a prevalence of RA five times the 1% rate reported in predominantly Caucasian North American and western European populations (37-39). The Pima Indians, also initially found to have a prevalence rate of 5% using the Rome criteria (22,41), were later found to have a prevalence of 2.5% based on the 1987 ACR criteria (42). Yakima Indian women were found to have a prevalence rate of 3.4% (43). Algonkian Indians in central Canada were recently found to have a prevalence rate of 2%, twice that of the surrounding predominantly Caucasian population (44). While the Indians in Southeast Alaska were found to have a prevalence of RA of 2.4% (5), the Eskimos in Alaska and northern Canada have a prevalence of RA of 0.6-1.1% (6,11,131), similar to that reported in North America in general. The Bella Bella (45), the Nuu-Chah-Nulth (12) and the Haida (46) Indians on the Canadian Pacific coast have a prevalence of RA of 1.3%, 1.4%, and 0.5-1.5% respectively, also not different from expected.

Information on incidence is more limited. A preliminary review of Indian Health Service hospital diagnostic codes for the 10-year period from 1980-1990 (14) has provided an estimate for the annual incidence of rheumatoid disease (Table 2). These data are difficult to interpret,

since seronegative spondyloarthropathies were included with RA, and the data are organized by geographic area rather than tribal group. However, it does illustrate the wide variation in incidence rates that exist. Because the data are based on hospital discharge diagnostic codes, it is likely that the incidence of rheumatoid disease is grossly underestimated for all regions.

There are no data on incidence and prevalence of RA among the large number of North American Indians living east of Manitoba in Canada.

Age of Onset: Some investigators report an earlier age of onset in Native American populations with high prevalence rates. Among Yakima Indian women, who had an overall prevalence of RA of 3.4%, the most striking finding was in the women under age 35, who had a prevalence rate for RA of 3.2%, compared to 0.06% for women in this age group in the National Health Examination Survey (17). Among the Tlingit Indians, 19/37 patients (51%) had onset of RA before age 35, with a striking scarcity of patients with onset after age 60 (1/37) (47). In the Southeast Alaska Indians (5), which include the Tlingit, the peak incidence rates occurred at age 30-39. Fifty-eight percent of Chippewa patients had onset of RA before 40 years (48), and the mean age of onset was less than 40 years in Mexican Mazahua women (49). The Kiowa Indians of Oklahoma also appear to have disease onset at a younger age, with a mean age at onset of 38 years, and onset before age 40 in 56% (50). The Bella Bella Indians on the Canadian Pacific coast also had an early age of onset, with a mean of 29 years (45). There were similar findings amongst the Nuu-Chah-Nulth Indians of Vancouver Island. The mean age at onset of RA in all patients was less than 38 years, and for those patients with non-erosive RA, and RA overlap syndromes, the mean age at onset was less than 30 (12). Two studies of Cree and Ojibway Indians in central Canada also found that the age of onset was on average 10 to 12 years earlier in the Cree patients than in the neighboring Caucasian population (44,51). A retrospective chart review done in Northern Ontario compared RA in Caucasians to RA in Aboriginal Canadians. The investigators found that 40% of Aboriginals had onset of RA before the age of 30, and only 8% had onset after the age of 49, compared to 12% and 41% of Caucasians, respectively (52). There is no evidence that the disease is milder in these groups with earlier onset. Rather, some authors report clinical impressions of quite severe disease (43,45,47,50). The implications of this earlier age at onset, in addition to contributing to the increased prevalence rates, include

increased lifetime accumulation of deformity, disability, drug toxicity, and perhaps higher premature mortality rates.

Disease Severity: Little data are available on differences in clinical manifestations or outcome in these populations (Table 3). While there are no controlled studies of disease severity, there is some evidence for increased severity in North American Indians. In a study of Yakima Indian women, the authors found their clinical impression of predominantly advanced disease supported by the finding of stage IV radiological changes in 64% of patients (43). In another study of Yakima women, 100% of RA patients had erosive disease (53). Wilkens et al (43) also reported an unusual pattern of joint involvement in Yakima women, characterized by extensive metacarpophalangeal and wrist involvement with relative sparing of the proximal interphalangeal joints. This pattern was not seen in age and sex matched Caucasian patients with RA. These same patients also had a high incidence of toxicity related to gold therapy. Eight of thirteen patients developed proteinuria (62%), three of whom also had hematuria (43). In Mexican Mazahua Indians, 65% of patients were reported to have 'severe destructive disease' with deformities, fused joints, marked disability, and muscular atrophy (49). Amongst the Pima Indians, 60% of RA patients had erosive disease (54). A cohort of central Canadian Cree and Ojibway Indians were recently found to have higher Lansbury scores than Caucasian patients in the cohort, and more persistently elevated erythrocyte sedimentation rates (51). Another group of central Canadian Indians with RA was found to have an average lifespan 20 years shorter than their Caucasian counterparts with RA (55). In a study of Tlingit Indians, the authors also reported a clinical impression of severe disease (5), and in a later study, they found that 76% of patients had erosive disease, and 46% had required joint surgery (47). Bella Bella Indians in British Columbia, Canada, were also recently found to have uniformly severe, erosive disease (45).

In addition to severe joint disease, the frequency of rheumatoid nodules and other extraarticular features also seems to be unusually high in many of these groups. Fifty percent of the Yakima Indian women (53), 46% of the Tlingit (47) and Pima Indians (22), and 42% of Chippewa patients (48) with RA had rheumatoid nodules. This is more than twice the usual frequency of 20% reported for seropositive Caucasian patients (56). Twenty-four percent of the

Tlingits had other extraarticular features (47). Amongst the Nuu-Chah-Nulth Indians on the pacific coast, the authors reported that 50% of patients with non-erosive RA had unusual extraarticular features such as cytopenia, nephritis, and alopecia. Of their patients with erosive RA, 54% had extraarticular features such as nodules (31%), Sjogren's syndrome, (15%), and pulmonary fibrosis (15%) (12).

Serology: Serological differences also exist (Table 3). Some Native American populations have a very high frequency of rheumatoid factor (RF) and antinuclear antibody (ANA) seropositivity in both affected and unaffected populations. RF, which is generally reported to be present in 75-80% of patients with RA (57), was found in greater than 92% of Yakima (53), Tlingit (47), Chippewa (48), Mazahua (49), Kiowa (50), and Oklahoma Indian patients including Comanche, Choctaw, Apache, and other tribal groups (50). Algonkian Indians in central Canada were also found to have higher RF titres than Caucasian RA patients (51), with an average titre of 800 IU/l in Natives, versus 440 IU/l in Caucasians.

In contrast, the Inuit and Yupik Eskimos, and the Nuu-Chah-Nulth Indians with RA have a frequency of RF of 78-83% (11-13). Interestingly, in a 1967 study, only approximately 40% of Pima and Blackfeet Indian RA patients were RF positive (40). This figure is unexpectedly low, since the same study found a frequency of RF of 19% in the unaffected population of Pima Indians, much higher than the figure of 1-5% found in apparently healthy subjects (58). The presence of RF was also found to be strongly predictive of the development of RA in otherwise healthy Pima Indians (59), but a more recent study of this same population found that only 75% of patients meeting 1987 ACR criteria for RA were RF positive (42). As a rule, the frequency of RF in the general population does not appear to correlate with the prevalence rate of RA. The Chippewa (48) and Blackfeet (40) Indians have a prevalence rate of RA almost identical to that of the Pimas, but a frequency of RF in the general population similar to that reported in Caucasian populations, rather than the markedly elevated rate found in the Pimas.

In several Native American populations, the frequency of positive ANAs in RA patients was found to be higher than expected. Thirty-four to 75% of the Yakima (43), the Tlingit (47), the Chippewa (4,48), the Mexican Mazahua (49), the Nuu-Chah-Nulth (12), and the Kiowa (50) Indians with RA had positive ANA tests (Table 3). A Northern Ontario study also reported more

frequent positive ANA tests in Indians with RA than in Caucasians, but no details were given (52). Only the Yupik Eskimos (13), the Inuit Eskimos (11), and a mixed group of Indians in Oklahoma (50) were found to have lower frequencies of ANA in RA patients, at 28%, 0%, and 27% respectively. The Tlingit, Chippewa, and Nuu-Chah-Nulth Indians also have higher than expected frequencies of ANA in the general population at 30%, 10.1%, and 11% respectively (12,47,48). As mentioned above, the Nuu-Chah-Nulth RA patients had a high frequency of unusual autoimmune features. This population and the Tlingits have also been reported to have a high frequency of SLE (12,47) (see below). Thirty-three percent of Kiowa Indians of Oklahoma with RA were found to have anti-Ro antibodies (50). Both RF and ANA are known to be markers of severe, chronic disease (60).

Genetic Markers: The HLA characteristics have also been determined for many of these indigenous populations in recent years. In Caucasians, RA is highly associated with either the Dw4(DRB1*0401) or the Dw14(DRB1*0404) genes, both of which share a sequence motif in the third hypervariable region of the DRB1 gene, called the 'shared epitope' (61,62). The majority of Caucasians who do not have the above alleles have the epitope on the HLA-DR1 positive haplotype, (DRB1*0101) (61). Initial studies of HLA genes in Native American populations produced conflicting results. In the Chippewa Indians, 68% of the general population and 100% of the RA cases were found to be DR4 positive (48,63), a statistically significant association. In this population, the relative risk for RA associated with the presence of DR4 was 13.4 (48,64). In Caucasians, approximately 30% of the general population are DR4 positive (65), leading the authors to conclude that, given the HLA trait, the relative risk of RA in the Chippewa population is similar to that of Caucasians (64). In contrast, the Inupiat and Yupik Eskimos also have high frequencies of DR4 at 81% and 67% respectively (66), but do not have a higher than expected prevalence of RA (6,13). Dw4 (DRB1*0401) was expressed by 63% of Inupiats (66), and 46% of Yupiks (66), much higher than the 16% frequency reported in Caucasians (61). In the Yakima (67), the Tlingit (47), and the Pima Indians (68), early studies found no association with DR4, the original HLA marker for RA susceptibility identified. Later studies identified the same 'shared epitope' on the Dw16 (DRB1*1402) gene (68). This gene is very rare in Caucasians (<1%) (67). In the Yakima Indians, 83% of RA patients and 60% of controls were found to have the Dw16

haplotype, for a relative risk of RA in those with the gene of 3.3 (67). In the Tlingit Indians, the Dw16 (DRB1*1402) allele was found in 91% of RA cases and 80% of controls (69). Another study reported similar findings in Pima Indians. Greater than 90% of full blooded Pimas express the HLA antigen HLA-Dw16, irrespective of whether RA is present (70). Williams et al summarized the data from these three populations, and calculated a Mantel-Haenszel summary odds ratio of 2.6, 95% confidence interval 1.1-6.5, for the association of RA and the haplotype (68).

The presence of the RA susceptibility epitope in Caucasian populations has been found to be associated with seropositive, erosive RA with increased extraarticular features (62). This would certainly fit the profile for the majority of Native American populations studied. In addition, a 'gene dosage' effect has been proposed, where patients with two copies of the RA susceptibility epitope have more severe disease than those with only one (71). This hypothesis may be particularly relevant in those Native American populations with extremely high frequencies of the epitope in the general population, where it would be expected that homozygosity for the epitope would be relatively common. Indeed this seems to be the case in the Chippewa Indians. In a study preceding DNA sequencing of DRB1 alleles, 67% of the Chippewa population (affected and unaffected) appeared to be homozygous for broadly reactive DR4 specificity (64). In another analysis, 36% of Chippewa RA patients were homozygous for the broadly reactive DR4 specificity, compared to 23% of the general population (63). More recently, homozygosity for the DRB1*1402 allele was found in 47% of Tlingit Indian RA patients compared to 31% of controls (69). In full-blooded Tlingits, 59% of cases were homozygous for the allele, compared to 38% of controls. In these patients, there was a trend toward younger age of onset and more extraarticular disease in the homozygous patients (69).

Because studies have shown that RA patients can be divided into functional subsets, based on their HLA and serologic characteristics (62), many investigators now feel that RA is a heterogeneous disease. Variable responses to treatment may well be determined at least in part by genetic or disease subset differences (62). In the search for candidate genetic or environmental causal mechanisms, the study of homogenous subsets of disease will likely become increasingly important. From the above data, it appears most likely that North American

Indians in general represent such a homogenous subset, and they appear to have the most severe form of this heterogeneous disease. They have a high frequency of seropositivity and extraarticular manifestations, a young age at onset, severe erosive disease, and a very high frequency of the "shared epitope". Prevalence rates are high. Of particular interest is the finding that, with the exception of the Tlingit Indians of Southeast Alaska, all of the tribal groups found to have increased prevalence rates, and/or unusual features of RA, are of Amerind ancestry (Table 4). It seems plausible that RA in North American Indians represents the 'original' form of this disease. This clinical, serological, and genetic homogeneity may prove invaluable in future studies. As stated by Weyand et al, "...if RA patients are heterogeneous in terms of clinical manifestations, disease course, treatment response, and etiology, then stratification of RA patients into homogeneous subsets may be important. Future clinical trials should take into consideration that patient to patient differences in treatment efficacy can be expected unless patients are stratified into appropriate subgroups." (62). In addition, study of such a relatively large homogenous group may speed the search for contributing genes.

Systemic Lupus Erythematosus & Other Connective Tissue Diseases

While information regarding connective tissue diseases in Native North Americans is limited, the available data suggest increased incidence and prevalence rates, at least in some groups.

Systemic Lupus Erythematosus: The prevalence of SLE has long been known to vary widely by ethnic group, with higher rates reported in Blacks, Hispanics and Asians than in Caucasians. Since Native Americans share genetic ancestry with Asians (23,26,27), it is perhaps not surprising that they also share an increased propensity for SLE.

In the major US studies of SLE, the prevalence ranges from 15 to 51/100,000 for the population as a whole (72-74) (Table 5). Similarly, the annual incidence rates vary from 2-8 cases per 100,000 (72-74). The differences in these figures have been attributed to a higher proportion of Blacks in the Kaiser Foundation (72) vs. the Rochester (73) study, and in better determination methods (75) in both of these compared to the New York study (74).

Acers et al reviewed hospital diagnostic codes for all of the nine Indian Health Services (IHS) regions in the US, including Alaska, for the 10 year period from 1980-1990 (14). All Native Americans residing on federal reservations receive free medical care through the IHS, and census figures are available for the reservations. Annual incidence rates in the different regions ranged from 1-4/100,000 (14) (Table 6), all similar to the range reported in the Kaiser, Rochester, and New York surveys mentioned above (72-74), which were population based. However, because the Acers study was based only on hospital discharge codes, the true incidence rates for all of these regions is likely higher, particularly in view of increasing outpatient treatment of SLE. Of note is that those IHS regions with higher incidence rates (Aberdeen, Alaska, and Billings) are also those regions that include tribes found to have high incidence and prevalence rates of SLE in independent studies (see below).

An earlier study, by Morton et al, also used IHS hospital discharge data for the years 1971-1975, to establish annual incidence rates of SLE in Native American tribes (7). However, rather than calculating rates for the separate geographic IHS regions, Morton et al calculated the rates for different Indian and Eskimo tribes, with interesting results when compared to the Acers study. The Morton study found that the annual incidence rates in 72 of the 75 tribes studied ranged from 0-7/100,000, similar to that reported in Caucasians, and similar to that reported by Acers et al. However, in 3 tribes, the Crow, the Arapahoe, and the Sioux, the annual incidence was much higher, at 27, 24, and 17 per 100,000 respectively. These tribes share a common ancestry as well as geography (7,25). It is almost certain that the Morton study figures represent an underestimate for all of the Native American tribes, since the study was also based only on inpatient records. It seems likely that the higher incidence rates in these three tribes were not apparent in the study by Acers because these tribal groups are distributed amongst more than one geographic region; and within each region, other tribal groups with lower incidence rates are included.

Morton et al performed a more detailed analysis of SLE in the Sioux tribe, which supported the hypothesis of an increased genetic tendency towards SLE in this tribe. The annual incidence rate for SLE in full-blooded Sioux was 31/100,000, compared to 21/100,000 for at least

half-blooded Sioux, and 17/100,000 for the total Sioux population (7). The annual incidence rate for the surrounding non-Indian population was estimated at 2-6/100,000 (7).

A study of the Nuu-Chah-Nulth of Vancouver Island (population approximately 2300) found an extraordinarily high minimal prevalence rate for SLE of 300/100,000 (12). This increased to 500/100,000 if cases meeting the criteria for both SLE and another connective tissue disease were included. SLE in these patients was reported to be generally mild, without neurologic or renal involvement. Of note, several SLE patients were also found to have RA.

The Indians of Southeast Alaska were also found to have a high prevalence rate of SLE. In a study of approximately 9770 Indians, (80% of whom were Tlingit Indians, the remainder being Tsimshian or Haida Indians), the crude prevalence rate of SLE was 92/100,000 (5). When these data were age-adjusted to 1970 US population data, the rate rose to 112/100,000. Unlike the Nuu-Chah-Nulth, the disease did not seem to be particularly mild. Thirty-nine percent had renal, 31% had neurological, and 54% had hematological involvement.

A population based study of SLE in central Canada, found a prevalence rate among Algonkian Indians (predominantly Cree & Ojibway Indians) of 31/100,000, compared to 14/100,000 for the surrounding non-Aboriginal population (76). The Indians also had a younger age of onset, had more renal involvement, higher fatality, and greater accumulation of damage over their disease course than did Caucasian patients.

The Eskimos in Alaska and Canada appear to have a normal to low prevalence of SLE. Pooled data from two studies of over 17,000 Alaskan Yupik and Inupiat Eskimos (5,6,13) found a prevalence rate of only 11/100,000. Of interest though, is the nearly equal sex ratio in Alaskan Eskimos. A study of 4000 Inuit Eskimos in the Canadian Northwest Territories found no cases of SLE (11).

Inflammatory Myopathies: Very little information is available for the inflammatory myopathies in Native Americans. The rarity and heterogeneity of these disorders make accurate determinations of incidence and prevalence difficult, but studies in predominantly Caucasian populations suggest the annual incidence and prevalence rates range from 1-8 and 10-63 per million population, respectively (77). The highest prevalence rate, at 63 per million, was from a

large, carefully conducted, population based study performed over 22 years in Tennessee (78). It included all inflammatory myopathies, as well as childhood-onset disease.

In a study of Mexican Mestizos, two cases of dermatomyositis (DM) were found in an area serving 30,000 Mestizos (49), for an estimated prevalence of 67 per million population. Comparison of this rate with the Tennessee rate suggests disproportionate disease in the Mestizos, since the Mexican paper included DM only, and only those cases attending a medical clinic over a 2-year period.

Separate studies of rheumatic disease in Inuit and Inupiat Eskimos found no cases of inflammatory myopathies in either group (6,11). In Southeast Alaska Indians, two cases of polymyositis were found in a population of close to 10,000, for an estimated crude prevalence of 200 per million population, higher than expected (5). Amongst the Nuu-Chah-Nulth Indians, 5 people were found to have polymyositis, out of a total population of 2300 (12), for an extraordinarily high prevalence estimate of 2174 per million population. It should be noted that all of the Nuu-Chah-Nulth patients with polymyositis were classified as having overlap syndromes, as each also met the criteria for another rheumatic disease, either RA or SLE or both (see below).

Systemic sclerosis: Three Nuu-Chah-Nulth patients were found to have systemic sclerosis (SSc), each also in the setting of an overlap syndrome, for an estimated prevalence of SSc in this population of 130/100,000 (12), well above the North American and European Caucasian estimates of 2-25/100,000 (79). Quite recently, the full-blooded Choctaw Indians in southeastern Oklahoma were found to have the highest prevalence of SSc yet found in any population (16). In this study of more than 250,000 Native Americans, case finding surveys were conducted in three separate Indian communities - the Oklahoma Choctaw Indian community, all other Native Americans residing in Oklahoma, and a Choctaw tribe located in Mississippi. Among the Oklahoma Choctaw, the prevalence rate was 469/100,000 for full-blooded Choctaw Indians, 31/100,000 for less than full-blooded Choctaws, and 66/100,000 overall. In non-Choctaw Oklahoma Indians, the prevalence of SSc was 10/100,000. Interestingly, no cases of SSc were found in the third group of 4500 largely full-blooded Mississippi Choctaw Indians,

where 21 cases might have been expected had the prevalence been the same as in the Oklahoma full-blooded Choctaws (16).

The authors also did a case control study of SSc, matching 12 Choctaw SSc cases for age, sex, and blood quantum to 4 Choctaw controls each (16). Using a detailed questionnaire, this study was unable to identify any significantly different environmental exposures between cases and controls. The case control study did find differences in HLA allele frequency between the two groups. HLA -DRB1*1602, DQB1*0301, DQA1*0501, B35, and Cw4 were each found in 100% of the cases, compared to 54%, 71%, 73%, 46%, and 50% of controls respectively. The HLA-DRB1*1602, DQB1*0301, DQA1*0501 haplotype was also found in 82% of Mississippi Choctaws, in whom no SSc was found. Only 8% of Mississippi Choctaws were ANA positive, compared to 100% of Oklahoma Choctaw SSc patients and 23% of Oklahoma Choctaw controls. The Choctaw SSc cases also demonstrated a remarkably homogeneous clinical picture, with 65% having diffuse skin involvement, 88% having Raynaud's phenomenon and pulmonary fibrosis, and 71% having anti-topoisomerase-1 antibodies (16).

The authors concluded that the high prevalence of SSc in Oklahoma Choctaws could be accounted for, at least in part, by high frequencies of certain class II MHC alleles, with the lack of disease in the Mississippi Choctaws, who had a high frequency of the same alleles, indicating that an additional genetic or environmental factor was needed. A further study identified a 2 cM haplotype on chromosome 15q containing the fibrillin-1 gene to be a major genetic contributor to SSc in this population (80). This haplotype was significantly increased in Choctaw SSc cases (7/18 versus 6/77 healthy Choctaw controls, $p=0.0024$). Interestingly, the authors were able to establish that 20 of the 25 contemporary Choctaw SSc cases were linked to five founding families in the late 1700's (80). The migration of the Choctaw Indians from several southeastern states, including Mississippi, to Oklahoma occurred in the early 1800's (16), suggesting that a founder effect occurred at that time with respect to SSc associated genes.

Atypical Connective Tissue Disease and Overlap Syndromes: Some community-based studies have also found frequent atypical rheumatic disease in Native populations. Amongst the Nuu-Chah-Nulth Indians, the authors found 52 cases of an unclassifiable articular syndrome, comprising nearly half of all of the rheumatology referrals in this population (12). The majority of

these patients were young women with periodic weather dependant joint swelling. Many had extraarticular features reminiscent of SLE, such as alopecia, cytopenias, vasculitis, nephritis, and serositis. Thirty-five percent of these patients were RF positive, and 31% were ANA positive. Another group of investigators working with Oklahoma Indians noted a high frequency of rheumatic diseases that were not easily classified under current nomenclature (50). In Morton et al's study of SLE in the Sioux, the authors commented that on review of medical records, they discovered many patients fulfilling only 2-3 criteria for SLE, who were therefore excluded from the prevalence calculations, and not examined or reviewed further (7). Amongst the Mille Lac Band of Chippewa Indians in central Minnesota, who had a prevalence of RA of 5.3%, an additional 6.8% of the population had a peripheral polyarthritis lacking the characteristic pattern of RA (4). Twenty-two percent of these patients were RF positive, 33% were ANA positive, and several had extraarticular features of autoimmune disease (48). Since these examples all occurred in populations with a high frequency of a defined rheumatic disease, one can speculate that such cases may also exist in other populations seemingly prone to autoimmune disease.

Overlap syndromes have been described in only one Native American population, the Nuu-Chah-Nulth Indians mentioned above. The authors found 9 patients with overlap syndromes, fully 6% of all referred patients, and 0.4% of the entire population (12). No data on the prevalence of overlap syndromes exists for any population, but these syndromes were found to make up 2.6% of a full-time academic practice in one study (81), suggesting an excess in the Nuu-Chah-Nulth. In each of these cases, the patients met the criteria for RA, as well as for one or two additional connective tissue diseases, either SLE, polymyositis, or SSc.

Summary: The Tlingit and the Nuu-Chah-Nulth emerge as being unusually prone to autoimmune disorders, although this tendency is expressed differently in the two groups. The Tlingit Indians have high prevalences of RA, SLE, and polymyositis (5), while the Nuu-Chah-Nulth have high prevalences of SLE, SSc, polymyositis, and overlap syndromes (12). These two groups have in common a high frequency of positive ANAs in the general population: 29% in the Tlingit (5) and 11% in the Nuu-Chah-Nulth (12). The Oklahoma Choctaw Indians, with a very high prevalence rate of SSc also have a high frequency of positive ANAs in the general population

(23%) (16). Atypical disease, which is difficult to classify, also appears to be common in a number of Native American groups.

SLE, like RA, is increasingly being viewed as a composite disease, with different MHC class II alleles mediating specific autoantibody subsets (82). Inflammatory myopathies and systemic sclerosis are also known to be heterogeneous diseases, with different autoantibodies conferring different clinical features and prognosis (83,84). In addition to MHC alleles, it is also probable that polymorphic TCR and immunoglobulin genes are involved in autoantibody production with the autoantibodies likely participating in the various clinical manifestations of the diseases (82,85). If this is indeed the case, study of underlying genetic mechanisms, treatment responses, outcomes, and contributing environmental factors may be enhanced by analyzing homogenous populations representing a single disease subset, with Native American tribal groups offering an excellent opportunity for such studies.

As is the case in rheumatoid arthritis, all of the tribal groups with an excess of connective tissue disease are Amerind Indians, again with the exception of the Tlingit Indians in Southeast Alaska.

Seronegative Spondyloarthropathies

Considerable data on the seronegative spondyloarthropathies in North American Aboriginals has been published over the last 20 years. Unlike the studies of RA described above, the spondyloarthropathies in North American Indians and Eskimos do not appear to be substantially different from the descriptions generally found in textbooks, with respect to clinical manifestations and disease course. Nevertheless, some important differences are worthy of discussion: First, the frequency of the HLA-B27 antigen appears to be relatively high in almost all Native North Americans, ranging from 9-50% (29) (Table 7). Second, while some tribal groups have extraordinarily high frequencies of the HLA-B27 antigen and correspondingly high rates of B-27 related arthropathies, other groups with a similarly high prevalence of B27 do not appear to develop an excess of spondyloarthropathies. Third, a striking polarity is seen in some of these indigenous populations, who appear to have a propensity to develop one B27 related disease

over another. Lastly, psoriatic arthritis (PsA) and enteropathic arthritis (EA) appear to be very rare in all North American Indian populations.

Table 7 lists the frequency of the HLA-B27 phenotype in North American Native, and North American and western European Caucasian populations. Studies of predominantly Caucasian populations reveal a phenotypic frequency of HLA-B27 of 2-18%, with a risk of ankylosing spondylitis (AS) of 2-8% in those who are HLA-B27 positive (86,87). The risk of Reiter's syndrome (RS) has been found to be as high as 20% (88) by some authors, although this figure is disputed. In populations with higher B27 frequencies, such as the North American natives, the risk of AS appears to be higher (86).

Haida Indians: The Haida Indians on the Queen Charlotte Islands on the Canadian Pacific coast, of Na-Dene ancestry, have one of the highest known prevalence rates of both HLA-B27 and AS (9,18,88,90). Fifty percent of the Haida Indians express the B27 antigen (89). Gofton et al surveyed 89% of Haida adults over the age of 15, from two communities on the Queen Charlotte Islands, and found a prevalence for AS of 6.2% (9,90) in males over 15, and 6.7% in males over 25 (18). No cases were found in females (90). An analysis of pelvic x-rays revealed a prevalence of sacroiliitis (Grade 3-4, New York criteria) of 9.5% in Haida males over the age of 25 (18), and a prevalence of 13.6% if grade 2 cases are included. This compares to a 1% prevalence of sacroiliitis in adult male pelvic x-rays in Watford, England (20), and confers a risk of developing sacroiliitis in HLA-B27 positive males of about 20% (18,86). No cases of RS, PsA, or EA were found in either study, and on questioning of local physicians caring for these people during the second survey, no cases over the preceding 10 to 15 years were recalled.

Interestingly, a survey of Southeast Alaskan Indians found only two cases of AS in Haida Indians (5), lower than expected based on the Canadian Haida data. The authors did find four cases of RS and stated that in their population of Haida Indians, the prevalence of RS was relatively high (5). The explanation for this discrepancy is unclear. While differing methodology may have been a cause of underdiagnosis of AS in the Alaskan study, (the Canadian studies were population based, the Alaskan study reviewed only those patients who had sought medical treatment for their problems; both used the Rome criteria the diagnosis), this would not explain the reversed results for the prevalence of RS. The frequency of HLA-B27 in the Alaskan Haidas

is unknown, and although it is believed that the two groups of Haida Indians are very closely related, it is possible that they are genetically less similar than expected. The authors of the Alaskan study also speculate that lack of exposure to the triggering organisms may be the cause of the low frequency of RS in the Canadian Haidas (5). One study did find a high prevalence of low-level antibodies to T. mycoplasmas (*Ureaplasma urealyticum*) in the Canadian Haida, but the antibody levels did not correlate with the presence of spondylitis or the HLA-B27 antigen (91). Another study investigated *Yersinia enterocolitica* as a possible cause of the increased prevalence of spondylitis in the Canadian Haida, and found no serologic evidence of *Y. enterocolitica* related to spondylitis (92).

Navajo Indians: The Navajo Indians in Arizona, also of Na-Dene ancestry, have a phenotypic frequency of HLA-B27 of between 26 and 36% (8,93,94). Initial HLA typing found that 36% of men and 26% of women were B27 positive (8), but the authors felt that the true frequency of B27 in men was likely closer to the 26% seen in women, due to biased selection of HLA-B27 positive men (94). This population appears to have a much higher prevalence of RS than AS. Over an 18-month period, 18 cases of RS were observed in a community hospital serving 6000 Navajo Indians, for an estimated annual incidence of 133/100,000, and a minimum prevalence of 300/100,000 (8). A review of hospital discharge records in the same population over a 3 year period found only 7 cases of AS but 22 cases of RS during the same period, for an estimated annual incidence for RS of 122/100,000 (93). These figures are much higher than a Finnish estimation of 30-40/100,000 per year (95). Because these studies were based on hospital discharges, and because of Navajo cultural reluctance to seeking medical care, milder cases were likely missed, suggesting that the true incidence and prevalence rates are higher (8). The high rate of RS may be due at least in part to the fact that this area is endemic for shigellosis (8), a known trigger for RS, combined with the high frequency of HLA-B27 in this population. Eighty-six to 88% of the patients with RS were B27 positive (8,93). A later study found a prevalence of radiological sacroiliitis of 11% in adult Navajos, and 83% of those with sacroiliitis who were HLA typed were HLA-B27 positive (96). The authors felt that the increased frequency of radiological sacroiliitis was due to RS, rather than AS, because 53% of RS patients previously reported by these authors had sacroiliitis (96).

The RS experienced by the Navajo may be somewhat different from that described in Caucasians. In 1971, 21 cases of "Navajo Arthritis" were reported over a 2-year period, described as an acute asymmetric polyarthritis, occurring predominantly in males, uniformly self-limited within 1-3 weeks (97). In all cases the knee was affected, most also had other joints affected. In general, the pattern of joint involvement was consistent with that described for RS. What was unusual was the complete absence of preceding dysentery and extraarticular features in this group of patients. (It should be noted that the authors excluded any patients with a history of prior or concomitant urethritis or conjunctivitis.) Recurrences also appeared less common than expected in this group, with the majority apparently entirely symptom free 1-2 years later. This "Navajo Arthritis" was later reassessed as most likely representing a variant of RS, given the ubiquity of Shigellosis, and given that during the same time period, only one definite case of RS was diagnosed at this hospital, a marked contrast to the numbers seen in neighboring centers (93). This serves to illustrate the subtle differences in the clinical features in rheumatic diseases in North American indigenous populations and the difficulties that may arise in applying classification systems designed for illnesses in non-Native American populations.

Bella Bella and Bella Coola Indians: There are limited data available on the Bella Bella and the Bella Coola Indians, both living on the coast of British Columbia. A survey of adult males over the age of 25, with a completion rate of 88-92%, found definite sacroiliitis in 9.2% of Bella Bella Indians and 3.5% of Bella Coola Indians (18). Definite AS (using New York criteria) was found in 7.6% of the Bella Bella and 3.1% of the Bella Coola (18). A later survey by the same authors reassessed the rate of definite sacroiliitis in the Bella Coola to be 2% (89), so it is possible that the other rates reported above were also overestimates. HLA typing showed that 25% of Bella Coola Indians were HLA-B27 positive, and 100% of those with sacroiliitis carried the antigen (89). In a later paper the risk of AS in B27 positive Bella Coola males was estimated to be 7% (98), much lower than the Haida (18) or the Pima Indians (99) (see below). Both Bella Bella and Bella Coola Indians of these groups are classified as Amerind Indians on the basis of language analysis (24), but the Bella Coola Indians appear to be a mixture of Amerind and Na-Dene based on mitochondrial DNA and Gm allotyping studies (26,100). No genetic studies are available for the Bella Bella Indians.

Pima Indians: The Pima Indians, who live in southwestern Arizona near the Navajo, but are Amerind Indians (25,26), have a phenotypic frequency of HLA-B27 of 18% (99,101). While Gofton et al (20) initially reported a relatively low prevalence of grade 2-4 radiological sacroiliitis of 3.9% in adult Pimas over the age of 25, (compared to 13.6% in the Haida, and 1.0% in Watford, England, and 0% for Jamaicans), a subsequent study of radiological sacroiliitis in randomly selected Pima Indians found a much higher prevalence of 16% in males over the age of 20 (101). In the same study, 14% of first degree relatives of the above men shown to have sacroiliitis also had grade 2 or higher sacroiliitis (101). An additional study confirmed this high rate, with 11% of 104 men having grade 3 or higher sacroiliitis (99). In this study, only 3% of female Pima Indians had grade 3-4 sacroiliitis (99). Two separate studies found the prevalence of AS to be 5% in Pima Indian males over the age of 30 (102), and 5.9% in Pima males over the age of 25 (18). The first study also examined adult female Pima Indians, and found no cases of AS (102).

In two studies, 50% (99) of Pima females, and 50- 73% (99,101) of males with sacroiliitis were HLA-B27 positive. The authors of one of these studies found that 53% of males but only 8% of females with HLA-B27 developed sacroiliitis (99). This risk of disease in males is considerably higher than the highest figure of 20% quoted for HLA-B27 positive Caucasians (88). In women, the numbers were too small to draw conclusions.

Although the rate of sacroiliitis and AS in Pima Indian males is strikingly high, especially when compared to the frequency of HLA-B27 in this population, the sacroiliitis appears to be somewhat milder. In the study by Gofton et al (20) mentioned above, 0.8% of Pima males had sacroiliitis of grade 3 or above, compared to 6.1% of Haida Indians males. A later study found that while 9.2% of Pima males had grade 2 or higher findings, only 4.5% had sacroiliitis of grade 3 or higher, compared to 13.6% and 9.5% in the Haida males (18).

In the Pimas, available information suggests the majority of the sacroiliitis is in fact due to AS, with a notable absence of RS, EA, and PsA. One of the above mentioned studies included data on 207 subjects, of whom 52 had grade 2 or higher changes of SI. No cases of RS, EA, or PsA were found amongst these 52 cases (101. No studies exist reporting any cases of RS, IBD, or PsA in Pima Indians.

Other Indian Tribes: In several other American Indian tribal groups, the prevalence of spondyloarthropathies appears to be either minimally or not at all elevated compared to North American and European Caucasians. In a survey of approximately 1000 Blackfeet Indians of northern Montana, a clinical diagnosis of AS was made in 1% of males (102). No cases of AS were found in female Blackfeet Indians. A later study of radiological sacroiliitis in the same population found a prevalence of 2.6% in males over the age of 25 (18). The frequency of HLA-B27 in this population is unknown.

The Hopi Indians of Arizona have a frequency of HLA-B27 of 9% (8), amongst the lowest recorded in any North American Native population, and within the range reported for Caucasians (29). It appears that the risk of clinical disease in this population is even lower than would be expected based on this frequency. Morse et al (8), who conducted the survey of the Navajo Indians, also surveyed the Hopi. Based on their known HLA-B27 frequency, and assuming the same risk of RS in HLA-B27 positive Hopi Indians as is seen in the Navajo, 4-5 cases of RS among the Hopi would have been expected, but none were found (8). These Hopi Indians share a geographical environment, including endemic Shigellosis, with the Navajo, yet in addition to finding no RS, very little B27 related disease of any sort was found. The authors concluded that the risk of RS in HLA-B27 positive Hopi Indians was considerably lower than that of the Navajo (8). While clinical disease appears to be minimal, a later study found a prevalence of radiological sacroiliitis of 8% in Hopi males, and none in females (94).

A survey of 85% of 2300 Nuu-Chah-Nulth Indians living on Vancouver Island, and subsequent examination and medical record review of those who had been referred to a rheumatologist in the past, found only 1 case of RS, 5 cases of sacroiliitis, and no cases of AS, PsA, or ES (12). All the cases of sacroiliitis were grade 2. It therefore appears that this group of Indians, living 150 miles south of the Haida, with a similar climate and lifestyle but distinct ancestry, have a very low prevalence of spondyloarthropathy. Two of the 5 patients with sacroiliitis were HLA-B27 positive, but the frequency of B27 in the general population is not known.

The prevalence of AS in Mexican Mestizos, who are a mixture of Caucasians (mainly Spaniards), and Mexican Mazahua Indians, is unknown, but several studies have found the

frequency of HLA-B27 to be 3-5.5% in this population in general, and 69-81% in those with AS, for an estimated relative risk of 66.5 for HLA-B27 positive individuals (103,104).

The Zuni Indians are a tribe of Pueblo Indians living in southwestern New Mexico, and are known to have a phenotypic frequency of HLA-B27 of 15% (105). A descriptive study of 24 Zuni Indians compared 12 HLA-B27 positive individuals to 12 age and sex matched B27 negative individuals (106). The authors found 1 case of uveitis, 1 case of RS, 6 cases of sacroiliac joint tenderness and/or back tenderness, and 3 cases of grade 2/4 radiological sacroiliitis, all in the 12 B27 positive individuals. There were no positive physical findings or relevant past history in the B27 negative individuals. The authors' assessments were blinded as to the subjects' HLA status, and the subjects had been randomly selected. Although these numbers are too small to draw definitive conclusions, it seems likely that the Zuni Indians also have a high prevalence of radiological sacroiliitis and other B27 related physical findings.

The only data that exists on the large number of Native Americans in Canada east of the Rocky Mountains is a pilot study of a group of Cree Indians in Alberta. In this study, 103 adults aged 20-42 years were examined and HLA typed. Fourteen (13.6%), were found to have HLA-B27 (107). Ten of the 14 underwent pelvic x-rays, and two had grade 2 sacroiliitis. Neither had definite AS. The resulting estimated prevalence of abnormal sacroiliac joints in 20% of B27 positive individuals approximates that described in the Haida Indians.

The Cree Indians (part of the Algonkian Indian group) above, as well as the Hopi, the Zuni, the Nuu-Chah-Nulth, and the Mazahua Indians are all of Amerind origin (24) (Table 4).

A study of rheumatic diseases in the Alaskan Indians of the Southeast coast did not find an excess of the spondyloarthropathies. In a regional Indian population of approximately 9770, a prevalence rate of 1.1% for all seronegative spondyloarthropathies in adults over the age of 20 was found (5). In this study, there were equal numbers of patients with RS and AS, although AS predominated in males, and RS in females. Interestingly, the male: female ratio for all spondyloarthropathies was also equal, due to the finding that 50% of females had an undifferentiated spondyloarthropathy, compared to 18% of males. The phenotypic frequency of HLA-B27 in Tlingit Indians, who make up at least 80% of this study population, was found to be 18% in a separate study (69), suggesting a lower risk of disease in B27 positive individuals than

described in other tribal groups above. Since the above study identified cases by virtue of their having sought medical care for their symptoms, the true prevalence of spondyloarthropathies may be higher.

Eskimo-Aleut: The Inuit Eskimos of northern Canada appear to have a similarly low prevalence of the spondyloarthropathies. A study of rheumatic disease among the Inuit of the Keewatin district of the Northwest Territories of Canada found a prevalence rate of 0.8% for all spondyloarthropathies in adults over the age of 15, and a yearly incidence of 60.1/100,000 (11). The prevalence rate for definite AS was 0.2%, and for RS, 0.1%. The remainder of the spondyloarthropathies included in the prevalence estimate were unclassifiable, with the exception of one case of psoriatic arthritis. The authors felt that these figures likely represented an underestimate. RS was somewhat more frequent than AS, with yearly incidence rates of 24.9/100,000 and 5.1/100,000, respectively (11). Presumably, the lower prevalence, but higher incidence figures for RS compared to AS are due to disease remissions in RS, but no clinical data is provided. In this population the male: female ratio was roughly 3:1 for all spondyloarthropathies. The frequency of HLA-B27 in a small group of control subjects in this population was 37%, while 87% of patients with spondyloarthropathies were B27 positive (11).

In Alaskan Eskimos, the prevalence rates of spondyloarthropathies are higher than in their Canadian counterparts. Alaskan Yupik and Inupiat Eskimos are known to have respective frequencies of HLA-B27 of 40% and 25% (6,13,15,66). The prevalence of all spondyloarthropathies was found to be 2.5% in adults over the age of 20, with no significant difference between the two Eskimo groups, in a total study population of approximately 6749 (15). The prevalence rate of AS was 0.4% in males and females, while for RS the prevalence rate was 1.2% in males, 0.6% in females, and 1.0% overall. AS was considerably less common in Eskimos than RS, perhaps surprising given the high frequency of B27 in this population, and PsA and EA were very rare. Also, there were a remarkable number of overlap spondyloarthropathies, where patients met the criteria for more than one disease, as well as undifferentiated spondyloarthropathies, the latter particularly in women (15).

Discussion: To summarize the above data; the Haida, the Navajo, the Pima, the Bella Bella and the Bella Coola Indians, and the Yupik and Inupiat Eskimos have high (although quite variable) rates of B27 related disease, while the Southeast Alaskan Indians, the Inuit Eskimos, the Blackfeet, the Nuu-Chah-Nulth and the Hopi Indians appear to have rates of disease that are either lower than or similar to published rates in Caucasians. Second, while the Haida, and the Pima appear to develop AS almost exclusively, the Navajo are more prone to RS; and Alaskan Indians, and all three Eskimo groups appear to develop both. Third, the B27 antigen appears to confer differing risks of disease in different populations, ranging from a high of 53% in Pima males, to an apparently very low risk in Alaskan Indians. These data are summarized in Table 8. Similar variations in risk of disease associated with the B27 antigen have been found in Caucasian populations (86).

It is evident that more than simply the frequency of HLA-B27 in a population is involved in determining the frequency of B27 related disease. While no definitive explanation currently exists there are several possible contributing factors. Some of the differences in disease prevalence and expression certainly relate to the triggering antigens. The natural peptides may have distinct binding affinities, and variations in exposure to pathogenic factors are also an obvious possibility. Studies of the Eskimos and Alaskan and Northwest Pacific Indians are an example of this. As mentioned above, only AS was described in the Canadian Haida, as well as in the Bella Bella and Bella Coola Indians, all of whom live on the Northwest Pacific coast. However, RS was found in the Alaskan Haida, living in an area where RS and AS were both described in the other regional Indian groups (Tlingit and Tsimshian Indians). All three Eskimo groups, both those in Alaska and Northern Canada, develop both AS and RS, suggesting the possible presence of a triggering antigen in the far north, which is absent on the Northwest Pacific Coast. At least amongst the Inuit, the prevalence of *Chlamydia trachomatis* urethritis is known to be high (108), with correspondingly high rates of RS, but this is not reported in other northern indigenous populations. That triggering antigens alone are an incomplete explanation is implied by data from southwestern USA. The Hopi and Navajo Indians both live in an area endemic for Shigellosis, but the Hopi have a very low frequency of reactive arthritis, while that in the Navajo is high.

Family studies in Caucasians have found that relatives of a patient with AS are more likely to develop AS than RS, and that relatives of a patient with RS are more likely to develop RS (109). Perhaps this family tendency to 'breed true' also applies to these relatively homogenous indigenous populations as a whole. The explanation for this phenomenon however, remains obscure.

B27 related EA and PsA are strikingly absent in essentially all of these populations. This likely relates to the lack of psoriasis and inflammatory bowel disease (IBD) in general in these populations. Data, although accurate, are limited, with the exception that the Inuit are known to have a very low prevalence of psoriasis (110), and the Algonkian Indians in western Canada have recently been shown to have a much lower prevalence rate of IBD than the surrounding local population (111).

While several subtypes of B27 have been described, it has been established that North American Indians and Eskimos carry the B*2705 subtype exclusively (112). This is also the most common subtype in Caucasians (113), therefore differences in disease susceptibility and expression are not due to B27 subtype differences.

One particularly fascinating aspect of these indigenous populations is the almost universal preservation of the B27 antigen at relatively high frequencies amongst these people on the North American continent, but not in Central or South America (112). While there is some clustering of B27 frequencies by ancestral groupings (114), with the highest B27 frequencies seen in the Na-Dene Indians and Eskimo-Aleuts (29), (both of whom reside predominantly in the north), and the lowest in the Amerinds Indians (29), a climatic gradient also appears to exist. This is quite dramatically illustrated by the distribution of B27 in the Amerinds. The northern, central and southern Amerinds all share a common ancestry (24), but B27 is virtually absent in Central and South American Indians, while prevalent at relatively high frequencies in northern Amerinds (112). This climatic B27 gradient appears to be duplicated worldwide, with the only exception being a small study of an isolated group of Papua New Guinea natives, who have B27 frequencies of 25-52% (115). HLA-B27 is present in lower frequencies in southern vs. northern Europeans and in southern vs. northern Indian Caucasoids (29). It is present in moderately low frequencies in the Middle East and Asia and is virtually absent in Australian Aborigines, Maori,

and African populations (29,112). Table 9 presents B27 frequencies in populations around the world. Neither genetic drift nor the founder effect can fully explain the clustering of high B27 frequencies in northern latitudes.

Native Americans are descended from northeast Asian populations, in whom the present day, B27 frequency ranges from 2-8% (112). The combined findings of clustering of high frequencies of B27 in northern latitudes, and the divergence of B27 frequencies in both the Amerinds (in North vs. Central and South America) and in present day Asian populations vs. their American Indian descendants lead to the speculation that HLA-B27 is preferentially conserved in northern climates. Conceivably HLA-B27 confers an unknown advantage in northern climates, or is in linkage disequilibrium with a gene that does so. HLA-B27 molecules have been shown to be one of the best class I molecules in terms of generating viral-specific immunity (116), so perhaps the answer lies in a 'northern' virus.

In general, Native American tribal groups are not only genetically homogenous, but also often live in relatively well-circumscribed areas. Since many also have a very high prevalence of HLA-B27 and related diseases, these populations may provide an ideal opportunity for further study of additional genetic and environmental influences on B27 related disease expression.

Juvenile Rheumatic Diseases

Published reports of the incidence of juvenile chronic arthritis (JCA) from Europe and the US range from 9-25/100,000 per year (117), while reports of prevalence range from 57-113/100,000 (36). In general, pediatric rheumatic diseases in Native Americans seem to parallel that found in the respective adult communities, with increased prevalence rate for both RA and spondyloarthropathies seen, but with much less published information available.

Hill and Walters were the first to report an apparent excess of JCA in North American Indians (118), at the provincial Children's Arthritis Program in British Columbia, Canada. They found that while North American Indian children comprised 3.6% of the total British Columbia childhood population, 18.6% of their patients with JCA were Indian. Hill later reported that the incidence of juvenile rheumatoid arthritis (JRA) for the years 1966-1975 was 7/100,000/year for Native children compared to 3/100,000/year for non-native children (19).

Rosenberg et al reviewed chronic arthritis in Native children in two pediatric rheumatic disease clinics, the Arthritis Centre in Vancouver, British Columbia, and the Children's Hospital in Winnipeg, Manitoba, Canada (10). In British Columbia, the Native children were primarily of the Haida, Cowichan, or Salish tribes, while the Manitoba Native children were primarily of the Cree, Assiniboine or Sioux tribes. They found a prevalence of JCA of 34/100,000 for non-Indian children, and a prevalence of 59/100,000 for Indian children. The prevalences of JRA for Caucasians and Indians were 20/100,000 and 36/100,000 respectively, while the prevalences of spondyloarthropathies in the Caucasian and NAI children were 4/100,000 and 29/100,000 respectively. The ratio of JRA to spondyloarthropathies in the Indian and non-Indian children was 1.2:1 and 5.4:1 respectively.

The serologic differences found in adult Indians with RA may also be present in children. In Rosenberg's study, 35% of Native children with JRA were RF positive, compared to 9.1% of Caucasians, and 53.3% of Native children were ANA positive vs. 28.8% of Caucasian children (10). Hill et al also found that 46% of Indian children were RF positive compared to 5.2% of non-Indian children (118). In general, the polyarticular RF+ subtype of JRA seems to be the most common presentation in Indian children. Rosenberg et al's study found that 59% of Indian children with JRA had a polyarticular onset versus 29% of the Caucasian children (10), while 6/8 Southeast Alaska Indian children had polyarticular RF+ JRA (5). In the report by Hill et al, a much lower percentage of North American Indian children had mono- or oligoarthritis compared to Caucasian children (118). In this report, 61% of Indian children were in Steinbroker functional class III, compared to 24% of non-Indian children. There are no other reports of differences in serological or clinical manifestations in Native children.

Both the overall excess of JCA, as well as an even greater preponderance of juvenile spondyloarthropathies compared to JRA has also been reported in other Native American populations. The Alaskan Inupiat Eskimos were found to have an average annual incidence rate of JCA of 28/100,000 (6). Only one of the 6 children found in this survey had JRA, and 5 of the 6 had spondyloarthropathies, all of whom were male, for an annual sex specific incidence rate of 47/100,000. In Yupik Eskimos, the average annual incidence rate of JCA was found to be 42/100,000 (13). Only 3 of 24 Yupik children had JRA, the remainder was diagnosed with

spondyloarthropathies. Amongst the Inuit Eskimos in northern Canada, there was a marked predominance of juvenile spondyloarthropathies over JRA, with respective annual incidence rates of 106 and 24 per 100,000 (11). Children again represented a large proportion of all spondyloarthropathies in this population, at 39%. Boyer et al found an average annual incidence of JCA of 39/100,000 in Southeast Alaska Indian children, with a prevalence rate of 83/100,000 for active JCA, 138/100,000 if inactive disease was included. In this group, 47% of children had spondyloarthropathic disorders, 32% had polyarticular, RF positive JRA, while the remainder had pauciarticular ANA positive JA (15).

Spondyloarthropathies with onset during childhood seem to make up a greater proportion of all spondyloarthropathies in many indigenous populations, regardless of the overall prevalence of spondyloarthropathies in the population. Children represented 38% of the entire spondyloarthropathies found in the Inupiat population (6), 31% amongst the Yupik (13), and 39% amongst the Inuit (11), compared to 10-21% of patients in Caucasian studies (119). The Mexican Mestizos also appear to have a preponderance of juvenile onset AS, with 54% of patients in one study presenting before age 16 (119), while the Mestizo population as a whole is not known to have an excess of spondyloarthropathies. The age of onset of all of the cases of sacroiliitis was in childhood or adolescence in the Nuu-Chah-Nulth Indians, who appear to have a very low prevalence of spondyloarthropathies (12).

Lastly, one other unusual feature of juvenile spondyloarthropathies in Native North American populations is that Reiter's syndrome, thought to be very uncommon in children (117,120), is seen relatively frequently. Four of 14 Indian children with spondyloarthropathies were diagnosed with RS in Rosenberg et al's study (10), described above, compared to 0/33 Caucasian children. There were 2 cases of RS diagnosed amongst 19 Southeast Alaska Indian children with JCA (5). One out of 24 Yupik Eskimo children (13), 2/6 Inupiat Eskimo children (6), and 3/11 Inuit Eskimo children (11) with JCA were diagnosed with RS. Reiter's Syndrome has also been reported in Navajo Indian children (121).

Osteoarthritis

The available literature on osteoarthritis (OA) in Native Americans is both minimal and confusing. A survey done in the 1960's including 86% of adults over 30 years of age found rather astounding rates of Grade 2 or higher radiographic OA of the hands of 68% in Blackfeet Indians, and 65% of Pima Indians (102). This survey included almost 1000 individuals in each tribe. Another early survey of more than 400 Alaskan Eskimos found a lower prevalence of Grade 2 or higher radiographic OA of the hands in 23.9% of adults over the age of 40, compared to a prevalence of 43.3% in US Caucasians over the age of 40 (122). The National Health Examination Survey, a radiographic survey also conducted in the United States at about the same time, found a prevalence of mild, moderate or severe OA of the hands of 32.5% in adults aged 25-74 (123). Each of these surveys used the same criteria for grading radiographs (124).

These rates can be compared to the Tecumseh Community Health survey of a Caucasian population from the same era, where the prevalence of OA diagnosed by history and physical examination was found to be 4.2% for males, and 9.0% in females over the age of 20 (36). The prevalence of symptomatic OA of the hands was estimated at 3.1% of adults aged 25-72, using data from the National Health Examination survey mentioned above (36).

More recently, a survey of about 4000 Inuit Eskimos found a low point prevalence of OA 1.2% in men and 2.1% in women (11). Patients in this survey were identified based on their recorded presentation with symptoms. Using similar methodology, a survey of approximately 2300 Nuu-Chah-Nulth Indians found that only 10 had been referred to a rheumatologist for OA over a 15-year period (12).

These more recent findings of apparently low prevalence rates are difficult to reconcile with the earlier higher estimates, although the differences in methodology may account for some of the differences in the results. Most Native American groups have experienced a dramatic shift in lifestyle over the last century, with evolution from predominantly agricultural or hunting communities to more sedentary lifestyles. The early studies would still have included many individuals exposed to more traditional lifestyles. Whether this may account for some of the

above discrepancies is uncertain. Certainly, larger, population based surveys would help to answer this question.

Conclusions

Seen in its entirety, the evidence points to a substantial burden of rheumatic disease in North American Indians and Eskimos. It is probable that the burden of disease is actually much larger, since there is no published information on the majority of indigenous groups, and very little on many others, with only suggestions of increased prevalence rates and unusual features. Certainly on encountering clinicians working in areas with large indigenous populations, the universal impression seems to be one of excessive rheumatic disease. As mentioned above, RA, SLE, and connective tissue diseases appear to be clustered in Indians of Amerind ancestry, while spondyloarthropathies predominate in Na-Dene and Eskimo-Aleut populations. It should be pointed out that the study of the migrations and ancestry of pre-Columbian Americans is far from being an exact science; with many uncertainties, controversies, and gaps in the knowledge (23-27). That being said, the correlation between the pattern of rheumatic diseases in Native North American and the pattern of ancestry based on linguistic, dental and genetic evidence is still remarkable.

It is probable that this excessive burden of rheumatic disease is genetic in origin. This is certainly borne out by the very high frequencies of the RA shared epitope, and the B27 antigen in many of these groups (48,63,66,67,69,70,89,94). Genetically, American Indians and Eskimos have been definitely linked to Asians, with a reduction in genetic variation from Asia to America (27), suggesting a founder effect as the probable reason for the high overall prevalence of disease. The decimation and forced migration of many Native populations at the time of European conquest likely resulted in population bottlenecks and renewed founder effects. The importance of such a founder effect has been demonstrated recently by Arnett et al (16), as discussed above, where a founder effect appears to be responsible for both the extremely high prevalence of SSc in Oklahoma Choctaw Indians, and its absence in another, closely related group of Choctaw Indians.

Several tribal groups have also demonstrated familial clustering of rheumatic diseases. The Chippewa (4), the Pima (54), the Choctaw(16), and the Bella Bella(45) Indians have all been found to display familial clustering. An environmental cause for this familial aggregation can not be ruled out, but the combination of the high prevalence of rheumatic disease in Native Americans across North America, the high prevalence of the HLA susceptibility loci, and the migration history of these populations is suggestive of a genetic cause.

It is now clear that histocompatability genes alone are not solely responsible for rheumatic disease susceptibility (54,62,65). This is most clearly illustrated by the very high prevalence of known associated genetic elements in some indigenous populations who do not have proportionally increased rates of disease, for example the RA epitope in the Alaskan Eskimo (66), and the B27 antigen in the Tlingit (69). It is most likely that combinations of genes, together with variations in environmental challenges encountered may well explain both the ubiquitous nature of autoimmune rheumatologic disease in the Native American population, as well as the variations in phenotype, frequency, and risk of disease encountered.

Wilma Bias et al (125), based on studies of families who were multiplex for rheumatic diseases, proposed that autoimmune disease is inherited as an autosomal dominant trait. According to this hypothesis of a primary autoimmune gene, the autoimmune phenotype expressed is influenced by other secondary genes, including HLA genes, and the penetrance modulated by sex steroids, as well as environmental challenges such as viral and bacterial infections.

Very recently, investigators found the familial distribution of RA in Pima Indians to be consistent with an autosomal recessive mode of inheritance (54). A recessive mode of inheritance for RA has also been supported by other studies (126,127). This theory would certainly be consistent with the high disease prevalence and frequent familial distribution of rheumatic disease often seen in native tribal groups, since their relative genetic homogeneity and cultural isolation are ideal circumstances to allow expression of recessive genes.

Regardless of the mode of inheritance of these non-HLA susceptibility genes, the North American Indian population represents a singular opportunity to study genetic contributions to rheumatic disease, since most Native American populations remain quite isolated, resulting in

relative genetic homogeneity. Nowhere else in the world can one find large population groups who have clinical disease at high rates, together with restricted polymorphism, and resultant high frequencies of relevant genes.

Obviously, the high prevalence of clinical disease has practical implications in this population as well. Certainly, the index of suspicion for rheumatic diseases in Native American populations should be high, and the atypical presentation of rheumatic disease in a number of Native groups should be kept in mind. For some indigenous groups, geographic isolation plays a role (128), while socioeconomic disadvantage, with its well-known negative prognostic implications, is a factor in many others (128). The severe disease that many Native Americans have been shown to have (3,5,17,19,43-45,47-49,76,118) further complicates this situation. Thus, there is likely a need for specialized clinical and educational programs in areas that serve Native Americans.

Tables.

Table 1: Prevalence and Incidence Rates of Rheumatoid Arthritis in Caucasians and Native North Americans.

Population	Geographic Region	Prevalence	Annual Incidence
Pima Indians (22,41,54)	Arizona	2.5-5.3%	422/100,000
Chippewa Indians (4)	Central Minnesota	5.3%	–
Blackfeet Indians (40)	Montana	5% females, 4% males	–
Yakima Indians (43)	Central Washington	3.4% females	–
Tlingit, Tsimshian, & Haida Indians (6)	Southeast Alaska	2.4%	122/100,000 female 46/100,000 male
Algonkian Indians (44)	Central Canada	2.0%	–
Nuu-Chah-Nulth (12)	Vancouver Island	1.4%	–
Haida Indians (46)	Queen Charlotte Islands	1-1.5% females, 0.5-1% males	–
Inupiat Eskimos (6)	Northwest Alaska	1.0%	–
Yupik Eskimos (13)	Southwest Alaska	1.1%	–
Inuit Eskimos (11)	Northwest Territories	0.6%	48/100,000
National Health Examination Survey (37)	USA	1.6% females, 0.7% males, 0.9% total	–
Rochester (38)	Minnesota	1.0%	22/100,000 males 48/100,000 females
England (39)	England	1.1%	–

Table 2: Incidence of Rheumatoid Disease in North American Indians in the US 1980-1990*

Indian Health Services Area	Population (1990)	Major Tribal Nations	Mean annual Incidence / 100,000
Aberdeen	75,000	Sioux, Cheyenne, Blackfeet, Crow	27
Alaska	86,000	Tlingit, Haida, Tsimshian Indians, Yupik & Inupiat Eskimos, Aleut	23
Albuquerque	66,000	Apache, Pueblo, Navajo	13
Bemidji	61,000	Sauk & Fox, Winnebago, Kickapoo	3
Billings	47,000	Sioux, Cheyenne, Crow, Arapahoe	23
Navajo	181,000	Navajo	9.5
Oklahoma	257,000	Cherokee, Creek, Choctaw, Chickasaw, Seminole, Kiowa, Shawnee, Comanche, Osage, etc.	4.2
Phoenix	120,000	Shoshone, Paiute, Nez Perce', Spokane, Yakima	22
Portland	101,000	Apache, Pueblo, Hopi, Zuni	6.6

*Modified from Acers et al, Oklahoma State Medical Journal, 1994 (14).

Table 3: Summary Of Unusual Clinical And Serologic Features In Native North Americans with Rheumatoid Arthritis

Tribal Group	Prevalence	Age at Onset (years)	RF Positive (%)	ANA positive (%)	Shared epitope frequency RA patients (%)	Shared epitope frequency Controls (%)	Comments
Tlingit (5,47)	⇑	51% <35	97	71	Dw16: 91 DR9: 18	Dw16: 85 DR9: 8	44% rheumatoid nodules 24% extraarticular features
Yakima (43,53)	⇑	peak prevalence <35	94	53	Dw16: 83	Dw16: 60	50% rheumatoid nodules 100% erosive disease 64% Stage IV x-ray changes
Chippewa (4,48)	⇑	58%< 40	92	75	DR4: 100	DR4: 68	42% rheumatoid nodules
Kiowa (50)	?	56%< 40	100	75	?	?	33% Anti-Ro positive
Non-Kiowa Oklahoma (50)	?	?	94	27	?	?	
Northern Ontario Aboriginals (52)	?	40% <30	?	⇑	?	?	
Central Canadian Algonkian (44,51)	⇑	Mean 35.6	?	?	?	?	higher Lansbury scores, more persistently elevated ESR, mean RF titre 800iu/l, vs. 440iu/l in Caucasians
Nuu-Chah-Nulth (12)	⇔	Non-erosive RA: mean 28 Erosive RA: mean 38 RA overlap: mean 24	79	75	?	?	28% had overlap syndrome 50% with non-erosive RA had unusual extraarticular features 54% with erosive RA had extraarticular features
Bella-Bella (45)	⇔	29					Severe, erosive disease
Mazahua (49)	?	mean <40 in women	100	34	?	?	65% deformities, fused joints
Pima (22,40,41,54)	⇑	?	40	?	Dw16: 98	Dw16: 95	
Blackfeet (40)	⇑	?	40	?			
Inuit Eskimo (11)	⇔	mean 56.8	83	0	DR4:80	DR4:– 63	83% erosive disease
Yupik Eskimo (13)	⇔	mean 46	78	28	Dw4: ?	Dw4: 46	

Table 4: Native American Ancestral Groupings* and Rheumatic Diseases

Ancestral Group	Tribal Group	Geographic Region	Rheumatic Disease Associations
AMERIND			
	Chippewa (4,48)	Minnesota	Rheumatoid Arthritis
	Blackfeet (40)	Montana	Rheumatoid Arthritis
	Arapahoe (7)	Midwestern States	SLE
	Crow (7)	Midwestern States	SLE
	Yakima (43,53)	Washington	Rheumatoid Arthritis
	Kiowa (50)	Oklahoma	Rheumatoid Arthritis
	Choctaw (16)	Oklahoma	Scleroderma
	Sioux (7)	Northern Ontario/ Midwest States	SLE
	Algonkian (44,51,76)	Canadian Prairie	SLE/ Rheumatoid Arthritis
	Hopi (8,96)	Arizona	Spondyloarthropathies
	Zuni (105)	New Mexico	Spondyloarthropathies
	Nuu-Chah-Nulth (12)	Vancouver Island	SLE/Myositis/Scleroderma/Overlap
	Bella Bella (18,45)	Pacific Coast	Rheumatoid Arthritis/ Spondyloarthropathies
	Tsimshian (5)	Alaska	Rheumatoid Arthritis
	Pima (20,41,42,54,98,99)	Arizona	Rheumatoid Arthritis, Spondyloarthropathies
	Mestizo (Mazahua)(49)	Northern Mexico	Rheumatoid Arthritis /Myositis
NA-DENE			
	Tlingit (5)	Alaska	Rheumatoid Arthritis/SLE/Myositis
	Haida (18)	Queen Charlotte Islands	Spondyloarthropathies
	Navajo(8,93,94)	Arizona	Spondyloarthropathies
	Bella Coola (18)	Pacific Coast	Spondyloarthropathies
ESKIMO-ALEUT			
	Inuit (11)	Northwest Territories	Spondyloarthropathies
	Yupik (13,15)	Alaska	Spondyloarthropathies
	Inupiat (6,15)	Alaska	Spondyloarthropathies

* Ancestral groupings from Greenberg JH, 'Language in the Americas' 1987 (23).

Table 5. Prevalence rates of SLE in selected North American Populations.

Population	Cases/100,000 population		
	Males	Females	Total
Nuu-Chah-Nulth Indian (12)	–	–	300-500
SE Alaska Indian (5)	22	166	92
Algonkian Indian (76)	–	–	35
Alaskan Eskimo (6,13)	11	11	11
Kaiser Foundation (72)	–	–	51
Rochester MN (73)	19	54	40
New York (74)	–	–	15

Table 6. Indian Health Services: Incidence patterns of SLE*

I.H.S. area	Population (1990)	Major Tribal Nations	Mean annual incidence 100,000
Aberdeen	75,000	Sioux, Cheyenne, Blackfeet, Crow	4.1
Alaska	86,000	Tlingit, Haida, Tsimshian Indians, Yupik & Inupiat Eskimos, Aleut	3.3
Albuquerque	66,000	Apache, Pueblo, Navajo	1.2
Bemidji	61,000	Sauk & Fox, Winnebago, Kickapoo	1.3
Billings	47,000	Sioux, Cheyenne, Crow, Arapahoe	3.2
Navajo	181,000	Navajo	2.0
Oklahoma	257,000	Cherokee, Creek, Choctaw, Chickasaw, Seminole, Kiowa, Shawnee, Comanche, Osage, etc.	1.5
Phoenix	120,000	Shoshone, Paiute, Nez Perce', Spokane, Yakima	3.0
Portland	101,000	Apache, Pueblo, Hopi, Zuni	1.4

* Modified from Acers et al, Oklahoma State Medical Journal, 1994 (14).

Table 7: Frequency of HLA-B27 in North American Native and Caucasian populations

Population	HLA-B27 frequency General Population (%)	HLA-B27 frequency Patients with AS/RS* (%)
Haida Indians (18,89)	50	100
Yupik Eskimos (13,66)	40	100
Inuit Eskimos (11)	37	87
Navajo Indians (8,93,94)	26-36	86-88
Dogrib Indians (29)	30	–
Inupiat Eskimos (66)	25	–
Bella Coola Indians (89)	25	100
Yakima Indians (29)	21	–
Pima Indians (98,99,101)	18	50-73
Tlingit Indians (5,69)	18	–
Cree Indians (107)	14	–
Zuni Indians (105,106)	15	–
Chippewa Indians (29)	11	–
Hopi Indians (8,94)	9	–
Papago Indians (29)	9	–
Mexican Mestizos (103,104)	3-5	69-80
Norway (29,88)	16	90-95
Western Europeans (29,88)	6-9	90-95
North American Caucasians (87,88)	8	90-95

* AS = ankylosing spondylitis, RS = Reiter's Syndrome

Table 8. HLA-B27 Frequencies & Disease Associations in North American Indians

Population	B27 frequency (%)	B27 related Disease	Risk of Disease in B27+ Individuals (%)
Pima Indians (98,998,101)	18	AS/SI	53 SI
Navajo (8,93,94)	26-36	RS/SI	30-44 SI
Haida (18,89)	50	AS/SI	20 SI
Cree Indians (107)	14	SI	20 SI
Bella Coola (18,89,98)	25	AS/SI	7 SI
Alaskan Indians (5,69)	18	SpA	6 all
Hopi Indians (8,96)	9	RS/SI	low RS

* AS = ankylosing spondylitis; RS = Reiter's Syndrome; SI = sacroiliitis; SpA = spondyloarthropathy

Table 9. Prevalence of HLA-B27 in World Populations

Population	Ethnic Group	HLA-B27 Frequency (%)
Caucasoids (29, 113)		
	Northern Sandinavians	10-18
	Western Europeans	6-9
	Southern Europeans	2-6
	Jews, Arabs, Armenians, Iranians	3-5
	Northern India	4-6
	Southern India	2-3
Asian (29,113)		
	Vietnamese	9
	Chinese	2-6
	Thai	6
	Korean	3-8
	Japanese	1
African (113)		
	North Africa	2
	West Africa	2
	Bantu	0
American Native (113)		
	Eskimo	25-40
	North American Indian	9-50
	Central American Indian	0
	South American Indian	0

References

1. 1990 US Census Data; Database C90STF1C2.
2. Statistics Canada, 1996 Census *Nation* Tables.
3. Hill RH, Robinson HS. Rheumatoid arthritis and ankylosing spondylitis in British Columbia Indians: their prevalence and the challenge of management. CMAJ 1969;100:509-11.
4. Harvey J, Lotze M, Stevens MB, Lambert G, Jacobson D. Rheumatoid arthritis in a Chippewa Band. I. Pilot screening study of disease prevalence. Arthritis Rheum 1981;24:717-21.
5. Boyer GS, Templxin DW, Lanier AP: Rheumatic diseases in Alaskan Indians of the southeast coast: High prevalence of rheumatoid arthritis and systemic lupus erythematosus. J Rheumatol 1991;18:1477-84.
6. Boyer GS, Lanier AP, Templin DW. Prevalence rates of spondyloarthropathies, rheumatoid arthritis and other rheumatic disorders in an Alaskan Inupiat Eskimo population. J Rheumatol 1988;15(4):678-682.
7. Morton RO, Gershwin E, Brady C, Steinberg AD. The incidence of systemic lupus erythematosus in North American Indians. J Rheumatol 1976;3:186-190.
8. Morse HG, Rate RG, Bonnell MD, Kuberski TT. High frequency of HLA-B27 and Reiter's syndrome in Navajo Indians. J Rheumatol 1980;7:900-3.
9. Gofton JP, Robinson HS, Trueman GE. Ankylosing spondylitis in a Canadian Indian population. Ann Rheum Dis 1966:25:525-7.
10. Rosenberg AM, Petty RE, Oen KG, Schroeder ML. Rheumatic diseases in Western Canadian Indian children. J Rheumatol 1982;9:589-92.
11. Oen K, Postl B, Chalmers IM, Ling N, Schroeder ML, Baragar, FD et al. Rheumatic Diseases in an Inuit population. Arthritis Rheum 1986;29: 65-74.
12. Atkins C, Reuffel L, Roddy J, Platts M,,Robinson H,,Ward R. Rheumatic disease in the Nuu-Chah-Nulth Native Indians of the Pacific Northwest. J Rheumatol 1988;15:684-90.

13. Boyer GS, Lanier AP, Templin DW, Bulkow L: Spondyloarthropathy and rheumatoid arthritis in Alaskan Yupik Eskimos. J Rheumatol 1990;17:489-496.

14. Acers TE, Acers-Warn A. Incidence patterns of immunogenetic diseases in the North American Indians. J Okla State Med Assoc 1994;87:309-14.

15. Boyer GS, Templin DW, Comoni-Huntley JC, Everett DF, Lawrence RC, Heyse SF, et al. Prevalence of spondyloarthropathies in Alaskan Eskimos. J Rheumatol 1994;21:2292-7.

16. Arnett FC, Howard RF, Tan F, Moulds JM, Bias WB, Durban E, et al. Increased prevalence of systemic sclerosis in a Native American tribe in Oklahoma. Association with an Amerindian HLA haplotype. Arthritis Rheum 1996;39:1362-70.

17. Beasley RP, Willkens RF, Bennett PH. High prevalence of rheumatoid arthritis in Yakima Indians. Arthritis Rheum 1973;16:743-8.

18. Gofton JP, Bennett PH, Smythe HA, Decker JL. Sacroiliitis and ankylosing spondylitis in North American Indians. Ann Rheum Dis 1972;31:474-81.

19. Hill RH: Juvenile arthritis in various racial groups in British Columbia. Arthritis Rheum 1977;20:162-4.

20. Gofton JP, Lawrence JS, Bennett PH, Burch TA. Sacro-ilitis in eight populations. Ann Rheum Dis 1966;25:528-33.

21. Beasley RP, Retaillia H, Healey LA. Prevalence of rheumatoid arthritis in Alaskan Eskimos. Arthritis Rheum 1973;16:737-742.

22. Del Puente A, Knowler WC, Pettitt DJ, Bennett PH. High incidence and prevalence of rheumatoid arthritis in Pima Indians. Am J Epidemiol 1989;129:1170-8.

23. Williams RC, Steinberg AG, Gershowitz H, Bennet WC, KnowlerWC, Pettitt DJ, et al. Gm allotypes in Native Americans: Evidence for three distinct migrations across the Bering Land bridge. Am J Phys Anthropol 1985;66:1-19.

24. Greenberg JH. Language in the Americas. Stanford, CA: Stanford University Press, 1987.

25. Greenberg JH, Turner CG, Zegura SL. The Settlement of the Americas: A comparison of

the linguistic, dental, and genetic evidence. Curr Anthropol 1986;27:477-97.

26. Torroni A, Schurr TG, Cabell JF. Asian affinites and continental radiation of the four founding Native American mtDNA's. Am J Hum Genet 1993;53:563-590.

27. Gibbons A. Geneticists trace the DNA trail of the First Americans. Science 1993;259:312-313.

28. Ward RH, Redd A, Valencia D, Frazier B, Paabo S. Genetic and linguistic differentiation in the Americas. Proc Natl Acad Sci USA 1993;90:1063-7.

29. Khan MA. HLA-B27 and its subtypes in world populations. Curr Opin Rheumatol 1995;7:263-9.

30. Rothschild BM, Woods RJ, Rothschild C, Sebes JJ. Geographic distribution of rheumatoid arthritis in ancient North America: implications for pathogenesis. Semin Arthritis Rheum 1992;22:181-187.

31. Short CL. The antiquity of rheumatoid arthritis. Arthritis Rheum 1974;17:193-205.

32. Woods RJ, Rothschild BM. Population analysis of symmetrical erosive arthritis in Ohio Woodland Indians (1200 years ago). J Rheumatol 1988;15:1258-63.

33. Rothschild BM,Turner KR, DeLuca MA. Symmetrical erosive peripheral polyarthritis in the Late Archaic Period of Alabama. Science 1988;241:1498-501.

34. Rothschild BM, Woods RJ. Symmetrical erosive disease in Archaic Indians: the origin of rheumatoid arthritis in the New World? Semin Arthritis Rheum 1990;19:278-84.

35. Snorrason E. Landre-Beauvais and his Goutte Asthenique Primitive. Acta Med Scand 1952 Suppl 266:115-118.

36. Lawrence RC, Hochberg MC, Kelsey JL, McDuffie FC, Medsger TA, Felts WR, Schulman LE. Estimates of the prevalence of selected arthritic and muskuloskeletal diseases in the United States. J Rheumatol 1989; 16: 427-441.

37. Engel A, Roberts J. Rheumatoid arthritis in adults, 1960-1062. Vital and Health Statistics series 11, No. 17, USDHEW, 1966.

38. Linos A, Worthington JW, O'Fallon WM, Kurland LT. The effect of rheumatoid arthritis in Rochester, Minnesota: A study of its incidence, prevalence and mortality. Am J

Epidemiol 1980;111:87-98.

39. Lawrence JS. Rheumatism in populations.London, Heinneman, 1977.

40. O'Brien WM, Bennett PH, Burch TA, Bunim JJ. A genetic study of rheumatoid arthritis and rheumatoid factor in Blackfeet and Pima Indians. Arthritis Rheum 1967;10:163-79.

41. Jacobsson LT, Hanson RL, Knowler WC, Pillemer S, Pettitt DJ, McCance DR, Bennett PH. Decreasing incidence and prevalence of rheumatoid arthritis in Pima Indians over a twenty-five-year period. Arthritis Rheum 1994;37:1158-65.

42. Jacobsson LT, Knowler WC, Pillemer S, Hanson RL, Pettitt DJ, McCance DR, Bennett PH. A cross-sectional and longitudinal comparison of the Rome criteria for active rheumatoid arthritis (equivalent to the American College of Rheumatology 1958 criteria) and the American College of Rheumatology 1987 criteria for rheumatoid arthritis. Arthritis Rheum 1994;37:1479-86.

43. Willkens RF, Blandau RL, Aoyama DT, Beasley RP. Studies of rheumatoid arthritis among a tribe of Northwest Indians. J Rheumatol 1976;3:9-14.

44. Peschken CA, El-Gabalawy HS, Roos LL, Esdaile JM. Algonkian Indians have twice the frequency of rheumatoid arthritis with a younger age of onset. (Abstract). Arthritis Rheum 1998;41:9;S558.

45. Coutts JV, Thommasen H. Prevalence of rheumatoid arthritis in the Heiltsuk people of Bella Bella. BC Med J 1998;40:6;250-251.

46. Gofton JP, Robinson HS, Price GE. A study of rheumatic disease in a Canadian Indian population.II. Rheumatoid Arthritis in the Haida Indian. Ann Rheum Dis 1964;23:364-71.

47. Templin DW, Boyer GS, Lanier AP, Nelson JL, Barrington RA, Hansen JA, et al. Rheumatoid arthritis in Tlingit Indians: clinical characterization and HLA associations. J Rheumatol 1994;21:1238-44.

48. Harvey J, Lotze M, Arnett FC, Bias WB, Billingsley LM, Harvey E, et al. Rheumatoid arthritis in a Chippewa band. II. Field study with clinical serologic and HLA-D correlations. J Rheumatol 1983;10:28-32.

49. Heimgartner E, Rosenthal M. La artritis reumatoide en una poblacion indigena (Mazahua) del altiplano de Mexico. Bol Of Sanit Panam 1979;86:283-92.

50. Scofield RH, Fogle M, Rhoades ER, Harley JB. Rheumatoid arthritis in a United States Public Health Service Hospital in Oklahoma: serologic manifestations in rheumatoid arthritis vary among tribal groups. Arthritis Rheum 1996;39:283-6.

51. Canvin MG, Hitchon CA, El-Gabalawy HS. Rheumatoid Arthritis presents 10 years earlier in Algonkian North American Indians. (Abstract) Arthritis Rheum 1997:40:9: S155.

52. Jacono J, Jacono B, Cano P, Segami M, Rubin L. An epidemiological study of rheumatoid arthritis in a northern Ontario clinical practice: the role of ethnicity. J Adv Nursing 1996;24:31-5.

53. Willkens RF, Nepom GT, Marks CR, Nettles JW, Nepom BS. Association of HLA-Dw16 with rheumatoid arthritis in Yakima Indians. Further evidence for the "shared epitope" hypothesis. Arthritis Rheum 1991;34 43-7.

54. Hirsch R, Jing-Ping L, Scott WW, Ma LD, Pillemer SR, Kastner DL, et al. Rheumatoid arthritis in Pima Indians. The Intersection of epidemiologic, demographic and genealogic data. Arthritis Rheum 1998;41:1464-1469.

55. Peloso PM, Hrynchak D, Canvin J, Blocka K, MarklandJ, Milne A, et al. More arthritis, less arthritis, or access bias? A study of North American Indians attending arthritis clinics.(Abstract) Arthritis Rheum 1997;40:9;S1096.

56. Matteson EL, Cohen MD, Conn DL. Rheumatoid arthritis: Clinical features and systemic involvement. In: Klippel JH, Dieppe PA, editors. Rheumatology. 2nd ed. Philadelphia PA: Mosby International. 1998. p. 5.4.1-7

57. Williams DG. Rheumatoid arthritis: Autoantibodies in Rheumatoid Arthritis. In: Klippel JH, Dieppe PA, editors. Rheumatology. 2nd ed. Philadelphia PA: Mosby International. 1998. p.5.9.1-8

58. Gran JT, Husby G. Seronegative polyarthritis. In: Koopman WJ, ed. Arthritis and allied conditions: A textbook of rheumatology. 13th ed. Philadelphia PA: Williams & Wilkins.1997. p.1145-53.

59. Del Puente A, Knowler WC, Pettitt DJ, Bennett PH. The incidence of rheumatoid arthritis is predicted by rheumatoid factor titer in a longitudinal population study. Arthritis Rheum 1988;31:1239-44.

60. Sellick K, Littlejohn G, Wallace C, Over R. Identifying subclasses of patients with rheumatoid arthritis through cluster analysis. J Rheumatol 1990;17:1613-1619.

61. Nepom GT, Gersuk V, Nepom B. Prognostic implications of HLA genotyping in the early assessment of patients with rheumatoid arthritis. J Rheumatol 1996;Suppl 44:5-9.

62. Weyand CM, Goronzy JJ. Inherited and noninherited risk factors in rheumatoid arthritis. Curr Opin Rheumatol 1995;7:206-13.

63. Harvey J, Arnett FC, Bias WB, Hsu SH, Stevens MB. Heterogeneity of HLA-DR4 in the rheumatoid arthritis of a Chippewa band. J Rheumatol 1981;8:797-803.

64. Bias WB, Hsu SH, Pollard MK, Harvey J, Lotze MT, Arnett FC, Stevens MB. HLA-DR characterization of a Chippewa Indian subpopulation with high prevalence of rheumatoid arthritis. Hum Immunol 1981;2:155-63.

65. Gregerson PKJ. Genetic analysis of rheumatic diseases. In: Kelley WN, Harris ED, Ruddy S, Sledge CB, Editors. Textbook of Rheumatology. 5th ed.Philadelphia, PA: W.B. Saunders.1997. p. 209-227.

66. Hansen JA, Lanier AP, Nisperos B, Mickelson E, Dahlberg S: The HLA system in Inupiat and Central Yupik Eskimos . Hum Immunol 1986; 16:315-28.

67. Willkens RF, Hansen JA, Malmgren JA, Nisperos B, Mickelson EM, Watson MA. HLA antigens in Yakima Indians with rheumatoid arthritis. Lack of association with HLA-Dw4 and HLA-DR4. Arthritis Rheum 1982;25:1435-9.

68. Williams RC, Jacobsson LT, Knowler WC, del Puente A, Kostyu D, McAuley JE, et al. Meta-analysis reveals association between most common class II haplotype in full-heritage Native Americans and rheumatoid arthritis. Hum Immunol 1995;42:90-4.

69. Nelson JL, Boyer G, Templin D, Lanier A, Barrington R, Nisperos B, et al. HLA antigens in Tlingit Indians with rheumatoid arthritis. Tissue Antigens 1992;40:57-63.

70. Jacobsson LT. Pillemer SR. What can we learn about rheumatic diseases by studying Pima Indians? J Rheumatol 1994;21:1179-82.

71. Weyand C, Hicok K, ConnD, Goronzy J. The role of homozygosity at the HLA-DRB1 locus in determining disease severity in RA. (Abstract) Arthritis Rheum 1991;34:S33.

72. Fessel WJ. Systemic lupus erythematosus in the Community: Incidence, Prevalence, outcome, and first symptoms: the High prevalence in black women. Arch Intern Med 1974;134:1027-35.

73. Michet CJ Jr, McKenna CH, Elveback LR, Kaslow RA, Kurland LT. Epidemiology of systemic lupus erythematosus and other connective tissue disease in Rochester, Minnesota, 1950 through 1979. Mayo Clin Proc 1985;60:105-113.

74. Siegel M, Lee SL. The epidemiology of systemic lupus erythematosus. Semin Arthritis Rheum 1973;3:1-54.

75. Hochberg MC: Systemic Lupus Erythematosus. Rheum Dis Clin North Am 1990;16(3): 617-639.

76. Peschken CA, Esdaile JM. Systemic lupus erythematosus in North American Indians: A population based study.(Abstract) Arthritis Rheum 1997;40:S161.

77. Cronin ME, Plotz PH. Idiopathic inflammatory myopathies. Rheum Dis Clinics North Am 1990;16:3;655-666.

78. Medsger TA Jr, Dawson WN, Masi AT. The epidemiology of polymyositis. Am J Med 1970;48:715-723.

79. Steen VD. Systemic sclerosis. Rheum Dis Clinics North Am 1990;16:3, 641-654.

80. Tan FC, Silvers DN, Foster MW, Chakrabouty R, Howard RF, Miilewicz DM, Arnett FC. Microsatellite markers flanking the Fibrillin-1 gene on human chromosome 15q are associated with scleroderma in a Native American population. (Abstract) Arthritis Rheum 1997;40:S73.

81. Epstein WV, Henke CJ. The nature of US rheumatology practice, 1977. Arthritis Rheum 1981;24:1177-1187.

82. Arnett FC, Reveille JD. Genetics of systemic lupus erythematosus. Rheum Dis Clin N Am 1992;18:865-891.

83. Plotz PH (moderator). Current concepts in the idiopathic inflammatory myopathies: polymyositis, dermatomyositis, and related disorders. NIH conference. Ann Intern Med. 1989;111:143-57.

84. Seibold JR. Systemic sclerosis-Clinical Features. In: Klippel JH, Dieppe PA, editors. Rheumatology. Ist ed. Philadelphia PA: Mosby International. 1994. p.6.8.1-10

85. Reveille JD, Moulds JM, Arnett FC. Major histocompatibility complex class II and C4 alleles in Mexican Americans with systemic lupus erythematosus. Tissue Antigens 1995;45:91-7.

86. Gran JT, Husby G. Epidemiology of ankylosing spondylitis. Semin Arthritis Rheum 1993;22:319-334.

87. Khan MA, van der Linden SM. Ankylosing spondylitis and other spondyloarthropathies. Rheum Dis Clin North Am 1990:16;551-580

88. Calin A. Spondyloarthropathy in Caucasians and non-Caucasians. J Rheumatol 1983;Suppl10:16-9.

89. Gofton JP, Chalmers A, Price GE. Reeve CE. HL-A27 and ankylosing spondylitis in B.C. Indians. J Rheumatol 1975;2:314-8.

90. Robinson HS, Gofton JP, Price GE: A study of rheumatic disease in a Canadian Indian population. Ann Rheum Dis 1963;22:232-6.

91. Ford DK, Henderson E: Serum antibody levels against T-mycoplasmas in two North American Indian populations predisposed to spondylitis. Arthritis Rheum 1976;19:1328-1332.

92. Ford DK, Henderson E, Price GE, Stein HB: Yersinia related arthritis in the Pacific Northwest. Arthritis Rheum 1977;20:1226-30.

93. Rate RG, Morse HG, Bonnell MD, Kuberski TT. "Navajo arthritis" reconsidered: relationship to HLA-B27. Arthritis Rheum 1980;23:1299-1302.

94. Morse HG, Rate RG, Bonnell MD, Kuberski TT. HLA-B27 related arthropathies in Hopi and Navajo Indians. Ariz Med 1981;38:510-3.

95. Isomäki H, Raunio J, von Essen R, Hämeenkorpi R. Incidence of inflammatory rheumatic diseases in Finland. Scand J Rheum 1978; 7:188-19.

96. Kuberski TT, Morse HG, Rate RG, Bonnell MD, Wood JG Jr, Bennett PH. A hospital-based survey of radiological sacroiliitis and HLA-B27 and Cw2 in Navajo and Hopi Indians. Hum Immunol 1981;3:77-83.

97. Muggia AL, Bennahum DA, Williams RC Jr. Navajo arthritis-an unusual, acute, self-limited disease. Arthritis Rheum 1971, 14; 348-355.

98. Gofton JP. Epidemiology, tissue type antigens and Bechterow's syndrome (ankylosing spondylitis) in various ethnical populations. Scand J Rheumatol. 1980; suppl32:166-8.

99. Lisse,JR, Kuberski TT, Bennett PH, Knowler WC, Gofton JP, Calin A,et al. High risk of sacroiliitis in HLA-B27 positive Pima Indian men. (Letter) Arthritis Rheum 1982;25:236-8.

100. Field LL, Gofton JP, Kinsella TD. Immunoglobulin (GM and KM) allotypes and relation to population history in native peoples of British Columbia: Haida and Bella Coola. Am J Phys Anthropol 1988;76:155-63.

101. Calin A, Bennet PH, Jupiter J, Terasaki PI: HLA B27 and Sacroiliitis in Pima Indians-association in males only. J Rheumatol 1977;Suppl 3:44-48.

102. Burch TA. Epidemiological studies on rheumatic diseases. Military Med 1966;131:507-11.

103. Fraga A, Gorodezky C, Lavalle C, Castro-Escobar LE, Magana L, Escobar-Gutierrez A. HLA-B27 in Mexican patients with ankylosing spondylitis. Arthritis Rheum 1979;22:302.

104. Arellano J, Vallejo M, Jimenez J, Mintz G, Kretschmer RR. HLA-B27 and ankylosing spondylitis in the Mexican Mestizo population. Tissue Antigens 1984;23:112-6.

105. Troup GM, Harvey RL, Walford RL, Smith GS, Sturgeon P. Analysis of the HLA, erythrocyte and gammaglobulin antigen system in the Zuni Indians of New Mexico. Histocompatability Test 1972; 339-344.

106. Searles RP, Voyles WF, Billowitz E, Troup GM, Messner RP. Prevalence of HLA-B27 and sacroiliitis in a prospective study of Zuni Indians. Tissue Antigens 1979;14:174-6.

107. Russell AS, Davis P, Schlaut J. Prevalence of ankylosing spondylitis and HLA-B27 in a North American Indian population: a pilot study. CMAJ 1977;16:148-9.

108. McMahn B, Armstrong MB. Reiter's syndrome in Eskimos. Arthritis Rheum 1974;17:971-972.

109. Calin A, Barnett M. Marder A. Marks S. The nature and prevalence of spondyloarthritis among relatives of probands with ankylosing spondylitis and Reiter's syndrome. (Abstract) Arthritis Rheum 1981;24:S78.

110. Horrobin DF. Low prevalences of coronary heart disease (CHD), psoriasis, asthma and rheumatoid arthritis in Eskimos: are they caused by high dietary intake of eicosapentaenoic acid (EPA), a genetic variation of essential fatty acid (EFA) metabolism or a combination of both? Med Hypotheses 1987;22:421-8.

111. Bernstein CN, Blanchard JS, Rossthorn P, Wadja A. Epidemiology of Crohn's disease and ulcerative colitis in a central Canadian province: A population based study. Am J Epidemiol 1999 (in press).

112. Lopez-Larrea C, Gonzalez-Roces S, Alvarez V. HLA-B27 structure, function, and disease association. Curr Opin Rheumatol 1996;8:296-308.

113. Gonzalez-Roces S, Alvarez MV, Gonzalez S, Dieye A, Makni H, Woodfield DG, et al. HLA-B27 polymorphism and worldwide susceptibility to ankylosing spondylitis. Tissue Antigens 1997;49:116-23.

114. Walsh B, Vocum DE, Khan MA. Arthritis and HLA-B27 in Native North American tribes. Curr Opin Rheumatol 1998;10:319-326.

115. Bhatia K, Prasad ML, Barnish G, Koki G. Antigen and haplotype frequencies at three human leucocyte antigen loci (HLA-A, -B, -C) in the Pawaia of Papua New Guinea. Am J Phys Anthropol 1988;75:329-340.

116. Khare SD, Luthra HS, David CS. HLA-B27 and other predisposing factors in spondyloarthropathies. Curr Opin Rheumatol 1998;10:282-291.

117. Singsen BH. Rheumatic diseases in childhood. Rheum Dis Clin North Am 1990;16:3;581-600.

118. Hill RH. Walters K. Juvenile rheumatoid arthritis: a medical and social profile of non-Indian and Indian children. CMAJ 1969;100(10):458-64.

119. Burgos-Vargas R, Naranjo A, Castillo J, Katona G. Ankylosing spondylitis in the Mexican mestizo: patterns of disease according to age at onset. J Rheumatol 1989;16(2):186-91.

120. Rosenberg AM, Petty RE. Reiter's Disease in children. Am J Dis Children 1979;133:394-398.

121. Morse HG, Rate RG, Bonnell MD. Reiter's Syndrome in a five-year-old girl.(letter) Arthritis Rheum 1980;23:960-61.

122. Blumberg BS, Bloch KJ, Black RL, et al: A study of the prevalence of arthritis in Alaskan Eskimos. Arthritis Rheum 1961;4:325-41.

123. Gordon T. Osteoarthritis in US adults, population studies of the rheumatic diseases: Proceedings of the third international symposium. Edited by Bennett PH, Wood PHN. New York Excerpta Medica 1968;391-397.

124. Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. Ann Rheum Dis1957;494-502.

125. Bias WB, Reveillle JD, Beaty TH, Myers DA, Arnett FC. Evidence that autoimmunity in man is a Mendelian dominant trait. Am J Hum Genet 1986;39:584-602.

126. Rigby AS, Silman AJ, Voelm L, Gregory JC, Ollier WER, Khan MA, et al. Investigating the HLA component in rheumatoid arthritis: an additive (dominant) mode of inheritance is rejected, a recessive mode is preferred. Genet Epidemiol 1991;8:153-75.

127. Evans TI, Han J, Singh R, Moxley G. The genotypic distribution of shared-epitope DRB1 alleles suggests recessive mode of inheritance of the rheumatoid arthritis disease-susceptibility gene. Arthritis Rheum 1995;38:1754-61.

128. Statistics Canada. 1991 Census Highlights On Registered Indians. Cat. No. R32-91/1995E.

It is evident from the above review of the literature that rheumatic diseases are widespread and severe in many native American populations, and that the overall burden of rheumatic disease is clearly in excess of that in the North American Caucasian population.

Review of the literature also makes it clear that Native North Americans are remarkably heterogeneous from the point of view of rheumatic disease susceptibility and outcome. Data gathered on one particular Aboriginal population can not by any means be applied to all North American indigenous populations.

Systemic lupus erythematosus (SLE) is a severe, multisystem autoimmune disorder with known ethnic variations in prevalence and disease course, but there is little data on SLE in the North American Indian population and none on SLE in central Canadian Aboriginals. The following study examines the prevalence, clinical course, and outcome of SLE in Manitoba Aboriginals compared to Manitoba Caucasians.

Systemic Lupus Erythematosus In Manitoba Aboriginals

Abstract:

Objective. To evaluate the prevalence, disease course, and survival of systemic lupus erythematosus (SLE) in over 116,000 North American Indians (NAI), and contrast the results to those in the non-Indian population.

Methods. The Manitoba provincial arthritis center database and the medical records of all rheumatologists, hematologists, nephrologists, and general internists with ≥1 SLE patient were searched for cases of SLE diagnosed between 1980 and 1996. A random survey of 20% of family physicians serving this population suggested that >85% of all SLE cases were identified. Demographics, SLEDAI scores, SLICC/ACR damage scores, clinical manifestations and therapy for NAI were contrasted with the results in Caucasians (CAUC).

Results. 257 cases meeting the ACR criteria for SLE were diagnosed between 1980 and 1996. There were 49 NAI cases, resulting in a prevalence of 42.2/100,000, compared to a prevalence of 21.8/100,000 for the remainder of the population ($p < 0.001$). NAI patients were younger at diagnosis (NAI = 31 years, CAUC = 37 years; $p = 0.01$), had higher SLEDAI scores at diagnosis (NAI = 11.8, CAUC = 9.7; $p = 0.05$), and had more frequent vasculitis (NAI = 38%, CAUC = 14%; $p = 0.001$), proteinuria (NAI = 46%, CAUC = 25%; $p = 0.01$), and cellular casts (NAI = 35%, CAUC = 12%; $p = 0.001$). There were no treatment differences at diagnosis or at two years, but NAI patients were significantly more likely to require treatment with prednisone or immunosuppressives at the last clinic visit ($p = 0.001$). The NAI patients had similar damage scores at diagnosis, but significantly higher scores at 2 years (SLICC/ACR damage index: NAI = 0.74, CAUC = 0.30; $p = 0.02$), and the last clinic visit (SLICC/ACR damage index: NAI = 1.62, CAUC = 0.81; $p = 0.02$). NAI ethnicity increased the likelihood of death more than four-fold (OR 4.6, 95% CI 1.3-16.5).

Conclusions. The prevalence of SLE was increased twofold in the NAI population. NAI patients had higher SLEDAI scores at diagnosis, more frequent vasculitis and renal involvement, required more treatment later in the disease course, accumulated more damage following diagnosis, and had increased fatality.

The prevalence of systemic lupus erythematosus (SLE) is known to vary widely between different ethnic groups. In the USA, African Americans (1), Asians (2), and Hispanics (3) have higher prevalence rates than Caucasians. Polynesians in New Zealand have a higher prevalence of SLE than Caucasians (4), and SLE has been shown to be common in China (5) and Southeast Asia (6). SLE is known to be rare in African Blacks (7). US and Canadian Eskimos have also been shown to have low prevalence rates of SLE (8-10). Morton et al found the prevalence of SLE to be high in 3 of 72 North American Indian tribes, while the remainder had rates comparable to the Caucasian population (11). Subsequently, the prevalence of SLE has also been shown to be high in Alaskan Tlingit Indians (12), and the Nuu-Chah-Nulth Indians (13) in British Columbia.

Disease severity, clinical manifestations, and outcome have also been shown to differ across ethnic groups. African Americans have been shown to have more frequent renal lupus (14), increased disease activity early in the disease course (15), and worse long-term outcomes than Caucasians (16). Both Asian and Afro-Caribbean SLE patients have been shown to have more frequent central nervous system lupus (17) and higher mortality rates (6,16), while Hispanic SLE patients were recently shown to have more frequent cardiac and renal disease (18), and more abrupt onset of SLE compared to Caucasian patients (15). In contrast, there are no studies comparing the clinical course and little clinical data overall regarding SLE in North American Indians compared to Caucasians.

The province of Manitoba in Western Canada, with a total population of almost 1.1 million (19) has a large population of North American Indians, primarily Algonkian Indians (Cree and Ojibway tribes). The 1991 Canadian Census recorded the North American Indian population of Manitoba to be 116,200 (19). It has long been suspected by local clinicians that this group of North American Indians has an increased prevalence of SLE.

In this study, we have evaluated whether the prevalence, clinical manifestations and severity of SLE differs in Manitoba North American Indians in comparison to the remaining Manitoba population.

Patients and Methods

Patient identification. This study attempted to identify all SLE patients resident in the province of Manitoba. For inclusion in the study, patients had to be resident in the province of Manitoba, must have met the 1982 ACR criteria for SLE (20), and must have been diagnosed between January 1st, 1980 and December 31st, 1996. The date of diagnosis was defined as the earliest date a patient both fulfilled the ACR criteria for SLE, and was diagnosed with SLE by a physician.

Two thirds of the total population of Manitoba live in the city of Winnipeg. Every medical subspecialist in Manitoba is located in this city, and only two other communities have general internists. This concentration of population and subspecialist physicians facilitated identification of SLE patients through caregiver surveys.

All general internists, rheumatologists, and nephrologists in Manitoba were surveyed. These physicians are those known to treat SLE in Manitoba. In addition, one oncologist known to have an interest in SLE was surveyed. The rheumatologists, nephrologists, and the above-mentioned oncologist were surveyed by phone, with follow-up in person for review of medical records. Similarly, the two general internists working with the Northern Medical Unit (NMU), which provides care to remote, primarily North American Indian communities were also surveyed by phone, with follow-up in person for review of medical records. Remaining general internists, including all those located outside the city of Winnipeg, were surveyed by mail. (See appendix.) Physicians were asked to identify the number of SLE patients in their care who met the inclusion criteria above, as well as year of birth, sex, year of diagnosis, race, and year of death, if applicable, for each patient.

To ascertain whether surveying only specialists would miss large numbers of SLE patients, 20% of the provinces' 500+ family physicians (FPs) were surveyed by mail. (See appendix.) The FP's were selected randomly for the survey from the Manitoba Medical Association (MMA) membership list with the exception that FP's working with the NMU were deliberately over-represented. A survey was mailed to all FP's who were identified as working with the NMU. All provincial physicians are required to be members of the MMA, which lists

members by specialty. 113 FP's were surveyed, 102 responded (90%). Five of the 102 respondents stated that they cared for SLE patients without specialist input, each of these having only one or two such SLE patients in their practices. (No data on individual patients was requested from FP's.) None of the NMU FP's cared for SLE patients without specialist input. Assuming that the survey results were applicable to all provincial FP's, then approximately 25 FP's in the province would be caring for 25-50 SLE patients who would be missed by surveying specialists only. It is probable that some of these patients were diagnosed prior to 1980, and would therefore not have been eligible.

Thirty-six of the 43 specialists surveyed responded (85%). The majority of non-respondents were general internists located in Winnipeg, who likely care for a smaller number of SLE patients because of the ready availability of subspecialists.

Seven of the eight rheumatologists in the province and the single oncologist surveyed maintained patient databases. One hundred ninety-five of the 257 eligible patients (76%) were identified through their databases, thus minimizing potential bias due to patient identification through physician recall. The remaining patients were identified through the mail survey of specialists, and through review of specialists' medical records. One rheumatologist declined to participate in the study. Nine patients followed by this rheumatologist were identified through the records of other specialists.

An analysis of the data from specialists showed that 22% of patients were identified from the databases or patient lists of more than one specialist. The combined findings of this overlap of patient lists and the good response rate from both FP's and specialists lead us to believe that the majority of the province's SLE patients diagnosed between 1980 and 1996 were identified.

Prevalence estimates. 1991 Census Canada data for the total population of Manitoba and the North American Indian population of Manitoba were used as population denominators. The total population of Manitoba was 1,079,390 (19). The North American Indian population was 116,200 (19). An accurate estimate of the Caucasian population of Manitoba is not available.

Clinical Comparisons. A review of medical records was conducted and clinical data were abstracted on 179 patients where records were accessible. Only records from North American

Indian (n = 42) and Caucasian (n = 137) patients were included. Patients belonging to other ethnic groups were not included in the clinical comparison study.

Disease activity, severity and damage. SLE Disease Activity Index (SLEDAI) scores, treatment index (TI) scores, and Systemic Lupus International Collaborating Clinics/ American College of Rheumatology (SLICC/ACR) damage scores were used to measure disease activity, severity and damage. Each was recorded for the date of diagnosis, 2 years following diagnosis, and the last follow-up visit. The SLEDAI is a validated instrument that identifies 16 different clinical manifestations and 8 laboratory manifestations attributable to SLE that are present at the time of the visit or in the preceding ten days (21). The SLEDAI has been found to be reliable when determined using retrospective chart review (22). The TI was developed by Lacaille et al (23) to assess the level of therapy. Patients received a score of 3 if they were receiving immunosuppressive therapy, a score of 2 if they were receiving high dose prednisone (>20mg/day), a score of 1 if they were receiving lower doses of prednisone, and 0 if they were receiving neither prednisone nor immunosuppressives. The SLICC/ACR damage score is a validated instrument used to measure permanent damage accumulated either directly related to SLE or secondary to the treatment of SLE (24).

Clinical variables. Table 1 lists the clinical and laboratory manifestations recorded. All except antibodies to extractable nuclear antigens were recorded at two intervals: those present prior to or at the time of diagnosis and those present at any time during the disease course. Antibodies to extractable nuclear antigens (anti-Sm, Anti-RNP, Anti-La, and anti-Ro) were not available in almost half the patients, and in the remainder had been measured only on a single occasion, generally at diagnosis. All measurements of extractable nuclear antigens were done at a single provincial laboratory. Myositis was defined as proximal muscle aching/weakness, associated with elevated creatine phosphokinase/aldolase, or electromyogram changes, or a biopsy showing myositis. Vasculitis was defined as ulceration, gangrene, tender finger nodules, periungal infarction, splinter hemorrhages, or biopsy or angiogram proof of vasculitis.

Statistical Analysis. Univariate analyses of the comparisons of demographics, clinical and laboratory manifestations, SLEDAI, Treatment Index, and SLICC scores between the two

ethnic groups were performed with the chi-square test for categorical variables and the student's t-test for continuous variables. Ninety-five percent confidence intervals were calculated for the difference in frequency of variables between the two groups. We then decided to focus on the predictors of damage and death in this patient cohort. The SLICC/ACR damage score was treated as a continuous variable, and forward, backward and stepwise linear regression were used to identify predictors of higher damage scores. Life tables were constructed to compare survival of Caucasians and North American Indians. The Gehan statistic was used to compare the overall survival distribution for the two groups. Forward, backward and stepwise cox regression analysis was used to identify variables increasing the probability of death. Stepwise, forward, and backward multivariate analysis yielded identical results in all cases. Ninety-five percent confidence intervals for prevalence rates are based on estimates of a Poisson-distributed variable.

Results

Prevalence. A total of 257 patients diagnosed with definite SLE between January 1,1980 and December 31,1996 were identified. Of these, 177 (69%) were Caucasians, 49 (19%) were North American Indians, 19 (7%) were Asian-Oriental, 7 (3%) were Asian-Indian, and 5 (2%) were African-American. The resulting prevalence rate of definite SLE diagnosed between January 1, 1980 and December 31, 1996 for the province of Manitoba was 23.8/100,000 (95% CI 14.9-34.7). The prevalence in the non-Indian population was 21.8/100,000 (95% CI 13.8-32.2), while the prevalence in the North American Indian population was 42.2/100,000 (95% CI 30.0-55.5); 95% CI of the difference between the two groups 12.8-31.7.

Demographic Parameters. Only North American Indian and Caucasian patients were included in subsequent analyses of clinical data.

There were no differences in the sex distribution between the two groups. (Table 2) Although the majority of North American Indian patients lived in rural areas, there was no clinically important difference observed in the time from symptom onset to diagnosis. North

American Indians were significantly younger at diagnosis, with a mean age of 31 years at diagnosis, compared to 37 years in Caucasians (p = 0.01).

Clinical and laboratory manifestations. Nineteen percent of North American Indians were positive for anti-Sm antibodies, compared to 4% of Caucasians (p = 0.02), and 57% of North American Indians were positive for anti-RNP antibodies, compared to 12% of Caucasian patients (p = 0.00). There was no difference in the frequency of antinuclear antibodies, anti-DNA antibodies, anti-La, and anti-Ro antibodies. (Table 3)

At diagnosis, 23% of North American Indians had thrombocytopenia versus 8% of Caucasians, for a difference of 15% (95% CI = 1.0, 29.0); and 20% of North American Indians had vasculitis versus 6% of Caucasians, for a difference of 14% (95% CI = 0.3, 26.00). North American Indians also had a trend towards more frequent seizures and cellular casts compared to Caucasians (Table 4). The findings were similar for the entire disease course. North American Indians had significantly more frequent cellular casts (35% versus 12%, 23% difference, 95% CI = 7.6, 39.1); proteinuria (46% versus 25%, 21% difference, 95% CI = 5.0, 38.3), and vasculitis (38% versus 14%, 24% difference, 95% CI = 8.4, 40.0) during their disease course, and a trend towards fewer oral/nasal ulcerations and more frequent thrombocytopenia, hemolytic anemia, and seizures than Caucasians. (Table 4).

Disease activity, treatment and damage. At diagnosis, North American Indian patients had a mean SLEDAI score of 11.8, compared to 9.7 in Caucasian patients (p = 0.05). There were no differences at 2 years, or at the last follow up visit for SLEDAI scores. (Table 5).

The treatment index was not significantly different at diagnosis, or at 2 years, but Aboriginals were significantly more likely to remain on prednisone or immunosuppressives at the last clinic visit compared to Caucasians (p = 0.001) (Table 6).

North American Indians sustained significantly more damage as measured by the SLICC/ACR damage index by 2 years and by the last clinic visit (Table 7). The increased damage was due primarily to the increased frequency of neuropathies, deforming arthritis, renal damage, pulmonary damage, diabetes, and venous thromboembolism (data not shown). In multivariate analysis, North American Indian ethnicity was predictive of more damage both at 2

years (ß = .460, p = 0.004) and at the last visit (ß = .622, p < 0.001), when age, sex, treatment index, SLEDAI score, and disease duration were controlled for (Table 8). At 2 years, the treatment index at diagnosis and at 2 years were also significant predictors of more damage; and at the last visit, disease duration and the treatment index at the last visit were also significant predictors (Table 8).

Mortality. Survival was significantly worse in North American Indians compared to Caucasians (p = 0.04) (Figure). When age, sex, disease activity, and damage were controlled for, North American Indian ethnicity still increased the likelihood of death (OR=4.6, 95% CI 1.3-16.5). Disease activity at the last visit (OR=1.2, 95% CI 1.1-1.3) also significantly increased the likelihood of death in these SLE patients (Table 8).

Discussion

This is the first study to examine differences in clinical manifestations and outcome, as well as the prevalence of SLE in North American Indians compared to non-Indians. The most significant findings were the increased prevalence of SLE and the excess damage and mortality in the North American Indian patients.

The Algonkian Indians in this study had a twofold-increased prevalence of SLE compared to the remaining non-Indian population. The reason for this, although presumed to be genetic, is unknown. High prevalence rates for SLE have also been found in the Crow, Arapahoe, and Sioux Indians (11) of the American Midwest, the Pacific coastal Nuu-Chah-Nulth Indians (13), and Southeast Alaskan Indians (12). While geographically widespread, these groups, with the exception of the Tlingit Indians of Southeast Alaska, share a common Amerind, or Paleo-Indian, ancestry (25). The Algonkian Indians of Manitoba also share this Amerind lineage (25). The common ancestry supports a genetic etiology for the high prevalence rates. To date, there are no studies examining the genetics of SLE in a North American Indian population.

Manitoba Algonkian Indians had the onset of SLE at a younger age compared to Manitoba Caucasians. While this has not previously been described for SLE in any other North American Indians, it has been noted in a number of North American Indians with rheumatoid

arthritis (RA), including these same Manitoba Algonkian Indians, who were found to have onset of RA 10-12 years earlier than Manitoba non-Indians (26,27). Tlingit (12), Nuu-Chah-Nulth (13), Yakima (28), Chippewa (29), Kiowa (30), and Mazahua (31) Indians have also been found to have an early age of onset of RA. Most of these groups also have high prevalence rates for RA (12,27-29), and a high frequency of the RA shared epitope (12,28,29). With the exception of the Tlingit, all are of Amerind ancestry (25). Thus, it is quite likely that the young age of onset of SLE seen in the Manitoba Algonkian Indians also has a genetic etiology, and might well be duplicated in other North American Indian groups with high prevalence rates for SLE. It is probable that causal genetic elements would also be found in high frequency in Algonkian Indians. An early age of onset has potentially far reaching consequences in terms of effect on fertility, work disability, cumulative damage, and premature mortality.

Despite treatment that was at least as aggressive as in Caucasians, Manitoba Algonkian Indians accumulated more damage and had higher fatality. The difference in damage scores was significant as early as 2 years after diagnosis. The reasons for this are not readily apparent, but we hypothesize that a combination of increased comorbidity, more severe disease, and lower socioeconomic status contribute to the poor outcome.

The odds of death in North American Indian SLE patients were more than 4 times that of Caucasian patients, even after accounting for damage and disease activity. It is likely that much of this excess mortality relates to comorbidity. Unfortunately, adequate data on comorbid diseases were not available. Canadian Indians are known to have overall shorter life expectancy and higher rates of illness than non-Indian Canadians (32).

The higher SLEDAI scores at diagnosis amongst Algonkian Indians, as well as the increased frequency of renal disease and vasculitis suggest that more severe SLE played a role in the increased damage and fatality. Certainly overall disease activity and renal lupus have been shown to contribute to mortality (33).

The similar time to diagnosis between the two groups and the aggressive treatment the Indians received suggest that access to medical care was not a factor in the poor outcomes for this patient group; but other socioeconomic factors likely played a role. While data on

socioeconomic status were incomplete because of the retrospective nature of this study, available data showed that the Algonkian Indian patients were more frequently unemployed or disabled, and had lower educational attainment than the Caucasian patients (data not shown). This is in keeping with national data on Canadian Indians, which has demonstrated that Canadian Indians have lower incomes, less education, and overcrowded and inadequate housing compared to the rest of Canada (32). Lower socioeconomic status has been shown to impact negatively on outcome in SLE in other studies (33,34), and has been shown to explain some of the difference in outcome between US Afro-Americans and Caucasians (34,35).

There are some limitations to this study. Clearly, the prevalence estimates arrived at in this study are underestimates. Because of reliance on physician recall for some physicians, and non-participation by others, some eligible SLE patients were likely not identified for this study. However, there is no indication that inclusion of the missing patients would have significantly changed the twofold increase in prevalence of SLE in North American Indians compared to non-Indians. The high percentage of patients identified by more than one source suggests a reasonable rate of capture, and the overall prevalence rate obtained is in line with that found in many other North American and European studies (36). Data from the provincial health care insurance organization, which provides comprehensive healthcare to the entire population, suggests that overall healthcare utilization is similar between Indians and non-Indians (27), and the similar time to diagnosis found in this study also suggests similar access to medical care. The likelihood of missing a disproportionate number of SLE patients is highest in the North American Indian group, as the majority of these live outside the single urban center. Such an ascertainment bias would result in a greater underestimate of the prevalence of SLE in the Indian group, and would mean that our finding of an elevated rate of SLE in this population is a conservative estimate.

Conclusions

In conclusion, North American Indian ethnicity was the major determinant of damage and death in this study, and was an independent marker of severe SLE. It may be that Algonkian Indians have a different subset of the disease than is described in the Caucasian population.

Autoantibodies such as anti-dsDNA, anti-RNP, anti-Sm, anti-Ro, and anti-La have been shown to be associated with specific clinical manifestations of SLE (37) (although not with outcome in SLE (38)), and the Indian patients were significantly more often positive for anti-Sm and anti-RNP antibodies. As autoantibodies were not measured consistently in all patients, nor measured at a consistent time in the disease course, it was not possible to measure the association between clinical manifestations, autoantibodies, and ethnicity. Further study of ethnic differences may provide important clues to both the role of autoantibodies, and the role of genetic factors in the pathogenesis and outcome of SLE. The known genetic homogeneity of North American Indians, combined with high prevalence rates of SLE, provide a unique opportunity to study genetic contributions in these patients. In addition, further study may assist in health care planning for regions with large North American Indian populations, and in developing improved monitoring and treatment protocols tailored to this group of patients with severe, early onset disease.

Tables

Table 1. Clinical and Laboratory Manifestations *

Clinical Manifestations	Laboratory Manifestations
Malar rash	Thrombocytopenia
Discoid rash	Hemolytic Anemia
Photosensitivity	Leucopenia
Oral/nasal ulcers	Lymphopenia
Arthritis	Cellular casts
Pleuritis	Proteinuria
Pericarditis	Antinuclear antibody
Seizures	Anti-dsDNA antibody
Psychosis	Anti-Sm antibody
Myositis	Anti-RNP antibody
Vasculitis	Anti-La antibody
	Anti-Ro antibody

*The definitions used for clinical and laboratory manifestations were those used in the 1982 revised ACR criteria for SLE (21), except when defined in the text.

Table 2. Demographic Features of Caucasian and North American Indian SLE patients.

	North American Indians (n=49)	*Caucasians (n=177)*	*Difference between Groups*	*95% CI of difference between groups*
Females (%)	90	89	1%	-8.6, 10.6
Age at diagnosis-mean years (SD)	31(13.4)	37(15.3)	6 years	1.8, 11.4
Symptom onset to diagnosis-mean months (SD)	28(39.1)	27(38.2)	1 month	-14.2, 13.2
Average follow-up from diagnosis-mean years (SD)	8.0(4.9)	7.3(4.3)	0.7 years	-0.9, 2.3
Residing in Winnipeg (%)	25	70	50%	36.1, 63.9

Table 3. SLE Autoantibodies in Caucasians and North American Indians

Antibody (N tested)	North American Indians (%)	Caucasians (%)	Difference between groups (%)	95% CI for difference between groups
Antinuclear antibody (179)	100	98	2	-0.02, 4.6%
Anti-dsDNA antibody (98)	77	74	2.5	-12.1, 17.2%
Anti-Sm antibody (98)	23.4	5.2	18.6	1.9, 35.3%
Anti-RNP antibody (98)	57.1	12.3	44.8	22.3, 67.3%
Anti-La antibody (98)	19.0	20.5	1.5	-17.6, 20.6%
Anti-Ro antibody (98)	30.0	35.1	5.1	-17.7, 27.9%

Table 4. Frequency of Clinical and Laboratory Manifestations in Caucasians and North American Indians

Manifestations at Diagnosis	North American Indian %	Caucasian %	Difference between groups %	95% CI of difference between groups %
Malar rash	44	41	3	-2.3, 15.4
Discoid rash	15	21	6	-7.5, 19.3
Photosensitivity	20	33	13	-2.5, 27.7
Oral/nasal ulcers	13	25	12	-0.5, 25.6
Arthritis	81	76	5	-8.4, 19.2
Pleuritis	18	16	2	-11.4, 15.2
Pericarditis	5	6	1	-6.7, 9.3
Cellular casts	17	6	12	-1.0, 23.0
Proteinuria	22	16	6	-8.6, 19.8
Seizures	8	2	6	-4.1, 15.9
Psychosis	8	2	6	-3.3, 13.7
Thrombocytopenia	23	8	15	**1.0, 29.0**
Hemolytic anemia	10	4	6	-3.9, 15.9
Leucopenia	21	26	5	-10.2, 20.2
Lymphopenia	40	45	5	-3.4, 23.0
Myositis	3	2	1	-4.9, 6.8
Vasculitis	20	6	14	**0.3, 26.0**

Manifestations over Disease Course	North American Indian %	Caucasian %	Difference between groups %	95% CI of difference between groups
Malar rash	56	50	6	-12.2 – 20.0
Discoid rash	24	25	1	-14.6 – 16.5
Photosensitivity	39	42	3	-15.4 – 20.6
Oral/nasal ulcers	17	33	16	**1.9 – 30.9**
Arthritis	90	82	8	-3.4 – 19.0
Pleuritis	25	26	1	-14.2 – 16.4
Pericarditis	22	12	10	-3.1 – 24.7
Cellular casts	35	12	23	**7.6 – 39.1**
Proteinuria	46	25	21	**5.0 – 38.3**
Seizures	10	3	7	-2.6 – 16.8
Psychosis	10	6	4	-5.9 – 14.3
Thrombocytopenia	29	15	14	-1.0 – 29.0
Hemolytic anemia	13	4	9	-1.8 – 20.2
Leucopenia	33	43	10	-4.5 – 23.1
Lymphopenia	60	65	5	-23.3 – 32.7
Myositis	7	2	5	-3.2 – 13.4
Vasculitis	38	14	24	**8.4 – 40.0**

Table 5. Mean SLEDAI Scores in North American Indians and Caucasians

SLEDAI scores (n)	*North American Indians Mean score (SD)*	*Caucasian Mean score (SD)*	*Difference in Mean Score*	*95% CI of difference*
At diagnosis (169)	11.8 (7.5)	9.7 (5.7)	2.1	**0.001, 4.3**
At 2 years (127)	5.0 (4.2)	4.4 (4.9)	1.6	-1.5, 2.6
At last visit (176)	3.9 (3.9)	3.4 (3.9)	0.5	-0.9, 2.0

Table 6. Treatment Index

		No Treatment*(%)	Prednisone <20mg (%)	Prednisone ≥20mg (%)	Immuno-Suppressives (%)	P**
At Diagnosis	Indian	14 (35)	5 (13)	17 (42)	4 (10)	
	Caucasian	56 (41)	28 (21)	40 (29)	12 (9)	0.38
At 2 years	Indian	9 (32)	10 (36)	4 (14)	5 (18)	
	Caucasian	57 (50)	33 (29)	11 (10)	12 (11)	0.34
At last clinic visit	Indian	10 (27)	14 (38)	6 (16)	7 (19)	
	Caucasian	78 (55)	39 (28)	4 (3)	20 (14)	0.00

* "No treatment" means no treatment with prednisone or immunosuppressives, antimalarials and NSAIDS were excluded. ** P values report on a trend between different levels of treatment.

Table 7. Mean SLICC Scores in North American Indians and Caucasians

SLICC scores (n)	North American Indians Mean score (SD)	Caucasian Mean score (SD)	*Difference in Mean Score*	*95% CI of Difference*
At diagnosis (179)	**0.19 (0.63)**	**0.07 (0.28)**	**0.12**	**-0.08, 0.32**
At 2 years (147)	**0.74 (0.97)**	**0.30 (0.62)**	**0.44**	**0.07, 0.81**
At last visit (179)	**1.62 (2.20)**	**0.81 (1.43)**	**0.81**	**0.07, 1.55**

Table 8. Multivariate Analysis of SLICC scores and Survival.

Dependant variable	Independent variable	Parameter estimate	Standard Error	*95% CI for parameter estimate*	*p*
SLICC score at 2 years*	North American Indian Ethnicity	.460	.155	0.153, 0.822	0.004
	Treatment Index at Diagnosis	.155	.061	0.007, 0.256	0.013
	Treatment Index at 2 Years	.131	.063	0.034, 0.276	0.038
SLICC score at last visit*	North American Indian Ethnicity	1.259	.309	0.647, 1.870	0.000
	Disease Duration	.123	.030	0.065, 0.182	0.000
	Treatment Index at last Visit	.661	.122	0.420 – 0.902	0.000
Death†	North American Indian Ethnicity	1.527	.6511	0.251, 2.803	0.019
	SLEDAI at last visit	.1534	.0486	0.058, 0.249	0.016

*Analyses done using stepwise, forward, and backward linear regression analyses. Results were identical for all measures. Covariates included were age, sex, ethnicity, SLEDAI at diagnosis and at 2 years, and Treatment index at diagnosis and 2 years for the 2 Year SLICC score as the outcome variable, and the above plus disease duration, and SLEDAI score and Treatment Index at the last clinic visit for the last visit SLICC score as the outcome variable.

†Analysis done using stepwise forward and backward Cox regression analysis. Results were identical for all measures. Covariates included were age, sex, ethnicity, SLEDAI score at the last visit, SLICC score at the last visit, and treatment index at the last clinic visit.

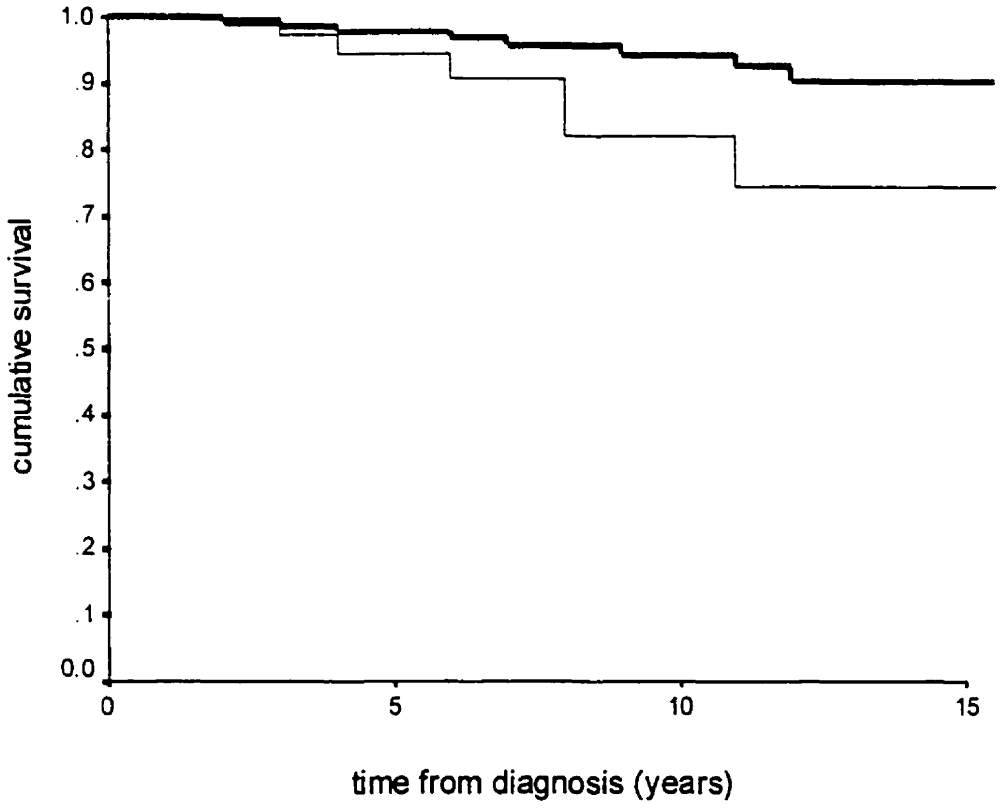

Figure. Cumulative survival of Caucasian (heavy line) and North American Indian (fine line) SLE patients. ($p = 0.04$)

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MANITOBA LUPUS PATIENTS

-Please include only Manitoba residents with definite SLE
-For ETHNIC please indicate whether patient is white, oriental, asian, black, or aboriginal

DATE OF BIRTH	SEX	ETHNIC	YEAR OF DIAGNOSIS	DECEASED

THANK YOU!!

Are You Currently Following Any Patients With Definite Systemic Lupus Erythematosus Who, To The Best Of Your Knowledge, Are **Not Being Followed By Any Specialist** For Care Of Their Lupus?

no_____ **yes**_____ **if yes, How Many?** 1-2___
3-5___
>5____

THANK YOU !!!

C. Systemic Lupus Erythematosus Disease Activity Index.

SLEDAI: DATA COLLECTION SHEET

Chart no _____ Date of Visit _____

I D _____

Enter weight in SLEDAI Score column if descriptor present at the time of the visit or in the preceding 10 days)

Weight	SLEDAI Score	Descriptor	Definition
8	____	Seizure	Recent onset. Exclude metabolic, infectious, or drug causes
8	____	Psychosis	Altered ability to function in normal activity due to severe disturbance in perception of reality. Include hallucinations, incoherence, marked loose associations, impoverished thought content, marked illogical thinking, bizarre, disorganized, or catatonic behavior. Exclude uremia and drug causes
8	____	Organic brain syndrome	Altered mental function with impaired orientation, memory, or other intellectual function, with rapid onset and fluctuating clinical features. Include clouding of consciousness with reduced capacity to focus, and inability to sustain attention to environment, plus at least 2 of the following: perceptual disturbance, incoherent speech, insomnia or [illegible] drowsiness, or increased or decreased psychomotor activity. Exclude metabolic, infectious, or drug causes
8	____	Visual disturbance	Retinal changes of SLE. Include cytoid bodies, retinal hemorrhages, [illegible] exudate or hemorrhages in the choroid, or optic neuritis. Exclude hypertension, infection, or drug causes
8	____	Cranial nerve disorder	New onset of sensory or motor neuropathy involving cranial nerve
8	____	Lupus headache	Severe, persistent headache; may be migrainous, but must be nonresponsive to narcotic analgesia
8	____	CVA	New onset of cerebrovascular accident(s). Exclude arteriosclerosis
8	____	Vasculitis	Ulceration, gangrene, tender finger nodules, periungual infarction, [illegible] hemorrhages, or biopsy or angiogram proof of vasculitis
4	____	Arthritis	More than 2 joints with pain and signs of inflammation (i.e., tenderness, swelling, or effusion)
4	____	Myositis	Proximal muscle aching/weakness associated with elevated creatine phosphokinase/aldolase or electromyogram changes or a biopsy showing myositis
4	____	Urinary casts	Heme-granular or red blood cell casts
4	____	Hematuria	>5 red blood cells/high power field. Exclude stone, infection, or other [illegible]
4	____	Proteinuria	>0.5 gm/24 hours. New onset or recent increase of more than [illegible] gm/24 hours
4	____	Pyuria	>5 white blood cells/high power field. Exclude infection
2	____	New rash	New onset or recurrence of inflammatory type rash
2	____	Alopecia	New onset or recurrence of abnormal, patchy, or diffuse [illegible] loss
2	____	Mucosal ulcers	New onset or recurrence of oral or nasal ulcerations
2	____	Pleurisy	Pleuritic chest pain with pleural rub or effusion, or pleural thickening
2	____	Pericarditis	Pericardial pain with at least 2 of the following: rub, effusion, or electrocardiogram or echocardiogram confirmation
1	____	Low complement	Decrease in CH50 [illegible] or [illegible] below the lower limit of normal for the laboratory
1	____	Increased DNA binding	>25% binding by Farr assay or above normal range for the [illegible]
1	____	Fever	>38°C. Exclude infectious cause
1	____	Thrombocytopenia	<100,000 platelets/mm3
1	____	Leukopenia	<3,000 white blood cells/mm3. Exclude drug induced
TOTAL SLEDAI SCORE	____		

D. Systemic Lupus International Collaborating Clinics/ American College of Rheumatology Damage Index

Systemic Lupus International Cooperating Clinics

SLE DAMAGE INDEX

[Damage (non-reversible change, not related to active inflamation) occuring since onset of lupus, ascertained by clinical assessment and present for at least 6 months unless otherwise stated. Repeat episodes mean at least 6 months apart to score 2. The same lesion cannot be scored twice.]

Item	Score	
OCULAR (Either eye, by clinical assessment)		
Any cataract ever	1	
Retinal change OR Optic atrophy	1	
NEUROPSYCHIATRIC		
Cognitive impairment (e.g. memory deficit, difficulty with calculation, poor concentration, difficulty in spoken or written language, impaired performance level)		
OR Major psychosis	1	
Seizures requiring therapy for 6 months	1	
Cerebral Vascular Accident ever (Score 2 if > once), or resection not for malignancy	1	2
Cranial or peripheral neuropathy (excluding optic)	1	
Transverse myelitis	1	
RENAL		
Estimated or measured GFR < 50%	1	
Proteinuria 24 h, ≥ 3.5 g	1	
OR		
End-stage renal disease (regardless of dialysis or transplantation)		3
PULMONARY		
Pulmonary hypertension (right ventricular prominence, or loud P2)	1	
Pulmonary fibrosis (physical and X-ray)	1	
Shrinking lung (X-ray)	1	
Pleural fibrosis (X-ray)	1	
Pulmonary infarction (X-ray) OR resection not for malignancy	1	
CARDIOVASCULAR		
Angina OR coronary artery bypass	1	
Myocardial infarction ever (Score 2 if > once)	1	2
Cardiomyopathy (ventricular dysfunction)	1	
Valvular disease (diastolic murmur, or a systolic murmur > 3/6)	1	
Pericarditis X 6 months, OR pericardiectomy	1	

		2
PERIPHERAL VASCULAR		
Claudication X 6 months	1	
Minor tissue loss (pulp space)	1	
Significant tissue loss ever (loss of digit or limb, including resection not for malignancy) (Score 2 if > one site)	1	2
Venous thrombosis with swelling, ulceration, OR venous stasis	1	
GASTROINTESTINAL		
Infarction or resection of bowel below duodenum, spleen, liver or gall bladder ever, for whatever cause (Score 2 if > one site)	1	2
Mesenteric insufficiency	1	
Chronic peritonitis	1	
Stricture OR Upper Gastrointestinal tract surgery ever	1	
Pancreatic insufficiency requiring enzyme replacement OR with pseudocyst	1	
MUSCULOSKELETAL		
Muscle Atrophy or weakness	1	
Deforming or erosive arthritis (including reducible deformities, excluding avascular necrosis)	1	
Osteoporosis with fracture or vertebral collapse (excluding avascular necrosis)	1	
Avascular necrosis (Score 2 if > once)	1	2
Osteomyelitis	1	
Ruptured tendon	1	
SKIN		
Scarring chronic Alopecia	1	
Extensive scarring or panniculum other than scalp and pulp space	1	
Skin ulceration (excluding thrombosis) for more than 6 months	1	
PREMATURE GONADAL FAILURE	1	
DIABETES (regardless of treatment)	1	
MALIGNANCY (Exclude dysplasia) (Score 2 if > one site)	1	2

References

1. Lawrence RC, Hochberg MC, Kelsey JL, McDuffie EC, Medsger TA, Felts WR, et al. Estimates of the prevalence of selected arthritic and muskuloskeletal conditions in the United States. J Rheumatol 1989;14:427.
2. Hochberg MC. The Incidence of systemic lupus erythematosus in Baltimore, Maryland,1970-1977. Arthritis Rheum 1985;28:80.
3. Hochberg MC. The epidemiology of lupus erythematosus. In: Wallace DJ, Hahn BH, editors. Dubois' Lupus Erythematosus. Baltimore: Williams & Wilkins; 1997. p. 49-65.
4. Hart HH. Ethnic differences in the prevalence of systemic lupus erythematosus. Ann Rheum Dis 1983;42:529.
5. Chang NC. Rheumatic diseases in China. J Rheumatol 1983;10, Suppl 10:41-45.
6. Feng PH, Boey ML. Systemic lupus erythematosus in the Chinese: The Singapore experience. Rheumatol Int 1982;2:151.
7. Lutalo SK. Chronic Inflammatory rheumatic diseases in black Zimbabweans. Ann Rheum Dis 1985;44:121.
8. Boyer GS, Lanier AP, Templin DW. Prevalence rates of spondyloarthropathies, rheumatoid arthritis and other rheumatic disorders in an Alaskan Inupiat Eskimo population. J Rheumatol 1988;15:678-682.
9. Boyer GS, Lanier AP, Templin DW, Bulkow L: Spondyloarthropathy and rheumatoid arthritis in Alaskan Yupik Eskimo. J Rheumatol 1990;17:489-496.
10. Oen K, Postl B, Chalmers IM, Ling N, Schroeder ML, Baragar FD, et al. Rheumatic Diseases in an Inuit population. Arthritis Rheum 1986;29: 65-74.
11. Morton RO, Gershwin E, Brady C, Steinberg AD. The incidence of systemic lupus erythematosus in North American Indians. J Rheumatol 1976;3:186-190.
12. Boyer GS, Templin DW, Lanier AP. Rheumatic diseases in Alaskan Indians of the southeast coast: High prevalence of rheumatoid arthritis and systemic lupus erythematosus. J Rheumatol 1991;18:1477-84.

13. Atkins C, Reuffel L, Roddy J, Platts M, Robinson H, Ward R. Rheumatic disease in the Nuu-Chah-Nulth native Indians of the Pacific Northwest. J Rheumatol 1988;15:684-90.

14. Ward MM, Studenski S. Clinical manifestations of systemic lupus erythematosus. Identification of racial and socioeconomic influences. Ann Rheum Dis 1994;153;675-80.

15. Alarcon GS, Roseman J, Bartolucci AA, Friedman AW, Moulds JM, Goel N, et al. Systemic lupus erythematosus in three ethnic groups: II. Features predictive of disease activity early in its course. Arthritis Rheum 1998;41:1173-1180.

16. Reveille JD, Bartolucci A, Alarcon-Segovia D. Prognosis in systemic lupus erythematosus. Negative impact of increasing age of onset, black race, and thrombocytopenia, as well as causes of death. Arthritis Rheum 1990;33:37-48.

17. Isenberg DA, Garton M, Reichlin MW, Reichlin M. Long-term follow-up of autoantibody profiles in Black female lupus patients and clinical comparison with Caucasian and Asian patients. Br J Rheumatol 1997;36:229-233.

18. Reveille JD, Moulds JM, Ahn C, Friedman AW, Baethge B, Roseman J, et al. Systemic lupus erythematosus in three ethnic groups: I. The effects of HLA Class II, C4, and CR1 alleles, socioeconomic factors, and ethnicity at disease onset. Arthritis Rheum 1998: 41;1161-72

19. 1991 Census of Canada, Catalogue 93-315: Ethnic Origin-The Nation.

20. Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF, et al. Special Article: the 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1982;25;1271-77.

21. Bombardier C, Gladman DD, Urowitz MB, Caron D, Chang CH. Committee on Prognosis Studies in SLE: Derivation of the SLEDAI. A disease activity index for lupus patients. Arthritis Rheum 1992;35:630-640.

22. Arce-Slaina A, Cardiel MH, Guzman J, Alcocer-Varela J. Validity of retrospective disease activity assessment in systemic lupus erythematosus. J Rheumatol 1996;23:846-49.

23. Lacaille D, Clarke AE, Bloch DA, Danoff D, Esdaile JE. The impact of disease activity, treatment, and disease severity on short term costs of systemic lupus erythematosus. J Rheumatol 1994;21:448-53.

24. Gladman DD, Ginzler E, Goldsmith C, Fortin P, Liang M, Urowitz M, et al. The development and initial validation of the Systemic Lupus International Collaborating Clinics/ American College of Rheumatology Damage Index for systemic lupus erythematosus. Arthritis Rheum 1996; 39:363-369.

25. Greenberg JH. Language in the Americas. Stanford, CA: Stanford University Press, 1987.

26. Canvin MG, Hitchon CA, El-Gabalawy HS. Rheumatoid Arthritis presents 10 years earlier in Algonkian North American Indians [Abstract]. Arthritis Rheum 40:9; S155, 1997.

27. Peschken CA, El-Gabalawy HS, Roos LL, Esdaile JM. Algonkian Indians have twice the frequency of rheumatoid arthritis with a younger age of onset [Abstract]. Arthritis Rheum 41:9;S558,1998.

28. Willkens RF, Blandau RL, Aoyama DT, Beasley RP. Studies of rheumatoid arthritis among a tribe of Northwest Indians. J Rheumatol 1976;3:9-14.

29. Harvey J, Lotze M, Arnett FC, Bias WB, Billingsley LM, Harvey E, et al. Rheumatoid arthritis in a Chippewa band. II. Field study with clinical serologic and HLA-D correlations. J Rheumatol 1983;10:28-32.

30. Scofield RH, Fogle M, Rhoades ER, Harley JB. Rheumatoid arthritis in a United States Public Health Service Hospital in Oklahoma: serologic manifestations in rheumatoid arthritis vary among tribal groups. Arthritis Rheum 1996;39:283-6.

31. Heimgartner E, Rosenthal M. La artritis reumatoide en una poblacion indigena (Mazahua) del altiplano de Mexico. Bol Of Sanit Panam 1979;86:283-92.

32. Final Report of the Royal Commission on Aboriginals. Hull, Quebec. Canadian Communications Group-Publishing, 1996.

33. Gladman DD, Urowitz MB. Systemic lupus erythematosus: Clinical features. In: Klippel JH, Dieppe PA, Editors. Rheumatology. 2nd ed. London: Mosby International; 1998. p. 7.1.1-18.

34. Ward MM, Pyun E, Studenski S. Long-term survival in systemic lupus erythematosus: patient characteristics associated with poorer outcomes. Arthritis Rheum 1995; 38:274-83.

35. Petri M, Perez-Gutthann S, Longenecker JC, Hochberg M. Morbidity of systemic lupus erythematosus: role of race and socioeconomic status. Am J Med 1991;91:345-353.

36. Hochberg MC. Sytemic lupus erythematosus. Rheum Dis Clin North Am 1990;16:617-39

37. Elkon KB. Systemic lupus erythematosus: Autoantibodies in SLE. In: Klippel JH, Dieppe PA, Editors. Rheumatology. 2nd ed. London: Mosby International: 1998. p. 7.5.1-10.

38. Gulko PS, Reveille JD, Koopman WJ, Burgard SL, Bartolucci AA, Alarcon GS. Survival impact of autoantibodies in systemic lupus erythematosus. J Rheumatol 1994;21:224-228.

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