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SPECIAL ARTICLE

Immune Dysfunction In Australian Aborigines

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SUMMARY An examination of the prevalence and phenotype of immune disorders in different ethnic groups may provide important clues to the etiopathogenesis of these disorders. Whilst still conjectural the restricted and somewhat unique polymorphisms of the MHC (and other genetic loci involving host defences) of the Australian Aborigines may provide an explanation for their apparent heightened susceptibility to newly encountered infections and their resistance to many (auto) immune and allergic disorders. In comparison with non-Aboriginal Australians, Australian Aborigines have heightened frequencies of rheumatic fever, systemic lupus erythematosus, various infections and post-streptococcal glomerulonephritis. In contrast various autoimmune disorders (e.g. rheumatoid arthritis, multiple sclerosis, CREST, biliary cirrhosis, coeliac disease, pernicious anaemia, vitiligo), B27 related arthropathies, psoriasis, lymphoproliferative disorders and atopic disorders appear infrequent or absent. Similarly various autoantibodies occur with increased or diminished frequency. With continuing racial admixture, social deprivation and deleterious lifestyles of these people it is likely that further changes in both the frequencies and phenotype of these immune disorders will occur. It is only with a full understanding of the pathogenic mechanisms involved in these immune disorders that meaningful and clinical relevant interventions will be possible.

Ancestors of the Australian Aborigines migrated to Sahul (continental land mass of Australia and New Guinea) 40-60,000 years before present and their descendents have continued to occupy the land to the present time. From a biological perspective the subsequent cultural and biological evolution of these isolated people in their unique environment can be viewed as an excellent opportunity to examine differences in disease expression in comparison with ethnic groups in other lands. If differences are observed they may provide clues to the aetiopathogenesis of these disorders. However, before examining the prevalence and phenotype of immune disorders in the Australian Aborigines we need to acknowledge recent changes in genetic and environmental influences.

Up until white settlement over 200 years ago the Australian Aborigines were considered to be anthropomorphically and genetically a fairly homoge-

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nous race but with some regional variations.[1,2] Furthermore, these indigenous people lived a hunter-gatherer lifestyle rich in cultural traditions but with little variation in their regional environmental influences. However, since settlement racial intermarriages have occurred with a mixture of white, Asian, Polynesian and Melanesian genes. In addition, there have been dramatic environmental changes including change in diet and nutrition, lifestyle and exposure to various new infections, chemical and toxic agents, etc. Thus today, tragically, the Australian Aborigines are characterised with high levels of obesity, diabetes, hypertension, chronic renal disease, hepatitis B, alcoholism, chronic unemployment and suicide.[3] It is important, therefore, to recognise that changes in disease prevalence or phenotype over the last 200 years may reflect these influences and that contemporary observations may not necessarily reflect the situation before white settlement. It should also be noted that immune disease prevalence and perhaps phenotype may also change over time, for example, the altered prevalence of rheumatoid arthritis (RA), multiple sclerosis and other autoimmune disorders in the past 200 years.[4]

Sources of information

The Australian Aborigines while rich in oral traditions have no written language and hence their own historic record from these people with regard to immune disorders is not available. We therefore seek other sources for this information. These alternative sources can be listed as (1) ethnographical-historic or (2) contemporary. Ethnographic evidence is obtained from the written historical records of observers who noted disease prevalence in their early contact with the Australian Aborigine. There is a rich source of this material and on many occasions involved informants who were medically trained. Contemporary data refers to the observation of current observers. In many instances the data are more complete but as discussed above, this information does not necessarily reflect the situation before white settlement. In the current study the sources of information systematically searched include:

1) Moodie and Peterson's 'The Health of Australian Aborigines: an annotated bibliography', 1972;
2) Medline search using a variety of index terms;
3) Annual Reports of the Menzies School of Health Research and the Clinical Research Centre for Aboriginal and Tropical Health.

Host defences

Innate immunity

Little is known concerning innate defence mechanism in healthy Australian Aborigines. Early observers were impressed how quickly severe lacerations and injuries healed in these people.[5] Circulating white cell counts including neutrophil numbers are generally normal although eosinophilia is a frequent observation in current times generally associated with endemic parasitism.[6] Complement pathways appear intact with some studies revealing a increased prevalence of C4 null alleles.[7] A recent study has suggested restricted polymorphisms for the mannin binding protein.[8] There is no data available concerning Toll like receptors in Australian Aborigines. Circulating NK cells appear increased.[9]

Adaptive immunity

Circulating lymphocyte counts are similar or slightly lower than Caucasians.[10] Studies in the Top End (Darwin) have shown that Australian Aborigines have significantly fewer CD4 helper cells with reduced mitogenic responses to PHA, ConA and PWM.[11] It is uncertain whether this depressed cell mediated immunity is genetic or acquired and this requires further research. The memory CD4 Ro positive lymphocyte subset appears diminished. Healthy Australian Aborigines produce similar levels of antibody to most vaccines in comparison with Caucasians although, as we will discuss later, protein calorie malnutrition (PCM), poor hygiene and social deprivation may lead to impaired responses.[12,13] Circulating immunoglobulins of all classes are elevated and this is observed from an early age.[14-16] Whether such elevated levels are genetically determined or reflect acquired environmental factors (e.g. parasitism) is yet to be resolved. Factors such as age, gender, human leucocyte antigen (HLA), geographical location and parasitism are all relevant in discussing immunoglobulin levels in Australian Aborigines.

Major histocompatibility complex

The major histocompatibility complex (MHC the region containing the genes on chromosome 6 involved in immune responsiveness) is the most polymorphic of all human genetic loci and this polymorphism has most likely evolved in response against a wide variety of infectious insults. Of interest in Australian Aborigines the MHC class I polymorphism is highly restricted and generally stable with few locally generated subtypes suggesting that the limited HLA repertoire reflects a small number of founder alleles which was able to provide the maximum protection for the population over the eons prior to white settlement.[1] In contrast, however, a substantial proportion of the MHC class II polymorphisms has been replaced with locally generated subtypes (accounting for approximately 30% of the DRBI gene frequencies) with striking regional variability.[2] This regional difference may be partly explained by a combination of factors such as those reflecting the allelic repertoire of the colonising population, geographical isolation, stochastic factors and selection from exposure to new infectious agents. However, it is still somewhat conjectural as to whether the restricted and differing polymorphic forms of the MHC in Australian Aborigines is the full explanation for their apparent heightened propensity to succumb to newly encountred infections (e.g. tuberculosis, influenzae, measles, smallpox) following colonisation (see below).[17]

Immune disorders

Immunodeficiency

To date no Aborigine has been reported with a definitive primary immunodeficiency such as IgA deficiency, common variable immunodeficiency or severe combined immunodeficiency but there is no reason to suggest that it does not occur in these people – it just needs diagnostic consideration particularly in those subjects with severe recurrent infections.

Examples of acquired immunodeficiency with impaired host defences are commonly seen in Australian Aborigines[18] particularly related to PCM, iron deficiency with parasitism, chronic infections, diabetes, smoking, alcoholism, kava ingestion, renal disease, social deprivation with poor hygiene, etc. All these environmental factors may impact dramatically on both innate and acquired immunological host defence mechanisms and be wholly or partly responsible for the increased prevalence of such infectious disorders as tuberculosis, leprosy, streptococcal disease, chronic diarrhoeal states, respiratory infections, middle ear infections, sexually transmitted disorders (STD), etc. More recently HIV infection has been noted in Australian Aborigines[18,19] and it is of great concern that it will become more prevalent because of the high current rates of sexually transmitted disorders and poor genital health.

Are Australian Aborigines more susceptible to these microbiological infections that they have not been previously exposed to and hence have not evolved effective and robust adaptive immunity?[17] The answer to this question is necessarily complex but is highly relevant particularly in view of the increasing HIV epidemic. Historically with the coming of the white settlement to their lands Australian Aborigines were devastated by such infectious diseases as smallpox (some observers believe that up to half their population was wiped out in several epidemics which swept across the continent in the late 18th and early 19th century), influenzae, measles, tuberculosis and enteric infections. STD disease may have caused reduced rates of fertility. The consequences of these infections together with the loss of their hunter gather lifestyle, loss of their lands and loss their independence and vitality is well recorded and is a black scourge on the recent history of Australia. Tragically, however, it is a common story when it comes to the colonisation of lands containing their indigenous populations. Would their history have been any different if they had been more resistant to these new infections? Whatever is the answer it is clear that we must now maximise our efforts in improving the social deprivation, nutrition and hygiene for those indigenous people and in producing useful and relevant education and vaccination to minimise the morbidity and mortality related to infectious disease.

Autoimmune disorders

The prevalence and phenotype of autoimmune disorders in Australian Aborigines is of much

interest but unfortunately there is little specific information or systematic documentation. An attempt has been made in Table 1 to summarise the frequency of a number or specific autoimmune diseases in Australian Aborigines as compared with their recurrence in non-aboriginal Australians. Much of this data is based on small studies, single case descriptions, personal observations or anecdotes and will almost certainly alter with new descriptions and more complete studies.

Rheumatic fever

The prevalence of rheumatic fever and associated streptococcal polyarthritis is high in central and northern Australian Aboriginal populations.[20,21] Indeed, one study in the Top End has shown the highest incident rates of rheumatic fever world wide with an annual incidence of acute rheumatic fever (1989-1993) between 2 to $7/10^4$ children aged 4 to 14 years and 3% of people having established rheumatic heart disease.[20] The cause of rheumatic fever is thought not to be caused any major predisposition based on ethnicity but by the high carriage rate of the M5 family (historic rheumatic fever associated M types) group A streptococcus in aboriginal subjects in tropical Australia, which in turn is related to over crowding, continuous poor living conditions and recurrent skin sepsis.[22,23] It is not known whether acute rheumatic fever occurred in Australian Aborigines before white settlement but case descriptions of acute rheumatism were increasingly recorded after settlement.[24]

Post streptococcal glomerulonephritis

This disease occurs either sporadically or in small epidemics particularly in the Top End with an incident rate amongst the highest documented in the world.[25]

Rheumatoid arthritis (RA)

There is no paleopathological or ethnographical evidence to support the existence of rheumatoid arthritis in indigenous people in Australia before or after white settlement.[26] Furthermore, an analysis of the recent historic and contemporary literature has revealed no description of classic or definite RA occurring in these people.[27-28] We have recently commented on the rarity of RA in Australian Aborigines and after a letter seeking further information, we have been able to describe the clinical, laboratory, and immunogenetic features of seven aboriginals with probable or definite RA.[29] It is of interest that these patients all derived from northern Queensland and at least two of them have genetic evidence of prior racial admixture. Since this initial

Table 1 Immune disorders in Australian Aborigines

High frequency	Low or rare frequency
Rheumatic fever	Lymphoma/myeloma
SLE/DLE	Atopic disorders
Infections	Thyroid disease
Post-streptococcal glomerulonephritis	Polymyositis
	Vitiligo
	Multiple sclerosis
	Rheumatoid arthritis
	Biliary cirrhosis
	CREST
	Coeliac disease
	Juvenile onset diabetes
	Pernicious anaemia
	B27 related arthropathies
	Psoriasis

description we are now aware of a further 18 Aboriginal patients with RA the majority, however, having evidence of prior racial intermarriage (personal communication).

Why should the occurrence of RA be so rare in the Australian Aborigine? Part of the explanation may arise from the scarcity of the shared rheumatoid epitope in these people. The shared rheumatoid epitope is a motif on the MHC class II molecule involving antigen presentation as coded by a number DR beta 1 alleles.[30] This shared epitope is found in approximately 35% of healthy white populations but in 85% of patients with RA and it may also be a risk factor for more severe disease outcome. The shared rheumatoid epitope occurs infrequently in the Australian Aborigine[2] but it was of interest to note its presence in four of the seven patients described above. In Australia, however, there is some regional variation where the shared rheumatoid epitope occurs with a higher frequency in the Aborigines of the Kimberley and Cape York (north Queensland) regions.[1,2] It will be of interest to see if RA occurs more commonly in these populations of indigenous people. RA also seems rare or non existent in New Guinea highlanders who probably have the same ancestral origins as the Australian Aborigine.[31] Again it will be interesting to determine if these people also lack the shared rheumatoid epitope. RA is absent in a rural Nigerian population.[32] These people lack the shared rheumatoid epitope encoded by chromosome 6. However, in contrast, in the Taiwanese Aborigines where RA is not observed HLA-DR4 is present (indicating the likely presence of the shared rheumatoid epitope) implying that there may be additional explanations for the rarity of RA in aboriginal populations.[33]

Systemic lupus erythematosus (SLE)

Four studies have revealed a high prevalence of SLE in Australian Aborigines, one in Western Australian,[34] one in Northern Queensland,[35] one in the Top End of the Northern Territory[36] and one in Central Australia.[37] This latter study reported a prevalence of SLE of 1:1,360 for Australian Aborigines compared with 1:5,170 for Caucasians whilst the prevalence in the Top End was 1:1,900, at least twice the estimated prevalence in non-aboriginal Australians. In both these more complete clinical studies high frequency of DNA antibodies, anti-Sm, anti-RNP were reported with the top end study noting high frequency of renal disease which was thought to contribute to the high mortality figures. In contrast renal involvement and mortality was low in the central Australian study. Dr. Green, an Adelaide dermatologist, has also commented on the high frequency of discoid lupus erythematosus (DLE) in Australian Aborigines living in widely separated geographical areas of the continent.[38] He noted an interesting clinical feature that DLE may be confined to the lips (especially lower lip).

The explanation for the high frequency of SLE and DLE in Australian Aborigines is uncertain. Initial studies from the Top End suggested that it might be related to the high frequency of C4 null alleles (29 percent compared with 17 percent of white controls),[39] although another study involving Central Australian Aborigines with SLE has not confirmed this finding.[40] In general C4 null alleles have been shown in most ethnic groups to be a common risk factor for SLE.[7] Grennan and Bossingham[35] alternatively, have suggested that the high frequency of SLE in indigenous Australians relates to excessive UV exposure and the high rates of infections.

Other connective tissue disorders

We have personally observed the presence of scleroderma, dermatomyositis and ANCA related vasculitis in Australian Aborigines whose ancestral origins may involve prior genetic admixture. However there is no reliable information regarding the precise incidence or prevalence of these disorders. Centromere positive limited scleroderma (CREST) appears distinctly uncommon.[41]

Multiple sclerosis

There are no reported cases of multiple sclerosis occurring in Australian Aborigines to date.[42]

Organ specific autoimmune disorders

The occurrence of such disorders as juvenile onset diabetes, coeliac disease, pernicious anaemia, thyroid disease, vitiligo and biliary cirrhosis all seem to be uncommon or rare in Australian Aborigines.[17] The rarity or apparent absence of these disorders is

generally ascribed to the absence or low frequency of the MHC alleles linked with these disorders in Caucasian and other ethnic groups[17] (e.g. coeliac disease is strongly linked with DR3, DR7 and DQW2 but these alleles are lacking in Australian Aborigines). However, the suspected low frequency of clinically overt thyroid disease is of some interest as thyroid autoantibodies have been shown in one study to be as equally as common as in Caucasian controls with increasing frequency being noted in the female gender and with increasing age in both ethnic groups.[43] Thus the apparent paradox of absent thyroid disease in Aborigines despite the presence of thyroid autoantibodies will need further research.

Ankylosing spondylitis (AS) and other B27 related arthropathies

There is no paleopathological, ethnographical, historical or contemporary evidence to support the occurrence of ankylosing spondylitis in the indigenous Australian Aborigines with pure ancestry. Some initial confusion arose when examination of axial skeletal remains suggested AS[44] but a close examination of the published illustrations indicate they were more probably represented subjects with localised vertebral ankylosing following an infective discitis or diffuse idiopathic skeletal hyperostosis (DISH). Recent studies have revealed that AS is a genetic disorder with approximately 97% of the variance being determined by genetic factors.[45] The HLA-B27 and its allotypes is one of the important genes underlying the propensity to AS. In tissue typing on Australian Aborigines B27 appears to be at a very low frequency (compared with 6 to 8 percent in white populations); indeed, in a study of 186 subjects in Central Australia it was not detected.[46] This absence could be in part, the explanation for the absence or low frequency of AS and other B27 related arthropathies in Australian Aborigines. As such, this finding in Australian Aborigines is similar to the absence of AS in other racial groups who lack the B27 antigen.[47]

Psoriasis

Dr. Green, the dermatologist mentioned above, has also commented on the rarity of psoriasis amongst Australian Aborigines.[48] He has personally examined over 3,000 of these people in central, northern and southern Australia and has not seen one example of psoriasis. The HLA-CW 6 which is linked with psoriasis in Caucasian populations is rare or absent in Australian Aborigines.[17]

Autoimmune serology

The Immunopathology laboratories at Flinders Medical Centre and the Institute of Medical and Veterinary Science in South Australia provide a comprehensive diagnostic service for a population which consists of approximately 25% Australian Aborigines. We have, therefore, been able to evaluate these requests with regards to immune test performed specifically in Australian Aborigines (Table 2). Indigenous ethnicity was based on the characteristic surname of these people and/or their geographical location (e.g. residence in remote aboriginal community, etc.).

Immunoglobulins of all classes were elevated in Australian Aborigines both in adults and children (Table 3) with particularly high values being seen in patients with encrusted scabies. Paraproteins were most uncommon. A positive rheumatoid factor was found in 53% of 89 of these specimens screened at random. Antinuclear antibodies were also more commonly found in Australian Aborigines as compared with non-Aborigines and frequently reflected the common presence of SSA, SSB and RNP (Table 4). The genetic MHC background of these Aboriginal subjects producing these extractable nuclear antibodies appears to be distinctively different to Caucasian populations.[49] DNA binding was mildly elevated in many Aboriginal sera often in the ab-

Table 2 Serological findings in Australian Aborigines

High frequency	Low or rare frequency
ANA	MPO
Ro/La	PR3
RNP	Centromere
DNA	Endomysial
Cardiolipin	Mitochondrial
RF	
↑ Ig's	
↑ CRP	

Table 3 Immunoglobulin levels in Australian Aborigines

	IgG[1]	IgA[1]	IgM[1]	IgE[2]
Australian Aborigines (Adults n = 104)	25.1 ± 1.0[1]	4.9 ± 0.26[1]	1.6 ± 0.09[1]	49,900 ± 7,400[2]
Australian Aborigines (Children n = 60)	18.9 ± 0.72	1.8 ± 0.14	1.5 ± 0.09	
Laboratory normal (adults, range)	6.5 - 16	0.6 – 4.0	0.5 – 3.0	< 150

[1]Mean ± SE (g/l)
[2]Mean ± SE (IU/l)

Table 4 Frequency of antinuclear antibodies in Australian Aborigines

Antinuclear antibody

		% ANA positive	% Specific patterns					
			Homogeneous	Speckled	Mixed	Nucleolar	Ro	Others
Northern Australia	**Aborigines** n = 311	19.6	15	36	23	14	9	3
	Non-Aborigines n = 1122	15.8	45	28	14	4	6	3
Adelaide	**Caucasians** n = 20,205	28	39.1	20.1	17.3	8.4	7.1	8

Extractable nuclear antibody

		% ENA positive	% Specific ENA				
			Ro	Ro/La	RNP	UPL	Others
Northern Australia	**Aborigines** n = 98	34	16.6	36.6	30	6.6	10.2
	Non-Aborigines n = 379	10.3	4.3	19	16	11	11
Adelaide	**Caucasians** n = 10,939	12.9	30.2	25.7	12.5	17	14.6

sence of a positive antinuclear antibody suggesting non-specific binding perhaps due to high immunoglobulin background.[50] The cut-off value for abnormal DNA binding will need to be adjusted for sera from Australian Aborigines. Low levels of anticardiolipin antibody were frequent but strong positive samples uncommon. Similarly ANCA were more commonly positive in Aboriginal sera but rarely were antibodies to PR3 or MPO detected. The anti-endomysial, anti-mitochondrial and anti-centromere antibodies were absent or rarely detected in Aboriginal sera.

Allergic disorders

The prevalence of type 1 hypersensitivity disorders in Australian Aborigines is generally thought to be lower than that in Caucasians living in the same region. The atopic status determined by the identification of positive prick skin test to common environmental allergens has been determined in a number of studies[51-53] with most reporting lower frequency in Australian Aborigines in comparison with Caucasian control groups. For example, Veal *et al*.[51] reports the overall prevalence of atopy in four abo-

riginal rural communities in three Australian states as varying from 21% to 34% (as compared with values approaching 50% in non-Aboriginals) with a corresponding low prevalence of asthma as compared with non Aboriginal Australians. Other studies in contrast[54] have reported higher rates of asthma in Australian Aborigines (similar to Caucasians) with a significant variation in the prevalence between communities. However, asthma can have both allergic and non-allergic (? infective) aetiologies. One explanation put forward to explain the lower rates of atopy in Australian Aborigines is that it is due to the higher rates of parasitism (as reflected in high circulating IgE levels) which acts as a potent modulator for specific IgE responses against common environmental allergens. The MHC may also be important in determining the IgE response. Indeed a recent study in Australian Aborigines has shown that the MHC DR beta 1 locus accounts for approximately 3% of the variance of the total serum IgE and 17% of the variance of the specific IgE against house dust mite.[55] The effects of the MHC on IgE levels was of an order of magnitude greater than that seen in Caucasians and the authors concluded that these findings were consistent with the hypothesis that the genetic predisposition to allergic diseases may be driven by adaptation to helminthic infections, and parasitism per se is not necessary protective against allergic disease. Other genetic loci, e.g. Fc epsilon R1-beta and its polymorphic variants have also been involved in worm resistance and total serum IgE.[56]

Lymphoproliferative disorders

Lymphoma and multiple myeloma appear to occur at a lower frequency in Australian Aborigines compared with non-Aboriginal Australians with the age-standardised incident ratios for lymphoma (indigenous versus non-indigenous) varying from 0.2 to 0.5.[57] The cause for this lower frequency is unknown but other solid tumours (e.g. breast, colon, rectum and prostate) also occur at a lower frequency whilst other tumours in which environmental causative factors are known (e.g. lung, [smoking], liver [hepatitis B], cervix [human papilloma virus]) occur at high frequencies.[57] Despite the relative high prevalence of serological evidence for HTLV-1 in Australian Aborigines (1 to 14% depending on geographical location) T-cell leukaemia, lymphoma is rare.[58-60] Some have hypothesised that Australian Aborigines are genetically resistant to the effects of HTLV-1 or that the phylogenetically ancient HTLV-1 as seen in Australian Aborigines are less pathogenic.[61] Immunoproliferative small intestinal disease (a spectrum ranging from benign lymphoplasmocytic infiltration of the lamina propria with alpha chain secretion to frank immunoblastic lymphoma) has been described in two indigenous patients in the Northern Territory.[62] An interesting radiological finding in Australian Aborigines is the pitted skull appearance found on the plain skull x-ray which superficially can be mistaken for myelomatous deposits.[63] These multiple translucent areas in the radiograph of the skull are due to prominent bony depressions or pits produced by arachnoid granulations.

Conclusions

An understanding of immune function and dysfunction in Australian Aborigines is of some importance as it allows one greater insight into the tragic consequences that have occurred to these proud people since white settlement of their lands over 200 years ago.

Whilst still conjectural the restricted and somewhat unique polymorphisms of the MHC (and other genetic loci involving host defences) of these people may provide a clue to their apparent heightened susceptibility to newly imported infections and their resistance to may (auto) immune and allergic disorders.[17]

Unfortunately over the last 200 years their continuing social deprivation, deleterious lifestyles and racial admixture has caused further distortion and perturbation of their immune mechanisms resulting in continuing infections and the emergence of new (to them) immune disorders[64]. It is only with a full understanding of the mechanisms involved in these immune disorders that meaningful and clinical relevant intervention will be possible.

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