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The Hyper-Immune Human Female: The Etiologic Role of Sleep Deprivation, Early Pregnancy Factor, Lactation and Woodsmoke Stressors

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INTRODUCTION

Numerous studies have unequivocally established that the human female has a superior immunity to the human male. This phenomenon is known as sexual dimorphism of the human immune response. Human females display a superior cellular and humoral immune response and are more resistant to a variety of infections compared to the human male (Bouman et al. 2005). Evidence for the basis of this dramatic differential in the sex specific steroid hormones estrogen and testosterone has been provided in several studies. It appears in this regard that the superior immunity of the female is directly owed to higher levels of estrogen and indirectly to lower levels of the androgen hormone testosterone. This is corroborated by several independent clinical experimental studies, which clearly demonstrate the immunosuppressive effects of the androgenic hormones (Luster et al. 1985; Roubinian et al. 1979; Waynforth et al. 1980). In addition, there is experimental evidence for the fact that females possess higher serum immunoglobulin levels compared with males (Sakans et al. 1978). Corroborative evidence gathered from other species demonstrates that estradiol enhances antibody production in vivo while testosterone depresses B and T cell differentiation and macrophage activation (Rai 1998; Wichmann et al. 1997).

Pathological studies also directly and dramatically demonstrate the immunosuppressive effects of the sex specific androgens testosterone and dihydrotestosterone. For Cutolo et al. (2002) it has been shown in both male and female patients suffering from rheumatoid arthritis (an autoimmune disease provoked and progressed by an excessively active immune system) that there is a marked lowering of the androgen:estrogen ratio.

The spectacular superiority of the human female immune response over that of the human male is most dramatically seen in situations of acute trauma. In a study involving 52 patients (19 females and 33 males) in the surgical intensive care unit of a hospital, it was found that the mortality rates were 70 percent in the male group while only 26 percent in the female group. The superior survival rate in the female presumably owing to the higher estradiol levels in the female group (Schroder et al. 1998). The purpose of this paper is to explain the various environmental factors that lead to the evolution of superior immunity in the human female.

COUNTER ADAPTATION TO THE IMMUNITY SUPPRESSING EFFECTS OF SLEEP DEPRIVATION / INTERRUPTION

One of the main immunologic challenges to the human female arises in the immediate period following delivery. In the past, infant mortality rates in human populations were so high that population sizes large enough to withstand the winnowing of epidemics, war and predation, were possible only if females were pregnant on a nearly continuous basis. Thus the pressures of infant feeding and nurturing were chronic and unrelenting. Isolated communities with low fertility rates and thus lower net population sizes simply went extinct when confronted by one or more of these decimating stresses. The newborn has anywhere between five to 15 crying episodes nocturnally, which forces the female into interrupted sleep patterns for months on end, resulting in profound physiologic and immunologic implications for her well being (Sander and Julia 1966).

To take an example from a mammalian species: in rats, it has been found that sleep restriction for 21 days drastically affects their immunologic profile. It was found that a critical component of the reticuloendothelial system, the spleen, underwent a gross reduction in weight following 21 days of sleep restriction. In addition, both total leukocyte count and lymphocyte numbers fell during the same period. Thus it is clear that the immune cellular response is substantially attenuated during chronic sleep restriction, and thus presumably a similar impairment occurs in the sleep deprived, infant-suckling human female (Zager et al. 2007).

In yet another direct study on humans, it was found that following 48 hours of sleep deprivation the number of natural-killer (NK) cells in peripheral venous blood decreased substantially. The percentage of natural killer cells returned to normal when ten male volunteers were allowed to sleep (Ozturk et al. 1999), which underscored that this observed phenomenon was due to sleep deprivation.

These findings are further reinforced by studies performed on sleep-deprived females. In an examination of 39 healthy females, it was found that females with high time awake after sleep onset had substantially poorer natural killer cell mobilization to a provoking stressor than females with low time awake after sleep onset. Since natural killer cells are one of the first lines of defense against tumorigenic cells and given that the nursing human female is subjected to carcinogenic cooking smoke on a diurnal basis, we see that the ingredients for oncogenic disaster were firmly in place in the vicinity of primordial hearths. That is, under such circumstances not only are more cancer cells being produced in the lung due to smoke inhalation but in addition the ability of natural killer cells to track down and destroy the tumorigenic cells is severely compromised (Wright et al. 2007).

Thus we see that severe Darwinian selection pressure was exerted on the human female in the prehistoric past for the development and genetic consolidation of super-robust immune systems, to handle the immunologic challenge imposed by the immune attenuating effects of sleep deprivation consequent to the demands of nocturnal infant feeding schedules.

EVOLUTION OF A DEFENSIVE STRATEGY AGAINST THE IMMUNE ATTENUATION PRODUCED BY EARLY PREGNANCY FACTOR (EPF)

It is not sleep deprivation alone that wreaks havoc on the human female's immune system. Remarkably, another challenge to the female immune system comes from a rather unexpected quarter—the human fetus. Since the human fetus has a genetic complement that is half paternal, it carries paternal antigens that would be perceived by the maternal immune system as foreign. Consequently, the fetus runs the risk of immune rejection and abortion. To counter this threat, the fetus, in the course of evolution, has developed a rather unusual strategy, namely the secretion of a specific protein factor called Early Pregnancy Factor. Its function is to

partially suppress the maternal immune response and thereby evade rejection. While this is good for the fetus it does present a problem to the pregnant mother who must now operate on a compromised immune system for well over the 8 to 9 months of pregnancy. To put this number in perspective it must be borne in mind that of the 4,000 odd mammalian species on the planet, less than ten (whale, donkey, camel, giraffe, rhino, Indian elephant, cow, horse and sea lion) have a gestation time that is greater than that of the human. Thus, while it would be predicted that all mammalian species would be subjected to this stressor, the stress would be of longer duration and severity in the human due to the excessively long gestation time involved.

The hobbled immune system must continue to perform its primary function of defending both the mother and the fetus over a period of several months, and consequently the operational complexity of the female immune system must have been subjected to considerable evolutionary selection pressures. In other words, there was intense selection not just for quantitative magnitudes of immune response but also for the more subtle qualitative mechanisms whereby the female immune system discharges its function of immune surveillance.

THE ROLE OF FIRE, SMOKE, AND PARTICLE AEROSOLS IN THE EVOLUTION OF HYPERIMMUNITY

There is persuasive evidence to strongly suggest that the evolution of the superior human female immune response is linked to one of the most ancient and momentous events in human evolution, namely the discovery of fire. Excavations at Gesher Benot Ya' Aquov, in Israel, provide indisputable evidence, in the form of burnt seeds, wood and flint for the utilization of fire by hominids nearly 700,000 years ago. Furthermore, the discrete locations of these charred strata clearly indicate the presence of hearths. Studies have revealed that wood of six different taxa were combusted at these sites. Examples include olive, wild barley, and wild grape (Goren-Inbar et al.

2004). While it is unclear exactly when *all* hominid populations began to use fire, given that at least *one* group was using fire as early as 700,000 BP, leads us to suspect that most, if not all, hominid populations were using it by 50,000 BP. This is an important point, for mitochondrial evidence suggests that all modern humans are descended from a small cohort of hominids that left Africa around this latter date. The utilization of fire for warmth and cooking came associated with a hidden biochemical hazard and brought about a set of adaptive evolutionary changes in physiology among which were the neoteny of the human face and, far more dramatically, the evolution of a peculiar kind of super-female, namely the hyper-immune female. Incidentally, neoteny refers to the retention of infantile traits in the adult stage, such as sparse body hair, flattening of the face, enlarged head etc.

The prime danger associated with wood fuel combustion is that it has been shown that bio-fuels, primarily wood, release volatile organic compounds and polycyclic aromatic hydrocarbons. Many of these chemical structures are potent mutagens and immunosuppressive agents (Boone et al. 1989). Cave shelters provided little to no ventilation, particularly in winter when potential exits to heat loss were deliberately sealed, which aggravated the concentration of mutagenic agents within the confines of the shelter.

The two most important pollutants in biomass smoke are particulate matter and carbon monoxide. Particulate matter with a size of less than 2.5 micrometers has an effect on humans as it can penetrate deep into the lungs due to its size and cause morphologic and biochemical changes. In laboratory studies conducted on animals it has been shown that particulate matter is immunosuppressive, possibly by inhibiting macrophage responses (Rinne et al. 2007).

With regard to the human female, the situation was particularly serious because one of the central features of the division of labor cross-culturally and since ancient times, has been the apportionment of

cooking duties to the human female (Murdock and Provost 1973). The lung tidal volume in females is about 500 ml and the concentration of particulate matter in biomass smoke is 2 mg/l, which means that the concentration of particulate matter entering the lungs comes out to 1 mg. Assuming even 50 percent capture, the deposition in the lungs would be 0.5 mg, a near supra-pharmacologic dose considering that this is the amount deposited in a single breath.

As a result, the human female was subjected to far higher and potent levels of these immunotoxins on virtually a daily basis, and thus intense Darwinian pressure was exerted for the selection of females with extremely robust immune systems that could compensate for the immunodeterioration produced by such toxins.

Innumerable studies have clearly documented that burning bio-fuels, particularly wood, produces a plethora of immunosuppressive agents. For Hamada et al. (1992), a study involving wood burning stoves in Brazil has demonstrated startlingly high levels of polycyclic aromatic hydrocarbons, which are well established mutagens and can result in genotoxic damage to lymphocytes, the cells which subserve immune functions. Indeed evidence suggests that wood smoke has 12 times the mutagenic power of cigarette smoke (Lewtas et al. 1991). In addition, a study on 58 Navajo Indians less than two years of age have shown that chronic exposure to smoke emanating from a wood burning stove increases the risk of lower respiratory tract infection four-fold (Morris et al. 1990).

The potent immunosuppressive power of wood smoke is underscored in a study wherein 21 percent of the mice subjected to wood smoke for six hours and then exposed to an aerosol of the bacterium *Streptococcus zooepidermicus* died in two weeks. Only five percent of the control group experienced mortality (Stone 1995), thus, once again, we have clear reasons for the emplacement of a more powerful immune system in the form of superior

antibody synthesis in the course of human female evolution.

Furthermore, it has been demonstrated that animals exposed to wood smoke show an immediate 25 percent deterioration in the lung's ability to clear bacteria. Also, after roughly 1.5 to 2.5 hours of exposure, this percentage deterioration rose to as much as 61 percent (Zelikoff 1994).

This evidence is not restricted to lab animal studies. Direct evidence of the immunosuppressive effects of wood smoke in humans has been obtained. For example, in a study involving 179 female subjects in India, it was shown that smoke generated from wood, cow dung and other traditional biomass fuels used in cooking produces chromosomal damage in peripheral blood lymphocytes. This would be expected to have significant consequences for the function of these immune effector cells (Musthapa et al. 2004). Furthermore, a decreased resistance to lung infection and enhanced vulnerability to respiratory infections has been documented in humans, and this decrease in immunity is presumably due to interference by the wood smoke in the ability of the macrophage to initiate phagocytosis (Brauer 1999; Dost 1991; Ward 1999). Apparently chemicals like acrolein in wood smoke, suppress the phagocytic ability of these macrophages thereby compromising immunity (Ward 1999).

In a study conducted in rural India, profound DNA damage was discovered in the lymphocytes of rural women using biomass fuels such as firewood and cow dung cakes as a cooking fuel (Pandey et al. 2005). Thus the chronic exposure of human females in evolution to the smoke from primordial hearths led to intense evolutionary selection for females that had superior immune systems, with higher levels of built-in redundancy, capable of resisting the immune suppressing onslaughts of the perpetual halo of wood smoke in which they were enshrouded. That is, those women who on a random basis had a less competent immune system died and their genes

were eliminated from the collective gene pool, while those women whose immune systems were superior survived and thus these “superior” immune genes were perpetuated. Over time this leads to females possessing superior immune systems.

Furthermore it is quite likely that these seemingly disparate immune stressors, that seem not to share any common features, act convergently via the endocrine axis. Just about all the stressors cited in this article—sleep deprivation, toxic chemicals, and psychological stress are known to cause an outpouring of the stress hormone cortisol from the Adrenal Gland, and it is an established fact that cortisol is a potent immunosuppressant that inhibits the action of lymphocytes.

CONCLUSION

In summary the Pleistocene female during her reproductive years, spanning an intergenerational period in excess of 800,000 years, was subjected to a barrage of immune suppressors and in some cases overtly immune-destructive influences which severely compromised her immunity. Consequently, there is little doubt that a great many hominid females succumbed to these combined pressures which crossed a specific deleterious threshold following the discovery of fire. However, some survived and this severe Darwinian selection imposed by these three major parameters—Early Pregnancy Factor, smoke mutagens and sleep deprivation—led in the course of several hundred thousand years to the creation of the super-immune human female.

It is, therefore, no coincidence that mate selection by the human male is now determined by hip-to-waist ratios, breast size, smooth skin, all of which are indicative of her estrogen levels and thus of the immune protection conferred by this steroid molecule. Indirectly, the human male is responding to the immune status of the human female prior to a mate selection decision. It is true that women too exercise biologic selection criteria in mate selection, but immunity (or its somatic indicators) which is

a long term advantage, could not have been one of them, for the dangers of war and hunting guaranteed an early death for the bulk of males in the pre-historic past.

The super-immunity of the human female, however, has had an unfortunate corollary in contemporary human society. In the Western world wood stoves are no longer used, the diet is adequate in protein, lactation stressors are fewer due to the extensive use of bottled milk and, most importantly, pregnancy is postponed to later ages due to women’s careers. The immune system of the modern female is no longer under suppression and her hyperimmunity, hitherto beneficial but now inimical, is expressed without hindrance. As a result, in present-day society the frequency of auto-immune diseases such as Lupus Erythematosus and Rheumatoid Arthritis is higher in women than in men. This gendered health disparity is a problem that must be addressed by the medical community.

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