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Pathology in euthermic bats with white nose syndrome suggests a natural manifestation of immune reconstitution inflammatory syndrome

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White nose syndrome, caused by *Geomyces destructans*, has killed more than 5 million cave hibernating bats in eastern North America. During hibernation, the lack of inflammatory cell recruitment at the site of fungal infection and erosion is consistent with a temperature-induced inhibition of immune cell trafficking. This immune suppression allows *G. destructans* to colonize and erode the skin of wings, ears and muzzle of bat hosts unchecked. Yet, paradoxically, within weeks of emergence from hibernation an intense neutrophilic inflammatory response to *G. destructans* is generated, causing severe pathology that can contribute to death. We hypothesize that the sudden reversal of immune suppression in bats upon the return to euthermia leads to a form of immune reconstitution inflammatory syndrome (IRIS). IRIS was first described in HIV-infected humans with low helper T lymphocyte counts and bacterial or fungal opportunistic infections. IRIS is a paradoxical and rapid worsening of symptoms in immune compromised humans upon restoration of immunity in the face of an ongoing infectious process. In humans with HIV, the restoration of adaptive immunity following suppression of HIV replication with anti-retroviral therapy (ART) can trigger severe immune-mediated tissue damage that can result in death. We propose that the sudden restoration of immune responses in bats infected with *G. destructans* results in an IRIS-like dysregulated immune response that causes the post-emergent pathology.

Key words: cave-hibernating bats, *Geomyces destructans*, hibernation-induced immune suppression, immune cell trafficking, immune reconstitution inflammatory syndrome (IRIS), *Myotis lucifugus*, white nose syndrome

Abbreviations: ART, anti-retroviral therapy; CD4 T cells, CD4 marker-positive T lymphocyte helper cells; IRIS, immune reconstitution inflammatory syndrome; LPS, lipopolysaccharide; TNF, tumor necrosis factor; WNS, white-nose syndrome

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Introduction: White Nose Syndrome in Bats

Mortality in cave hibernating bats was first documented late in winter of 2006–2007 in caves of central New York. White nose syndrome (WNS) was the name assigned to the novel infectious disease described as the cause of the declines in hibernating bat populations because of the white powdery blooms seen on the muzzles of many affected bats. WNS has since spread to seven species of hibernating bats in 17 US states and four Canadian provinces, killing an estimated five million bats.[1,2] Recently published results of infectivity trials confirmed that *G. destructans* is the causative agent of WNS.[3] Evidence suggests that this pathogen may have been introduced from Europe where infection with *G. destructans* is not associated with bat mortality.[4-6] *G. destructans* belongs to a genus of organic decomposers, yet this fungal infection has caused catastrophic declines in cave hibernating bats that surpass any other cutaneous fungal infections of mammals documented to date. Research to determine how this fungus has spread so quickly and resulted in such a large number of deaths is just beginning. The body temperature of hibernating bats ranges from 2–15°C, which closely matches optimal temperatures for the growth of *G. destructans*.[7-9] As

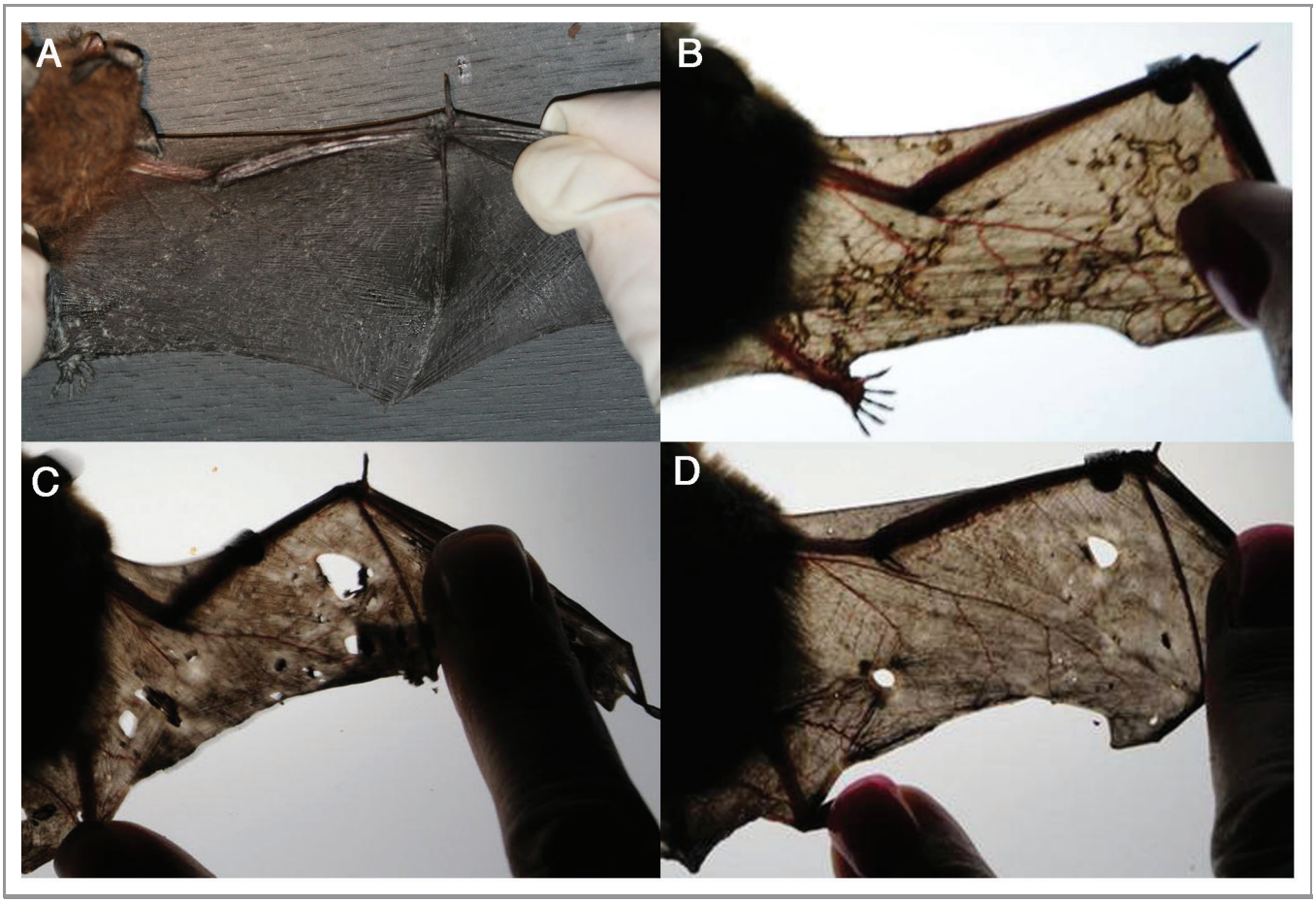

Figure 1. One of 30 Little Brown Bats with white-nose syndrome collected from hibernation April 13, 2010 and taken into rehabilitation. Warmth, food, and water were provided and this bat was photographed over time. Photographs were used with permission from Gregory Turner, Mick Valent and Jackie Kashmer. (**A**) Photograph taken with top lighting in hibernacula at collection April 13, 2010. No gross lesions can be seen, but the dusting of white material on the wing surface is evidence of fungal infection. (**B**) Photograph of bat (A) taken on April 29, 2010 after 16 d of rehabilitation. The transilluminated wing was photographed outstretched over a light box and shows a reticular pattern of wing damage. (**C**) Photograph of bat (A) taken May 11, 2010 shows progressively worsening of wing damage 29 d after being taken into rehabilitation. Loss of tissue is evident and the wing membrane is fragile. In the wild, without provision of food, water, and protection, this bat would be unlikely to survive. (**D**) Photograph of bat (A) taken May 20, 2010, where there is evidence of wing healing 9 d after photograph 1C and 38 d of rehabilitation.

the hibernation season progresses, fungal colonization and erosion of the wing membrane can become severe, potentially disrupting physiological processes that control water and electrolyte balance, torpor length and energy conservation during hibernation.[10-12] In spite of extensive colonization of wing membrane by *G. destructans* during hibernation, little appreciable gross pathology is evident (**Fig. 1A**). WNS positive bats collected from caves near the end of hibernation and held in captivity and provided with warmth, food and water have shown a progression of increasing wing pathology that begins approximately three weeks post arousal and continues for another three weeks (**Fig. 1B and C**) until visible signs of healing can be seen (**Fig. 1D**).[13] Thus far, little attention has been directed toward explaining the lack of effective immune response to *G. destructans* infection during hibernation and processes that contribute to and complicate recovery after bats emerge from hibernation.[13]

Immunity during Hibernation

Like most other mammalian species, bats are homeotherms and maintain their body temperature at 35–39°C at considerable energy cost.[14] Hibernation allows survival during winter months when food is unavailable and temperatures can drop below freezing. During hibernation, bats enter a state of torpor where their body temperature drops to near ambient temperatures with intermittent short periods of arousal. Torpor is accompanied by reductions in physical activity, metabolic rate, heart rate and respiratory rate, as well as a switch in metabolism from carbohydrate-based (glycolysis) to fat catabolism.[14-16] Immune responses are temperature sensitive and metabolically costly[17,18] and recent work suggests that aspects of immune function are also downregulated in bats during hibernation.[18] Recent advances in microscopy tools that enable the tracking of immune cell movement in live mice[19] have revealed the exquisite temperature sensitivity of immune cell motility and function; some cell types, such as lymphocytes, may be more sensitive than others (Mandl JN, unpublished results).[20] Data are lacking on

regulation of immune function in hibernating mammals and it is unclear whether they have adapted to retain specific immune functions even at low body temperatures. Traditional bat pathogens likely replicate less efficiently when the bat host is less metabolically active and have reduced transmission rates with reduced host mobility. If this is the case, the normal physiological immunosupression that occurs in the context of torpor may not necessarily render hibernating bats more susceptible to typical, co-evolved pathogens.

Very little is currently known about the immune system of bats, either during hibernation or their euthermic, active period.[16] Although data from studies of immune function during hibernation in other mammals do exist, it is still unclear which aspects of immunity are altered during this down-regulated state.[20] As early as the 1960s, experimental infections of hibernating ground squirrels with Colorado tick fever virus showed that animals had protracted viremia and reduced antibody titers when they were infected just prior to induction of torpor.[21] More recent studies showed that unlike euthermic animals, injections of LPS in hibernating ground squirrels did not result in fever.[22] While this implies that innate immune cell function is altered in torpid animals, it remains unknown whether innate sensing pathways, cytokine production, cell recruitment or other aspects of innate immune cell function are affected. Furthermore, consistent with observed effects of temperature on the motility of immune cells, it is becoming clear that hibernation results in substantial changes in the trafficking behavior of cells of the adaptive immune system, T and B lymphocytes. Both in hibernating ground squirrels and Syrian hamsters, circulating blood lymphocyte counts are dramatically decreased compared with euthermic animals, with B and T cells being sequestered in secondary lymphoid organs at low body temperatures.[23,24] Similarly, following the experimental induction of torpor using 5'AMP injected into mice,[25] lymphocyte egress from secondary lymphoid organs is greatly reduced (Mandl JN, unpublished results). The retention of lymphocytes within secondary lymphoid organs during hibernation may be a means to ensure survival of this specialized population of cells. However, sequestration of lymphocytes would also prevent them from homing to sites of infection reducing both immune surveillance and limiting the generation of cellular immune responses that play an essential role in pathogen clearance. Further evidence that lymphocyte activation, function and/or homing are restricted during torpor is the successful maintenance of skin allografts transplanted during hibernation which are subsequently rejected when animals return to euthermia at the end of the hibernation season.[26]

Bats infected with WNS during hibernation not only show no gross evidence of pathology, but histopathology indicates that the initiation of inflammatory responses and/or the recruitment of immune cells to sites of *G. destructans* infection does not occur when animals are hibernating (**Fig. 2A and B**).[11,13] The unique histology of *G. destructans* is diagnostic for bats with WNS and consists of dense aggregates of robust hyphae that form a defined interface with skin and erosion along the leading edge of contact.[11] Yet, in spite of the invasive nature of *G. destructans*, neutrophils and macrophages are characteristically absent from sites of pathogen invasion in hibernating bats with WNS (**Fig. 2B**).[11] Not only is the low body temperature of hibernating bats conducive to the replication of this novel emerging pathogen, but the absence of histologically visible inflammatory responses in the skin suggests that, at least during torpor, this fungus is not being limited by effective immune control.

Role of Immunopathology in WNS

If natural immune suppression during hibernation is a key aspect of the lack of resistance of bats to WNS, then the return to euthermia and the reestablishment of immunocompetence should allow bats to mount effective immune responses that clear the infection. Restoration of immunity in hibernating animals following arousal from torpor has presumably evolved to be rapid to prevent increased susceptibility to traditional active pathogens in a "euthermic world." Indeed, blood lymphocyte counts return to normal levels within hours of the establishment of normal metabolic activity in ground squirrels.[24] Yet, paradoxically, the restoration of immunity in bats following arousal may actually contribute to a substantial worsening of WNS pathology in affected bats. Weeks after emergence from hibernation, bats can be found moribund and unable to fly, or dead. These bats, as well as bats observed in rehabilitation, have visible pathology of wing membrane (**Figs. 1 and 2C**). While wings of infected bats often look normal during hibernation (**Figs. 1A and 2A**) and infection can only be identified microscopically (**Fig. 2B**), overt wing damage appears within weeks of euthermia concomitant with histologic evidence of inflammation (**Fig. 2C–F**).[13] The post-emergent bats had intense neutrophilic inflammation associated with invasive *G. destructans*; inflammation that is characteristically absent in torpid animals.[11] A recent example of this was a submission of nine female Little Brown Bats to the US Geological Survey's National Wildlife Health Center. These bats were found distant from wintering hibernation sites in April and May on an island off of the coast of Maine; their wings were damaged and they were unable to fly. Wing membranes were dry, stiff, fragile and contracted with loss of elasticity (**Fig. 2C**). In spite of eagerly eating the food and water provided during rehabilitation, these bats died within 30 h (Ann Rivers, personal communication). Wing histopathology of the nine bats from Maine also had multifocally intense neutrophil infiltration with areas of associated acute necrosis and edema (**Fig. 2D**) and regions of dense degenerating neutrophil aggregation (**Figs. 2D and E**) This rapid restoration of the inflammatory response and mobilization of inflammatory cells with associated wing damage after hibernation is typical of what has been seen in WNS positive bats two to three weeks after they have become euthermic (**Figs. 1 and 2C–E**).

We suspect that this pathology in North American bats that become euthermic while infected with *G. destructans* is due to a phenomenon documented in humans called immune reconstitution inflammatory syndrome (IRIS). IRIS was first documented in HIV positive humans co-infected with opportunistic pathogens and treated with antiretroviral therapy.[27-30]

Immune Reconstitution Inflammatory Syndrome in Humans Following Reversal of Immunosuppression

During HIV infection, immunosuppression occurs as a consequence of the

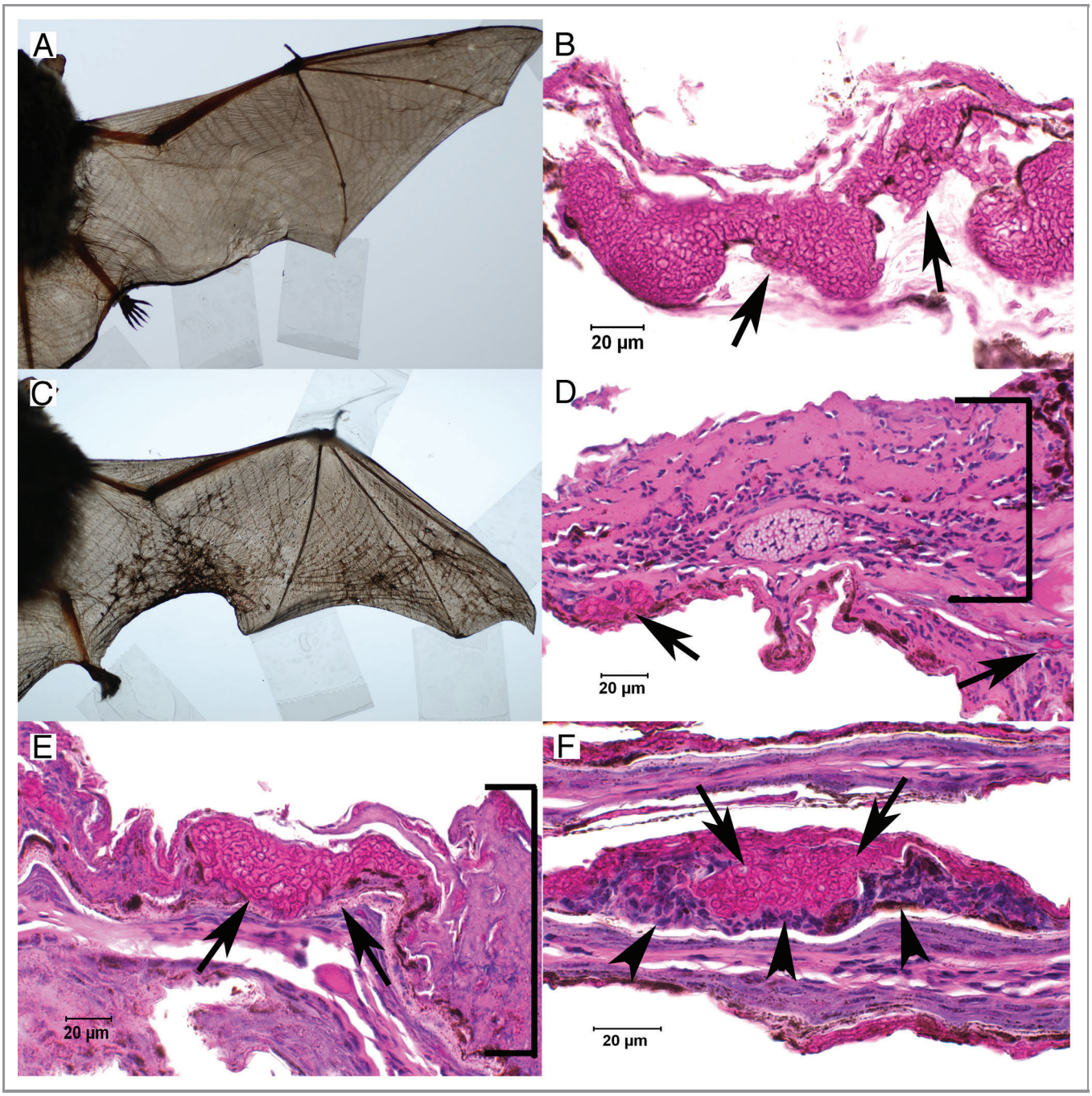

Figure 2. (**A**) Little Brown Bat found February 8, 2009 frozen outside of the small opening of a copper mine. The transilluminated wing was photographed outstretched over a light box and shows no evidence of wing damage. (**B**) Periodic acid Schiff stained section of wing membrane from bat (2A) shows characteristic dense aggregates of robust hyphae forming a defined interface with the skin, erosion along the broad zone of skin contact (arrows) and no visible inflammatory response. (**C**) One of nine Little Brown. Nine bats were found on the ground and unable to fly between April 4 and May 7, 2012. This bat was collected April 4, taken into rehabilitation, ate and drank, but died within 18 h of arrival. The wing was photographed outstretched over a light box and visible damage can be seen with dark areas of contraction and loss of elasticity. (**D**) Periodic acid Schiff stained section of wing membrane from the bat in **Figure 2C**. Severe neutrophilic inflammation and edema (bracket) in response to fungal hyphae (arrow). (**E**) Different field from same slide as in **Figure 2D** shows a thick layer of degenerating neutrophils (brackets) at the margins of a dense aggregate of fungal hyphae eroding epidermis (arrow). (**F**) Little Brown Bat in **Figure 2C**. Degenerating neutrophils (arrowheads) surround the dense aggregate of fungal hyphae (arrows).

depletion of CD4 T cells, a critical immune cell population of the adaptive immune system. The HIV-induced loss of CD4 T cells results in host susceptibility to many opportunistic infections and the recovery of CD4 T cell function following treatment with antiretroviral therapy usually restores resistance to these microbial infections.[31] However, within a few weeks after starting antiretroviral therapy, some AIDS patients undergo a rapid deterioration in symptoms rather than the expected clinical improvement. This paradoxical adverse event of antiretroviral therapy, IRIS, occurs most frequently in patients who are severely CD4 T cell deficient and harbor a microbial co-infection at the time of ART initiation.[29,32,33] Interestingly, IRIS also tends to occur in individuals with the best and most rapid response to ART, as measured by the decrease in HIV viral loads, and with a sudden increase in CD4 T cell numbers. IRIS has been documented in patients with a diverse array of co-infections, and the manifestation of disease depends on the particular opportunistic pathogen and the site of infection. Fungal infections in particular are often associated with HIV-IRIS events, and meningeal infection with *Cryptococcus neoformans* in HIV positive individuals treated with antiretroviral therapy results in the most lethal form of IRIS.

The mechanisms of HIV-IRIS are not well understood,[33] but the prevailing hypothesis suggests that when HIV viral replication is inhibited by ART, the ensuing recovery of CD4 T cells drives an over-exuberant destructive immune response against the underlying microbial co-infection with subsequent damage to infected tissue. Data from a recently developed model of experimentally induced mycobacterial IRIS support the idea that although CD4 T cells are normally required for control of mycobacterial infections, they can also mediate damaging responses during IRIS.[34] It has been shown that both wild-type and T cell deficient mice are able to survive with disseminated *M. avium* infection for many months. However, when T cell deficient mice harboring an established *M. avium* infection are injected with purified CD4 T cells, the mice develop a severe inflammatory disease and die within 1 to 3 weeks after T cell transfer.[34] This adoptive transfer of CD4 T cells does not lead to inflammatory disease in *M. avium* infected mice that have normal numbers of circulating T cells or in T cell deficient mice without *M. avium* infection. This basic observation illustrates the fundamental immunological phenomena of IRIS: once a microbial infection is established in an immunodeficient host, immune recovery can be more detrimental to the host than the opportunistic infection itself, at least in the short-term.

IRIS also occurs following recovery from other forms of immunosuppression.[27-30] For example, tumor necrosis factor (TNF) blockade for the treatment of rheumatoid arthritis or Crohn disease can increase susceptibility to *M. tuberculosis* infection, but rapid removal of TNF blocking drugs after *M. tuberculosis* infection is established in these patients can further exacerbate the pathology.[35] In some multiple sclerosis patients who are treated with the integrin blocking drug natalizumab to prevent lymphocyte migration into the CNS, a quiescent infection with JC polyoma virus may reactivate, leading to progressive multifocal leukoencephalopathy. Rapid removal of the integrin blocking drug can lead to severe worsening of CNS inflammation as the lymphocytes rush back into the brain in response to both the multiple sclerosis and JC polyoma virus replication.[36,37] As a final example, patients with hematologic malignancies who receive chemotherapy to kill the malignant hematopoietic cells in the bone marrow can develop progressive aspergillosis as a result of the resulting neutropenia, but recovery of neutrophil numbers is sometimes associated with a worsening of pulmonary radiological findings and clinical symptoms despite signs of effective antifungal drug treatment.[38]

WNS as a Form of IRIS

Collectively, HIV-IRIS and other examples of IRIS that are caused by a detrimental outcome of treatment with immunosuppressive therapies, demonstrate that IRIS results from a cycle of immunosuppression, outgrowth of an opportunistic microbial infection and sudden restoration of immune function. This disease course is directly paralleled in WNS and we propose that the pathology of WNS is a form of IRIS akin to what occurs in humans. In hibernating species that have been studied,[20] the cold core body temperatures reached during hibernation result in immune suppression. Histologic evidence suggests that this down-regulation of immunity also occurs in hibernating bats,[11,13] enabling the unabated growth of the cold-loving *G. destructans* and leading to the development of progressive fungal infection on the muzzle and glabrous surfaces of their body. Once the bats become euthermic and body temperatures return to normal, immune function is quickly reestablished. At this point, the reanimated populations of immune cells suddenly encounter the fungal infection which progressed in severity during hibernation. The resulting response is an exuberant mobilization of neutrophils to the sites of fungal infection,[13] resulting in necrosis with edema (**Fig. 2D**) and sequestering of fungal hyphae in networks of degenerative cell material resembling neutrophil extracellular traps (**Fig. 2E and F**).[39] As with IRIS in humans, the intensity and extent of tissue infection determines if the exuberant inflammatory response associated with rapid reconstitution of immunity will cause severe tissue damage and death, or eliminate the pathogen and result in host recovery.

Conclusions and Implications

We hypothesize that a perfect storm of pathogen and host factors leads to IRIS in newly post-hibernal emergent euthermic bats with WNS and that this is a key determinant of pathology in WNS positive bats that have survived the hibernation period. Thus far, the occurrence of IRIS has only been associated with pharmaceutical interventions in infected humans and experimentally induced in mice. However, similarities in the course of disease in bats with WNS suggests that the absence of an immune response to *G. destructans* during torpor enables uncontrolled infection with *G. destructans* at low hibernation body temperatures and the subsequent rapid reversal of hibernation-induced immune suppression when the bats become euthermic, leads to a fulminate inflammatory response and consequent immune-mediated tissue destruction. Immunological studies of bats during hibernation,

euthermia and in the period where immunity is reestablished at the end of hibernation are critical to understanding how these natural immunologic states influence pathogen virulence, recovery and survival of bats with WNS.

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