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Health: Infection and Immunity

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An independent academic psychologist, based in England, who has written extensively on different areas of psychology with an emphasis on the critical stance towards traditional ideas.

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1. CIRCADIAN RHYTHMS IN INFECTION AND IMMUNITY

1.1. OVERVIEW

Infectious diseases show rhythmic patterns. For example, infection susceptibility in humans varies over 24 hours (appendix 1A) [1], or the timing of flight in malaria-carrying mosquitoes [2], or viral replication is faster at certain times of the day (Edgar et al 2025). "The environments that parasites experience within hosts change dramatically over 24 hours" (Holland et al 2025 p1).

Edgar et al (2025) explained: "Circadian clocks co-ordinate organisms' activities with daily environmental rhythms, enabling them to cope with the predictable consequences of the Earth's solar rotation. Thus, life in a rhythmic world dictates the timing of activities for many organisms. This includes pathogens, for which the environments within their hosts and vectors change dramatically over 24 h, in fundamental cellular processes (eg: transcription, translation, bioenergetics), systemic physiology and homeostasis (eg: metabolism, body temperature, immune responses) and whole-organism behaviours (eg: locomotor activity, reproduction, foraging). These myriad daily rhythms of hosts and vectors offer opportunities for pathogens to exploit and they present dangers to evade at certain times of day. Vice versa, hosts and vectors can deploy their rhythms, or may need to overrule certain rhythms, to evade and defend against pathogens" (p4) [3].

[1] "Time-of-day differences" describes how virus particles at the primary infection site can progress to other tissues depending on when this happens in the 24-hour clock (Major-Styles et al 2025).

[2] The time of day of biting by insect vectors of malaria parasites varies by season (eg: mosquito Anopheles stephensi bites earlier in the evening in the winter in Asia) (Rund et al 2025). In the case of African populations of the same mosquito, Rund et al (2025) found in an experiment that bite timing was "phase-locked to dawn", and so flight timing behaviour was optimised to protect against heat dessication and cold immobility.

[3] The biology of circadian rhythms is commonly studied in "mouse models". For example, activity of a neurotransmitter molecule histamine varied in the tuberomammillary nucleus (TMN) in the brain (which is involved in circadian rhythms) (Sardar and Kuttateladze 2025).

Edgar et al (2025) outlined five key areas of research:

i) The physiological mechanisms that control host circadian response to infection.

ii) Whether pathogens possess circadian rhythms or depend on their host's rhythms.

Hirako et al (2025) argued, for instance, that Plasmodium chabaudi (rodent malaria) is aligned to host rhythms and does not have its own intrinsic clock. They stated: "In particular, that parasite cell cycle is aligned with the daily rhythms of host feeding. We hypothesise that parasite dormancy, differentiation and replication are aligned with nutrient availability during the 24 h period of the host. Because Plasmodium parasites are entirely dependent on host glucose, we conjecture that raising glucose levels in the blood soon after feeding allows parasite replication when the host is hypoglycaemic [low blood sugar level]" (p6).

iii) The opportunities and dangers to pathogens from the host's rhythms.

Pathogens that can align their migration and reproduction to the host's rhythms will optimise the use of energy. For instance, the migration of Wuchereria bancrofti (parasitic roundworm transmitted by mosquito) between the bloodstream and tissues is sensitive to the level of oxygen in the host's blood, which has a daily rhythm. The migration "from the pulmonary capillary barrier to peripheral blood when the level of oxygen in the pulmonary artery and vein drop below 55 mm Hg. This drop occurs at night when human hosts are resting, providing a cue for the nocturnal biting activity of their mosquito vector" (Hirako et al 2025 p3).

iv) Whether pathogen and host rhythms co-evolve.

Some parasites can disrupt the circadian rhythms of the host. For example, Trypanosoma brucei that causes sleeping sickness advances the time of day of sleeping (Hirako et al 2025).

v) The relationship between circadian rhythms and immune responses in hosts.

For instance, disruption of the circadian rhythms of a host increases their susceptibility to both viral and bacterial infections (food- and airborne), research has found (Horako et al 2025).

The multiplication rate of a pathogen is "the fold change in numbers over a generation" (p1), and it influences disease progression, immunity, and within-host evolution (Greischar and Childs 2025). "Distinct from the evolutionary consequences, multiplication rates govern pathogenic organisms' capacity to harm their hosts, and preventing or slowing multiplication is hence a target of both artificial interventions (drugs, vaccines) and evolved host defences" (Greischar and Childs 2025 p2).

Modelling the malaria parasite, Greischar and Childs (2025) found that multiplication rates were linked to synchrony (ie: pathogens match their developmental timing to host rhythms). In the case of circadian rhythms, this includes host meal times and availability of resources, and incubation periods to coincide with host social behaviour rhythms (Greischar and Childs 2025).

In a study with actual malaria parasites, Holland et al (2025) found that "parasites alter the duration of their replication rhythm to resonate with host rhythms..." (p1). In experiments mice were kept in controlled environments of 21-hour or 27-hour cycles (by controlling the periods of light and darkness). The malaria parasite was able to adapt its replication to the shorter cycle (ie: infected the hosts to the same degree as the usual 24-hour cycle), but not the longer one.

1.2. SLEEP

Sleep disturbance correlates with infectious disease risk. "Short sleep duration has been specifically linked with an increased risk of respiratory infections. However, the role of other sleep parameters, including sleep quality, sleep timing and sleep regularity, for the susceptibility to acute infections is less clear" (Martinez-Albert et al 2025 p1).

Martinez-Albert et al (2025) investigated this topic with data from an online survey. Over 600 adults from Germany and Spain volunteered to self-report information on colds and infections (including covid-19) in the previous month and year, as well as sleep habits. These included sleep duration (typical number of hours per night), and quality (eg: time to fall asleep; feeling refreshed the next day; use of sleep medications), as well as chronotype, and "social jet lag" (eg: disrupted circadian rhythms by rotating shift work) [4].

[4] One sign of social jet lag is that individuals have significantly different sleep-wake patterns on non-work days compared to work days. One study found that nearly three-quarters of 65 000 people showed

"Compared with participants who reported sleeping 7–8 h per night, both short sleepers (≤ 6 h of sleep per night) and long sleepers (≥ 9 h of sleep per night) were significantly more likely to report a cold in the past 30 days, independently of age, sex, survey season and country" (Martinez-Albert et al 2025 p3). Sleep quality was not associated with colds. Higher social jet lag was associated with more colds in the past year. The "definite evening chronotype" reported more colds than the "intermediate chronotype". There was no significant association between infections and any of the sleep and other variables.

1.3. MENSTRUATION

Atopic dermatitis (AD) is a skin condition that can flare up and down. The menstrual cycle may be involved in this process through changes in oestrogen and progesterone. McSwiney et al (2025) reviewed the evidence.

Sixteen relevant studies were found, and they showed "pre-menstrual deterioration in the control of AD, typically occurring in the week before menstruation" (McSwiney et al 2025 p1748). The individual studies varied in the prevalence of menstrual cycle and AD exacerbation (eg: 13.5% to 50%), but all agreed that AD flare up was pre-menstrual.

The methodological quality of the studies was rated as low, overall. For example, nearly half the studies were narrative reviews, and few were designed to allow the establishing of causality. Self-reporting measures were common, along with convenience samples, and the questionnaires used were not always validated.

1.4. APPENDIX 1A - CHRONOTYPE

Interacting with the general circadian rhythms is a predisposition called "chronotype", best described as a "morning person" (morningness) or an "evening person" (eveningness) (which has a genetic basis at around 350 loci; Landvreugd et al 2024).

"Circadian rhythms are subjected to both genetic and environmental factors, but these factors do not act separately; they also depend on each other. This is

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such a pattern (Roenneberg et al 2012). Shift workers have been found to have increased risk of various health problems including cancer, diabetes, cardiovascular disease, and viral infection, for instance (Rees et al 2025).

called ‘gene-environment correlation’: your environmental exposure depends on your genetic makeup” (Landvreugd et al 2024 p271). For example, Burns et al (2023) found, from a study of over 280 000 individuals, that, put simply, “people with a genetic predisposition to seek out more daylight also tend to be morning people” (Landvreugd et al 2024 p271).

Genetic associations have been found between chronotype and aspects of physical and mental health. For example, morningness and a positive correlation with subjective well-being, a negative correlation with depressive symptoms, but no correlation with type 2 diabetes (Landvreugd et al 2024).

Landvreugd et al (2024) investigated the association between circadian rhythms and mental health further with data from the “Netherlands Twin Register” (n = 14 021 adults). Chronotype was measured by one question, “Are you a morning-active or evening-active person?”, answered from 1 to 5. Self-reports of well-being, depressive symptoms, and physical health were also taken. Individuals with a genetic predisposition to being a morning person had fewer depressive symptoms.

1.4.1. Chronopsychiatry

“Chronopsychiatry” is “the pathophysiological and clinical interface between circadian rhythms and mental illness. It draws on multiple disciplines, encompassing neuroscience, endocrinology, psychology, psychiatry and public health” (Smith et al 2024 p526).

Circadian rhythms, based on 24 hours, regulate many physiological and behavioural processes. “In modern society, there are now multiple environmental disruptors of circadian function, including dim daytime light, excess artificial light at night, night-time screen use (including social media), sedentary behaviour, noise pollution and irregular work patterns (shift-work and night-work). In essence, our ancient physiological mechanisms of sleep homeostasis are ill suited to modern living, and the resulting disruption can be particularly toxic for individuals with a vulnerability to mental illness” (Smith et al 2024 p526).

Seasonal variations in day length can also impact mental health (eg: individuals with depression experience more episodes in autumn and winter months when there are shorter daylight periods) (Smith et al 2024).

“The precise mechanisms that link circadian disruption and mental illness are not yet fully

understood. There is some evidence of shared genetic vulnerability between sleep/circadian phenotypes (such as evening chronotype) and conditions such as bipolar disorder and major depression, and genetic risk factors for schizophrenia may be associated with abnormalities of sleep structure. However, more work is needed in this area, not least because genetic studies have been limited by incomplete diagnostic and sleep/circadian phenotyping, small sample sizes and cross-sectional designs. In the area of clinical trials, factors such as timing of medication dose, season and latitude are typically not considered" (Smith et al 2024 p526).

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2. IMMUNOTHERAPY

Immunotherapy is a common treatment for allergic conditions. Put simply, small amounts of the allergen are introduced slowly to the sufferer (eg: grass pollen extract and hay fever). Sub-cutaneous immunotherapy (SCIT) (ie: injected under the skin) is the most established method (Jakymec et al 2024).

There are a variety of different administration routes, and dosing schedules (ie: build-up of the allergen over time). Patient adherence to treatment, particularly over a long period of time, is crucial, and Gehrt et al (2022) reported rates ranging from 23 to 89%.

An allergic reaction is the immune system "over-reacting" to the allergen as a major pathogen, and so immunotherapy builds up a tolerance of the allergen in order to stop the major reaction. This is the simple principle, whereas the immune processes are more complex (eg: the creation of allergen targeting anti-bodies that limit the response of immunoglobulin-E (IgE) activity) (Jakymec et al 2024).

SCIT has been studied for effectiveness/efficacy, for example, with house dust mite allergy (eg: over three years; Ren et al 2023), and allergic asthma (eg: meta-analysis; Dhami et al 2017). "Sub-cutaneous immunotherapy is administered in two stages: a build-up stage and a maintenance phase. In standard SCIT, the build-up phase occurs over 8–28 weeks with a starting dose ranging between a 1000-fold or 10 0000-fold dilution of the intended maintenance dose. The frequency of doses during this period typically occurs once to three times a week, with an increase in dose on each administration. The maintenance period is reached once the patient achieves a dose that provides symptomatic relief without adverse effects. Once a maintenance dose is achieved, it takes between 1 and 2 years for maximum clinical benefit to be realised" (Jakymec et al 2024 p522).

Alternatives to SCIT include sub-lingual (allergen as tablets or drops), intra-lymphatic (directly into a lymph node), and epicutaneous (on the surface of the skin) immunotherapy, as well as allergoids ("allergen extracts chemically modified to reduce their allergenicity profile while still promoting immune system modification"; Jakymec et al 2024 p524).

The safety of immunotherapy is a major concern. The speed of build-up is important here. For example, systemic reactions ("which are adverse reactions involving organ systems distant from the injection site and can range from mild to fatal"; Jakymec et al 2024

p524) seem to be higher for "rush schedules" (faster build-up) (eg: Cox 2006). But slower build-ups require greater time commitment by patients with the higher possibility of drop-out (Jakymec et al 2024).

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3. AUTOIMMUNE DISEASES

3.1. NUTRITIONAL SUPPLEMENTS

Autoimmune diseases are where the body attacks itself, in everyday language, or, more formally, "an inflammatory autoimmune response to self-tissues" (Hahn et al 2022 p1). Treating them is not easy.

One possibility is nutritional supplements, particularly vitamin D, and marine derived long chain omega 3 fatty acids. Supportive evidence comes from in vitro studies, and non-human animal experiments, but there are conflicting results from observational studies with humans (Hahn et al 2022).

Hahn et al (2022) reported a large scale study (VITAL - "Vitamin D and omega 3 Trial"). It was a randomised, double-blind, placebo trial with over 25 000 US adults. Participants were randomised to intervention (vitamin D or omega 3 supplements) or placebo (soybean oil for vitamin D or olive oil for omega 3 fatty acid). The main outcome was physician-assessed autoimmune disease incidence during follow-up (median of five years).

Overall, 123 participants in the vitamin D group had confirmed autoimmune disease compared to 155 in the vitamin D-placebo group, while 130 and 148 respectively in the omega 3 intervention and placebo groups respectively. The vitamin D group was statistically significantly different to their placebo, but not the omega 3 group.

Though the trial involved a large, diverse sample followed for a number of years, the participants were over fifty years of age (mean 67 years). "The US population is ageing and increased auto-anti-body and autoimmune disease prevalence is reported. Because participants were older adults, the results might not generalise to autoimmune diseases that primarily have their onset in younger people. However, the pathogenesis of many of the specific autoimmune diseases observed (eg: rheumatoid arthritis and psoriasis) is similar in younger adults" (Hahn et al 2022 p8).

Only one dose dose level and formulation of the

supplements was tested, and there were a small number of cases during the study period (0.02% of total sample).

The presence of an autoimmune disease was established in this way: "Participants who reported a new incident autoimmune disease were asked to sign a release for medical records. Two trained physicians (including a board certified rheumatologist, endocrinologist, and gastro-enterologist), blinded to treatment assignment, reviewed each record and confirmed or disconfirmed the autoimmune disease according to classification criteria when available" (Hahn et al 2022 p2). Sometimes, however, insufficient documentation was available.

3.2. ALOPECIA AREATA

"Alopecia areata (AA) is a chronic immune-mediated condition characterised by non-scarring hair loss, often presenting as small well-circumscribed patches on the scalp or other hair-bearing areas such as the beard, eyelashes, eyebrows and extremities. In severe cases, it can progress to complete loss of scalp hair (alopecia totalis) or total body hair loss (alopecia universalis)" (Christou et al 2025 p459). The lifetime prevalence is about 2% (Christou et al 2025).

Christou et al (2025) reported on the psychological impact of AA with data from the "Alopecia+Me: Disease Impact Study" in the UK in 2021-2024. Around six hundred patients volunteered to participate and completed online a number of questionnaires, including:

a) "Dermatology Life Quality Index" (DLQI) (Finlay and Khan 1994) - Ten items assessing the impact of dermatology diseases on the individual's quality of life (eg: "Over the last week, how embarrassed or self conscious have you been because of your skin?"; "Over the last week, has your skin prevented you from working or studying?").

b) "Hospital Anxiety and Depression Scale" (HADS) (Zigmond and Snaith 1983) - Fourteen items (eg: "I feel tense or 'wound up'"; "I get sudden feelings of panic").

c) "Stigma Scale for Chronic Illnesses 8-item" (SSCI-8) (Molina et al 2013) - Perceptions and actual experience of stigma related to illness (eg: "Because of my illness, some people feel uncomfortable with me"; "Because of my illness, people avoid looking at me").

d) "Brief Illness Perception Questionnaire" (BIPQ) (Broadbent et al 2006) - Nine items measuring cognitive and emotional perceptions (eg: "How much does illness affect your life?"; "How much control do you feel you have over your illness?").

Many respondents reported high levels of anxiety, depression, stigma, and poor quality of life, and these were linked to perception of illness severity rather than actual severity. Illness perception was influenced by feeling of lack of control over illness progression.

Two groups were distinguished - "coping" (53% of sample) and "distressed". The latter had significantly more negative scores on the measures. For example, the median DLQI score was 4 (out of 30) for the coping group compared to 12 (where a higher score indicates a more impaired quality of life), and 5 and 9 respectively (out of 21) for the HADS depression score (where 8 is used as a clinical cut-off; Christou et al 2025)).

3.3. MULTIPLE SCLEROSIS

Cognitive impairment is common in Multiple Sclerosis (MS), and it manifests as impacting information processing speed, working memory, sustained attention, and executive functioning, for instance (Lerede et al 2025). But the knowledge about MS-related cognitive impairment is poor. "This is partly due to the limitations of standard neuropsychological assessments, which are typically conducted in person, require a trained examiner, and are either lengthy or, in the case of shorter assessments, lack comprehensiveness. As a result, large-scale and longitudinal evaluations remain impractical, and systematic data on MS-related cognitive impairment are scarce—hindering progress in understanding its mechanisms, impact, underlying aetiology, associations with disease-related factors, and the efficacy of available treatments on cognition" (Lerede et al 2025 p1). Online cognitive tests are a possibility here.

Lerede et al (2025) reported the development of an online cognitive assessment battery of tests tailored to MS with the "UK MS Register" (UKMSR). Over 19 000 individuals were invited to participate, and over 4500 UK people with MS volunteered. A 12-task battery was validated, but also a MS sub-type was identified. This group showed "significant cognitive deficits with minimal motor impairment. Disability in this group is currently

unrecognised and untreated" (Lerede et al 2025 p1).

3.4. NEURO-IMMUNE INTERACTIONS

The term "neuro-immune interactions" describes "the mechanisms that mediate cross-talk between the nervous and immune systems", or, more formally, "a specialised case of cell–cell communication involving a cell of the nervous system and an immune cell, which could be either tissue-resident or recruited from circulation. This communication should modify the activity of at least one of the cells involved" (Wheeler and Quintana 2025 p333).

This is a relatively new concept as "early studies [in mid-20th century onwards] suggested that immune activity was limited in the CNS [central nervous system], and that the nervous and immune systems operated independently. These ideas have since been abandoned, and we now know that neuro-immune interactions involving classic immune pathways and neural circuits participate in development and homeostasis, and when dysregulated, drive tissue pathology" (Wheeler and Quintana 2025 p333).

The aim of growing research today is "a detailed map of all the interactions between cells of the nervous and immune systems throughout the body" (Wheeler and Quintana 2025 p333) (the "neuro-immune connectome").

Environmental chemical exposure, and the microbiota have been shown to interact with the immune and nervous systems. For example, with the latter, rodents on a high-salt diet have changes in intestinal cells which lead to cognitive deficits (Faraco et al 2018). The impact of the environment on sleep is a potential mechanism for changes to the immune and nervous systems (Wheeler and Quintana 2025).

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4. MISCELLANEOUS

4.1. HIV

There are rare cases of individuals infected with human immuno-deficiency virus (HIV) who can suppress the virus without medication. There is interest in establishing how such individuals achieve the suppression.

Blazkova et al (2021) reported two individuals (known as "Participant 04" and "Participant 30") found during a vaccine trial in the USA. These two individuals had been receiving anti-retroviral therapy (ART) for some time (6-7 years), but stopped during the vaccine trial. However, there was no HIV rebound as usually seen in individuals who stop ART.

Reference

Blazkova, J et al (2021) Distinct mechanisms of long-term virologic control in two HIV-infected individuals after treatment interruption of anti-retroviral therapy Nature Medicine 27, 1893-1898

4.2. PHAGES

Analyses of toothbrushes and showerheads have found viruses that infect bacteria (known as bacteriophages or phages). Huttelmaier et al (2024) found over 600 such viruses in swabs from ninety-two showerheads and 36 toothbrushes from volunteers in Illinois in the USA. Bacteriophages are "absolutely expected" to be on moist surfaces around the home (Erica Hartmann of Huttelmaier et al in Wong 2024). Note that bacteriophages are not harmful to humans.

Bacteriophages "might hi-jack the molecular machinery of a bacterium to make copies of itself, and then kill the bacterium as it exits. Or it can integrate into the bacterial genome and change how bacteria behave" (Wong 2024 p13).

4.2.1. Food

Phages could be used to destroy bacteria harmful to humans in food (eg: salmonella; listeriosis). But the problem is that "each phage targets only one specific bacterial strain, so a mixture of phages is required to kill all the strains that might be present. This means a cocktail that proves potent in the U.S., say, might not work in other countries. And because bacteria are always evolving, the effectiveness of each phage needs to be constantly monitored and the mixture tweaked as necessary" (Le Page 2022 p14).

Obtaining regulatory approval is thus not straightforward for phage producers. For example, the company "Intralytix" took four years to get U.S. approval for "ListShield" in the early 21st century (Le Page 2022).

Furthermore, "food processors are somewhat reluctant to apply viruses on their food" (Alexander Sulakvelidze of "Instalytix" in Le Page 2022).

Phages that target bacteria that cause food to rot is another possibility, and this would extend the shelf life of fresh produce, and reduce food waste (Le Page 2022).

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Wong, C (2024) Toothbrushes are teeming with hundreds of viruses New Scientist 19th October, p13

4.3. NOROVIRUS VACCINE

Norovirus is highly contagious, causing sickness and diarrhoea. "Most people recover in days, but it can be more serious for very young and older people" (Wong 2025 p18). A small trial (Flitter et al 2025) of a vaccine using a protein from the GI.1 norovirus variant has shown potential with older adults (>55 years old) (Wong 2025).

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4.4. ANTI-BIOTIC RESISTANCE

The more sparing use of anti-biotics has become important in recent years with the emergence of treatment-resistant microbes (eg: methicillin-resistant Staphylococcus aureus; MRSA). There is evidence that short courses of anti-biotics for days can be as effective if not more so than courses lasting weeks (eg: 3-5 vs 5-14 days for community-acquired pneumonia) (Wallis 2021).

But both many patients and physicians hold beliefs that longer courses are better (Wallis 2021).

Note that weeks of anti-biotics are appropriate in certain situations (eg: infections around prosthetic joints) (Wallis 2021).

Reference

Wallis, C (2021) With anti-biotics, less is often more Scientific American August, p24