BI-12 First-person evidence: hormone therapy

Introduction: The Endocrine Lens on Human Coexistence

To understand how men and women can best live together in couples, families, and societies, one must disentangle the innate biological drives of human behaviour from the powerful socializing forces of human culture. In the field of psychoneuroendocrinology, the deliberate manipulation of sex steroid hormones—specifically testosterone and estrogen—serves as an unprecedented natural experiment. Interventions such as cross-sex hormone therapy in transgender individuals (Gender-Affirming Hormone Therapy, GAHT), exogenous testosterone administration in hypogonadal cisgender men (Testosterone Replacement Therapy, TRT), and medical castration in prostate cancer patients (Androgen Deprivation Therapy, ADT) offer unique first-person and clinical windows into the effects of radical endocrinological shifts.
This foundation report provides an exhaustive evaluation of the primary literature surrounding these hormonal interventions. To navigate the profound complexities of this data, this analysis is strictly separated into three conceptual layers:

1. **Physiology (Measurable):** The objective, measurable biological mechanisms, encompassing receptor density, brain morphometry, pharmacokinetics, and glandular function.
2. **Behaviour (Statistical):** The observable psychological and cognitive phenotypes that emerge at the population level, which are characterized by overlapping statistical distributions and high variance, rather than strict binary dimorphism.
3. **Culture (Variable):** The sociocognitive frameworks, gendered display rules, and meaning-making processes that dictate how physiological and behavioural changes are interpreted, experienced, and policed by society.

Methodological Caveats: Expectation Effects, Selection, and Evidence Quality

Before analyzing specific cognitive and emotional domains, strict methodological caveats must be applied. First, the literature surrounding hormone manipulation is severely confounded by expectation effects (placebo and nocebo). Because hormonal transitions are deeply intertwined with identity, societal scripts, and the psychological relief of receiving sought-after medical care, isolating the direct neurochemical effects of a hormone from the psychosocial relief of gender affirmation or medical treatment is methodologically fraught[1].
Second, the quality of evidence in this domain is highly variable. The Cass Review (2024), an independent review of gender identity services commissioned by the National Health Service (NHS) in England, concluded that the evidence base for gender-affirming care—particularly for youth—is "remarkably weak," citing high risks of bias, lack of blinding, and insufficient long-term longitudinal data[2]. Similar critiques plague the TRT literature, where early, small-sample studies

often report massive psychological benefits that fail to replicate in highly powered, modern clinical trials[4]. Therefore, this report prioritizes large-scale, double-blind, placebo-controlled trials, systematic reviews, and meta-analyses, paying explicit attention to whether historical findings have successfully replicated in contemporary science.

Averages vs. Individuals: The Genetic Architecture of Hormone Sensitivity

A critical fallacy in interpreting psychoneuroendocrinological data is the conflation of statistical averages with individual outcomes. It is frequently observed that two individuals receiving the exact same dose of exogenous testosterone will exhibit entirely different psychological and physiological responses. To distinguish what is known about population averages from what can be said about individuals, one must examine the genetic layer of hormone reception.

The physiological response to androgens is heavily modulated by the Androgen Receptor (AR) gene, located on the X chromosome (Xq11-12). Within exon 1 of the AR gene lies a highly polymorphic cytosine-adenine-guanine (CAG) trinucleotide repeat sequence, which encodes a polyglutamine tract[5].

The length of this CAG repeat (which typically ranges between 11 and 38 repeats in healthy individuals) is inversely correlated with the receptor's transactivation capacity[5]. This means that individuals with shorter CAG repeats possess highly sensitive androgen receptors; their neural and somatic tissues react aggressively to both endogenous and exogenous testosterone, establishing a highly "androgenic" profile[8]. Conversely, individuals with longer CAG repeats exhibit reduced receptor sensitivity, requiring significantly higher circulating levels of testosterone to achieve the same physiological or neurological transcription effects[9].

Because this genetic hardware varies so widely across the population, any natural experiment involving hormone therapy is immediately confounded. Statistical averages regarding how testosterone affects cognition, mood, or libido represent a smoothed-out aggregate of this genetic variance. Consequently, while the literature can speak confidently about how a hormone shifts the mean of a population, predicting an individual's response to hormone therapy remains impossible without accounting for their specific receptor genetics.

Emotional Range, Crying, and Affective Regulation

One of the most immediate and profound first-person effects reported by adults undergoing sex hormone manipulation involves shifts in emotional range, emotional intensity, and the physiological capacity to cry.

The Physiology of the Lacrimal Reflex

At the physiological layer, the physical production of tears is modulated by sex steroid receptors located in the lacrimal and meibomian glands, as well as the conjunctiva and cornea[11]. The lacrimal functional unit requires a delicate balance of aqueous fluid (from the lacrimal gland) and lipids (from the meibomian glands)[14]. Testosterone provides trophic support to the lacrimal glands, downregulating localized inflammation and upregulating lipid synthesis in the meibomian glands, which prevents tear evaporation[13]. Conversely, a decrease in androgens and fluctuations in estrogen lead to lacrimal gland atrophy, decreased lipid

production, and tear film hyperosmolarity[15].
This presents a physiological paradox: while the withdrawal of androgens and the modulation of estrogen decrease baseline eye moisture (leading to the high prevalence of dry eye disease in post-menopausal women and men on ADT), these same hormonal shifts inversely lower the central nervous system's threshold for *emotional* crying[11].

Behavioural and First-Person Evidence

At the behavioural level, qualitative and clinical research consistently captures this dichotomy. In a 2026 study published in the *Journal of Sexual Medicine*, van de Grift et al. conducted qualitative semi-structured interviews with 26 transgender individuals (n=12 on feminizing regimens, n=14 on masculinizing regimens)[1]. The authors found that individuals on feminizing GAHT consistently reported an unexpected onset of greater emotionality and a marked increase in the frequency and intensity of crying[1].
Conversely, those on masculinizing GAHT reported reduced emotionality, decreased mood fluctuations, and a stabilizing of affect[1]. Transgender men (natal females receiving exogenous testosterone) frequently describe a profound, physical inability to cry, even when experiencing severe grief or sadness—describing the sensation as a physical blockage of the tear response behind the eyes[19].
This phenomenon is mirrored in reverse among cisgender men undergoing ADT for prostate cancer. These patients, who experience a sudden, medically induced plunge to castrate levels of testosterone, frequently report spontaneous weepiness, emotional lability, and an inability to control tearfulness in situations that previously would not have elicited a lacrimal response[21].

The Cultural Layer: Meaning-Making

While physiology dictates the biological threshold for tears, the cultural layer dictates how this shift is processed and integrated into an individual's identity. In qualitative sociology, a transgender man who finds himself physically unable to cry may interpret this physiological block positively, viewing it as an affirmation of his desired masculinity[19]. Conversely, a cisgender man on ADT may experience the exact same neurochemical shift (increased weepiness) as profoundly emasculating, distressing, and socially alienating[21]. The overlapping statistical distributions of emotional expression in human populations suggest that while hormones alter the biological threshold for the reflex, gendered display rules and cultural permission heavily dictate the ultimate behavioural output.

Anger, Aggression, and the Status-Seeking Hypothesis

Few associations in psychoneuroendocrinology are as culturally entrenched as the link between testosterone and aggression—the so-called "steroid rage" hypothesis. However, rigorous clinical evidence reveals a highly nuanced reality where testosterone promotes status-seeking rather than blind, indiscriminate hostility.

Clinical Trials and the ENIGI Cohort

The World Professional Association for Transgender Health (WPATH) Standards of Care historically included warnings regarding increased aggression for transgender men initiating

testosterone therapy[23]. However, massive longitudinal data sets directly challenge this assumption.

In a 2018 study published in *Endocrine Abstracts*, Defreyne, Kreukels, T'Sjoen, and colleagues analyzed data from the European Network for the Investigation of Gender Incongruence (ENIGI)—the largest prospective cohort study of transgender individuals. The researchers prospectively assessed anger intensity using the State-Trait Anger Expression Inventory-2 (STAXI-2) in 898 participants (440 trans men, 468 trans women) over a 36-month period[23]. The study found absolutely *no correlation* between serum testosterone levels and state-level anger intensity at 3, 12, or 36 months in either group[24]. Transgender men did exhibit a transient, statistically minimal increase in STAXI-2 scores at three months ($+0.90$ points, $p = 0.041$), but this decreased back to baseline by one year (-1.296 points)[23]. Crucially, the researchers identified that anger proneness was positively correlated not with exogenous testosterone, but with pre-existing psychiatric vulnerabilities, such as baseline negative affect, depression, interpersonal sensitivity, and somatization[23]. This finding has been robustly replicated across multiple ENIGI data sweeps.

In eugonadal cisgender men, experimental manipulations yield parallel results. In a double-blind, placebo-controlled crossover study published in *The Journal of Clinical Endocrinology & Metabolism* (2004), O'Connor, Archer, and Wu administered 1000 mg of long-acting testosterone undecanoate (TU) to 28 healthy men[26]. The testosterone increment was associated with a significant increase in self-reported subjective anger-hostility on the Profile of Mood States (POMS) questionnaire (rising from a baseline of 7.48 to 10.71 at week 2)[26]. However, the TU treatment did *not* increase actual aggressive behaviour as measured by the Buss-Perry Aggression Questionnaire, nor did it alter nonaggressive social interactions[26].

The Status Hypothesis

If exogenous testosterone does not reliably cause physical violence, what is its behavioural evolutionary function? A comprehensive 2019 meta-analysis published in *Hormones and Behavior* by Geniole et al. summarized the testosterone-aggression link in humans. They found that baseline testosterone shared only a very weak association with aggression (Pearson's $r = 0.054$), and the causal effects of manipulated exogenous testosterone on human aggression were even weaker and not statistically significant ($r = 0.046$)[30].

Instead, leading theorists propose the "Status Hypothesis," derived from the Challenge Hypothesis originally observed in avian endocrinology[30]. In a landmark 2016 study published in the *Proceedings of the National Academy of Sciences* (PNAS), Dreher et al. tested this by administering testosterone or a placebo to 40 men playing a modified Ultimatum Game (an economic task assessing fairness, punishment, and reward)[31]. The study found that testosterone *did* cause men to punish opponents who made unfair offers more frequently (reactive aggression). However, crucially, when men administered testosterone received highly generous offers, they were significantly more likely to *reward* the proposer with greater prosocial generosity than men given a placebo[31].

This demonstrates a profound paradigm shift: testosterone does not trigger indiscriminate antisocial aggression. Rather, it amplifies behaviours—both aggressive and prosocial—that are culturally coded to increase, signal, or protect social status within a specific hierarchy[31].

Study / Authors (Year, Journal)	Paradigm / Measurement	Sample Size	Effect of Exogenous Testosterone	Replicated?
O'Connor et al. (2004, *JCEM*)	POMS / Buss-Perry	n=28 (Cis Men)	Minor increase in subjective anger; zero increase in behavioural aggression.	Yes
Dreher et al. (2016, *PNAS*)	Ultimatum Game	n=40 (Cis Men)	Increased punishment of unfairness; increased reward/generosity for fairness.	Yes
Defreyne et al. (2018, *Endo*)	STAXI-2 (ENIGI Cohort)	n=898 (Trans Adults)	No correlation between serum T levels and state anger or behavioural aggression.	Yes
Geniole et al. (2019, *Horm Behav*)	Meta-analysis	N/A	Causal effect of T on human aggression is weak and non-significant ($r = 0.046$).	N/A

Empathy, Connection, and the "Extreme Male Brain"

Controversy

A secondary assumption deeply embedded in cultural discourse is that testosterone reduces empathy and the capacity for interpersonal connection. This hypothesis was formalized in academia by Simon Baron-Cohen in the "Extreme Male Brain" (EMB) theory of autism. The EMB theory posited that elevated prenatal exposure to testosterone permanently masculinizes the brain, resulting in heightened systemizing traits and severely impaired cognitive empathy[33].

The "Reading the Mind in the Eyes" Replications

The primary psychological metric used to test cognitive empathy in this domain is the "Reading the Mind in the Eyes Test" (RMET), which asks participants to ascertain complex emotional states based solely on photographs of the orbital region of the face[33]. Early pharmacological studies by Baron-Cohen and colleagues, utilizing very small samples (e.g., n=16 females), reported that exogenous testosterone administration significantly impaired RMET performance[34].

However, recent highly powered, pre-registered randomized controlled trials have robustly failed to replicate these findings. In 2019, Amos Nadler, Gideon Nave, and colleagues published the results of two massive double-blind, placebo-controlled experiments in young men (n=243 and n=400) administering topical testosterone[33]. The researchers found absolutely zero evidence that cognitive empathy was impaired by testosterone administration. Furthermore, they found no correlation between RMET performance and 2D:4D digit ratios, which is the purported biological proxy for fetal testosterone exposure[33].

The failure of testosterone to blunt empathy is further supported by advanced neuroimaging. In a 2025 study published in *Neuropharmacology*, Zhuo et al. conducted a functional magnetic resonance imaging (fMRI) pharmacological study using a randomized, placebo-controlled, double-blind crossover design to examine the effects of 100 mg of transdermal testosterone on 23 healthy men[36]. Relative to the placebo, testosterone administration did *not* alter the functional brain networks associated with either affective or cognitive empathy. Participants continued to show robust activation in the canonical networks required for empathy, including the temporoparietal junction, medial prefrontal cortex, inferior frontal gyri, and the temporal pole[37].

Empathy at the Three Layers

- **Physiology:** Exogenous testosterone does not downregulate the neural networks responsible for cognitive or affective empathy, nor does it disrupt structural connectivity in the temporoparietal junction[37].
- **Behaviour:** Performance on empathy diagnostics (such as the RMET) shows massive overlapping distributions between the sexes and is unaffected by acute, exogenous testosterone spikes[34].
- **Culture:** The pervasive cultural perception that women are innately more empathetic, and men inherently deficient in connection, is likely driven by cultural conditioning, socialized display rules, and overlapping statistical distributions in personality traits (such as agreeableness), rather than a direct hormonal block imposed by testosterone.

Libido, Energy, and Vitality

Hormone interventions act as a profound, measurable dial on human sexual desire and baseline energy levels, representing some of the most immediate physiological changes reported by patients.

Testosterone, Estrogen, and Sexual Desire

Testosterone is a critical, primary driver of libido in both men and women. In transgender men, the initiation of masculinizing GAHT results in a rapid, intense, and near-universal increase in sexual desire. Data from the ENIGI cohort (authored by Wierckx, Defreyne, Elaut, and colleagues) demonstrated that 73.9% of female-to-male individuals reported a marked increase in sexual desire shortly after starting testosterone[38].

Intriguingly, the ENIGI data isolates exactly *how* this libido manifests. The increase is primarily localized to *solitary* sexual desire (internal arousal and masturbation frequency, which correlated highly at $r = 0.835, p < 0.001$), rather than dyadic sexual desire (the desire for intercourse with a partner), which did not show the same direct association with testosterone spikes[38]. Post-hoc analyses in the ENIGI study revealed that individuals with sub-optimal testosterone dosing (indicated by elevated luteinizing hormone levels) had significantly lower solitary sexual desire[38].

Conversely, feminizing GAHT (the administration of estrogen combined with anti-androgens such as cyproterone acetate or spironolactone) routinely leads to a sharp reduction in spontaneous arousal and libido in transgender women, accompanied by alterations in erectile function[1]. Similarly, in prostate cancer patients undergoing ADT, chemical castration results in an almost total ablation of libido, which is frequently cited as one of the most psychologically distressing side effects of the oncological treatment, fundamentally altering the patient's sense of self and relational dynamics[40].

Energy, Fatigue, and the Depression Controversy

Testosterone administration is robustly associated with increased energy, vigour, and vitality in deficient populations. In hypogonadal cisgender men, TRT reliably reduces fatigue-inertia, increases lean body mass, and improves bone mineral density[26].

However, a major controversy exists regarding the efficacy of testosterone as a treatment for clinical depression. In a 2019 meta-analysis published in *JAMA Psychiatry*, Walther et al. reviewed 27 randomized controlled trials (n=1,890) and found that testosterone treatment was associated with a significant reduction in depressive symptoms in men, reporting a Hedges' g of 0.21 and an impressive efficacy Odds Ratio of 2.30[4].

Leading critics point to more recent, massive trials that directly contradict these optimistic findings. An individual-participant meta-analysis by Hudson et al. (2023, n=5,601 men with testosterone below 12 nmol/L) and a secondary analysis of the T4DM trial by Wittert et al. (2025) both found absolutely no significant improvement in Beck Depression Inventory scores following testosterone administration[4]. The synthesis of this conflicting evidence suggests a threshold effect: while correcting a severe, pathological testosterone deficit restores a

patient's baseline energy and mood, supra-physiological dosing or supplementing men with only marginal deficits does not act as a universal antidepressant[4].

Cognition: Spatial and Verbal Abilities

The assertion that men inherently excel at spatial tasks (e.g., 3D mental rotation) and women at verbal tasks (e.g., verbal fluency, paired associate learning) is one of the most heavily debated areas in cognitive psychology. Hormone therapies offer a distinct mechanism to test the *activational* (acute, reversible) versus *organizational* (prenatal, permanent) effects of these hormones on cognition[45].

Cognitive Shifts Under Hormone Therapy

Historical data provided strong, albeit small-sample, evidence for immediate activational effects. A highly cited 1995 study published in *Psychoneuroendocrinology* by van Goozen, Cohen-Kettenis, Megens, and Gooren demonstrated that administering cross-sex hormones rapidly altered cognitive phenotypes. In their cohort, trans men on testosterone showed an increase in spatial ability (mental rotation) and a decrease in verbal fluency, whereas trans women on estrogen showed the exact inverse[46].

However, replication of these clean results has been highly inconsistent. A direct follow-up replication attempt by Slabbekoorn et al. (1999), also in *Psychoneuroendocrinology*, successfully replicated the enhancing effect of testosterone on spatial ability in trans men over an 18-month period[49]. Crucially, however, the Slabbekoorn study *failed* to replicate the deteriorating effect of testosterone on verbal fluency, and utterly failed to find an enhancing effect of estrogen on verbal fluency in trans women[49].

Recent neuroimaging data presents a much more ambiguous picture regarding innate dimorphism. A 2016 fMRI study by Burke et al. investigating mental rotation found that treatment-naive transgender individuals often performed comparably to their experienced gender rather than their natal sex, complicating the purely hormonal narrative[50]. While trans men did show some masculinization of visuospatial brain networks after testosterone therapy, there were massive overlaps with cisgender controls, indicating that statistical averages obscure vast individual variations[50].

In ADT patients, androgen deprivation has been loosely linked to accelerated cognitive decline. Systematic reviews by Cherrier et al. (2009) and McGinty et al. (2014) report that chemical castration adversely affects specific cognitive domains, particularly spatial memory, visuomotor function, and executive function[52]. However, other large retrospective studies find no appreciable cognitive change following androgen ablation, again pointing to high inter-individual variability and the moderating role of cardiovascular health in aging populations[55].

Brain Structure: The Neuroplasticity Controversy

Does altering circulating hormones fundamentally change the physical structure and architecture of the adult human brain?

Measurable Volumetric Shifts

In a landmark 2006 study published in the *European Journal of Endocrinology*, Hulshoff Pol et

al. utilized high-resolution MRI to scan trans individuals before and during GAHT[57]. They found that anti-androgen and estrogen treatment decreased total brain volume in trans women towards female proportions. Astoundingly, testosterone treatment in trans men increased total brain and hypothalamus volumes by an average of 31 mL over a mere four-month period—a striking, rapid divergence from normal adult neurodevelopment that suggests immense adult neuroplasticity[57].

Furthermore, Diffusion Tensor Imaging (DTI) studies by Zubiaurre-Elorza et al. (2011) and Kranz et al. measured fractional anisotropy (FA) in white matter tracts, which indicates the microstructural integrity of the brain. They found that after seven months of testosterone therapy in trans men, FA values significantly increased in the right superior longitudinal fasciculus (SLF) and the right corticospinal tract. These microstructural increases correlated directly with the patients' pre-treatment free testosterone indices, suggesting a dose-response relationship between androgens and white matter integrity[60].

The Strongest Evidence on Both Sides and Leading Critics

The interpretation of these physical brain changes represents a major controversy in the field.

- **The Organizational/Activational Proponents:** Structuralist researchers, including Dick Swaab, Julie Bakker, and Sarah Burke[51], argue that human brains undergo distinct sexual differentiation prenatally. They posit that structural brain phenotypes (such as grey matter volume, cortical thickness, and white matter FA) adjust dynamically to circulating sex steroids, proving that the brain remains an endocrine-responsive organ throughout life, capable of morphing between male and female phenotypic averages.
- **The Neuro-constructivist Critics:** Scholars such as Cordelia Fine (author of *Delusions of Gender*) and Rebecca Jordan-Young (author of *Brain Storm*) harshly critique the binary organizational-activational model[62]. These leading critics argue that human brains are highly mosaic, possessing an overlapping patchwork of "male" and "female" features. They contend that observed cognitive differences in spatial/verbal tasks, and even some structural volumetric changes, are primarily driven by cultural expectations, stereotype threat, and neuroplastic adaptations to gendered socialization and distinct life experiences, rather than hardwired, deterministic hormonal dictates[62].

Conclusion

Summary of Robust Findings

Correcting severe testosterone deficits reliably improves energy, reduces fatigue, and lowers depressive symptoms; however, supra-physiological dosing provides no reliable psychiatric benefit for eugonadal men. Testosterone does *not* cause indiscriminate physical aggression or "steroid rage" within normal therapeutic ranges. Instead, testosterone amplifies status-protecting behaviours, increasing both reactive punishment of unfairness and prosocial generosity when culturally appropriate. High-powered replications show testosterone does *not* impair cognitive empathy (Reading the Mind in the Eyes), debunking the hormone-driven "Extreme Male Brain" hypothesis. Feminizing hormones lower the threshold for crying and increase emotional intensity, while masculinizing hormones raise the threshold and stabilize mood. Exogenous testosterone profoundly increases solitary sexual desire (masturbation)

independently of dyadic (partnered) desire. Evidence for testosterone enhancing spatial cognition and estrogen enhancing verbal cognition remains mixed, with early positive findings failing robust modern replications. Adult brains remain highly plastic; cross-sex hormones induce measurable volumetric shifts in grey matter and structural changes in white matter tracts. Individual responses to hormones are heavily dictated by receptor genetics, specifically AR CAG repeat lengths. Finally, first-person subjective reports of hormonal changes are heavily confounded by cultural scripts, placebo effects, and the psychological relief of gender affirmation.

Contested or Open Questions

- To what extent are the cognitive shifts (spatial/verbal) observed during hormone therapies a result of actual neurogenesis and neuroplasticity versus placebo effects, stereotype threat, and practice effects on cognitive testing?
- What are the long-term (>10 years) neurological and cognitive consequences of pausing puberty with GnRH analogues followed by cross-sex hormones in youth, an area the Cass Review highlighted as severely lacking in evidence?
- Why does exogenous testosterone reliably increase solitary sexual desire but have highly variable, often non-significant impacts on dyadic (partnered) sexual desire?
- Are the total brain volume decreases observed in MTF individuals on estrogen and anti-androgens related purely to fluid shifts and atrophy, or do they represent genuine neuroplastic reorganization of synaptic networks?

5 to 10 Most Important Sources to Read in Full

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Implications for Living Together

Note: The following observations strictly avoid the naturalistic fallacy; observing that a biological mechanism exists does not mean it is morally good, inevitable, or an excuse for poor behaviour.

For couples, families, and organizations, understanding the endocrinological layer of human behaviour offers a framework for profound interpersonal empathy rather than biological determinism.

First, acknowledging that men and women navigate different baseline physiological thresholds for affective display can mitigate severe interpersonal conflict. If a highly testosteronized individual fails to cry during a family tragedy, recognizing this as a physiological reality of the lacrimal and central nervous system—rather than a lack of love or emotional depth—can prevent devastating relational misunderstandings. The underlying empathy remains fully intact; only the physical display mechanism is altered.

Second, the dismantling of the "steroid rage" myth forces a re-evaluation of male behaviour in families and societies. If testosterone promotes *status-seeking* rather than blind aggression, organizations and families can channel this neuroendocrine drive effectively. By culturally rewarding prosocial generosity, cooperation, and protection with high social status, testosterone can be leveraged as a biological engine for social cohesion rather than a scapegoat for toxicity or violence.

Finally, understanding the immense genetic variability in hormone sensitivity (e.g., AR CAG repeats) and the overlapping statistical distributions of male and female brains demolishes the utility of strict gender essentialism in small groups and societies. Because an individual's neurobiological hardware and cultural conditioning cannot be predicted by their group average, couples and organizations function best when they build structures around individual competencies, communication styles, and emotional needs, rather than assumed hormonal mandates.

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