Guest Editorial

Negative Evidence: COVID-19 Vaccine and the Endocrine System

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"What is essential is invisible to the eye."

The Little Prince, Antoine de Saint-Exupéry

Introduction

The COVID-19 pandemic is frequently described as a singular event in modern history. That unexpected global novel viral outbreak and associated unprecedented policies have left many dark marks. Unlike previous pandemics, COVID-19 was characterized by an unparalleled authoritarian overreach that has caused more damage than the plague itself.[1] The heavy-handed measures, allegedly introduced to protect the public, disrupted daily life, brought economic ruin, and increased the pre-existing political polarization.

The COVID-19 Global Health Emergency gave birth to many cultural, social, and ideological paradoxes. The incredibly rapid scientific advancements were associated with a swift decrease in the credibility of traditional scientific experts. The informational overload facilitated by amazing digital technologies has ushered in the era of confusion and division. It became increasingly difficult to determine the truth regarding the prevention, treatment, and origin of COVID-19.[1-4] The objective facts have been overshadowed by the conflicting partisan narratives.[5-7] The Right Wing has accused the Left of being biased by their "Woke Ideology."[8] In turn the Left Wing claimed that the Right's perception of COVID-19 is skewed by "Right Wing Folklore."[9] The term "misinformation" has lost its original meaning, since it has been used to denote not just obvious lies but anything contradicting the Left-Wing narrative.[10,11]

Over the past several years, the goal of this series of guest editorials has been to search for the objective facts related to COVID-19 pandemic that are not tainted by partisan narratives and agenda-driven interpretations in order to reveal what is truly known and truly unknown, and to determine why this is so. Analysis of the "negative evidence"—the conspicuous absence of reasonably anticipated information—may signal that essential details have been intentionally concealed to mask misconduct. Prior editorials have discussed the origin and treatment of COVID-19 and vaccine safety,[1-4,10,12-19] focusing on the most noticeable and hence commonly discussed adverse events attributed to the COVID-19 vaccine.[10,12-17] In contrast, this paper will review the cluster of potential side effects of COVID-19 mRNA vaccine that are stealthy and inconspicuous and yet extremely dangerous—the classic endocrine disorders. Unlike the previously considered[14] reproductive endocrine disorders, they develop slowly and present with nonspecific and mild symptoms. When overlooked, those initially "silent" endocrine diseases can seriously maim and kill.

Endocrine Adverse Effects: an Example of Hidden Harms

The deceptively subtle manifestations of endocrine adverse reactions to vaccine underscore the crucial role of active search for hidden complications of any new modalities. Without robust preemptive vigilance, the stealthy endocrine complications of mRNA-based vaccination will remain hidden and deadly, while affected vaccine recipients remain unaware about the real cause of their "unexplained health problems."

Therefore, any sensible person should ask: Is there a possibility that significant endocrine side effects of COVID-19 vaccinations are being potentially overlooked not only by the biased authorities but also by the vaccine-skeptical general population, and if so, why?

The response to the first part of this question is easy. As discussed below, such a possibility cannot be excluded because the adverse effects vigilance is not sufficiently robust. The second part of the question cannot be answered as confidently without engaging in speculation. Yet, there are at least two obvious reasons for which such "unexpected oversight" (i.e., "negative evidence") would occur. The surveillance apparatus is not fine-tuned for the detection of elusive side effects such as endocrine disorders. Moreover, the very nature of endocrine diseases and of endocrinology practice makes such conditions difficult to detect.

Examining the Robustness of Adverse Events Surveillance

Many proponents of vaccination point out that as of Mar 20, 2023, more than 13 billion COVID-19 vaccine doses had been administered worldwide, with the United States accounting for almost 672 million of this total.[20] They argue that with such huge numbers of vaccination events, a clear signal for significant endocrinological complications should be detected by current large-scale vaccine safety surveillance. However, nothing of this sort has occurred.

This explanation sounds plausible until one realizes that one will not find anything if one is not searching for it diligently enough. However, one would assume thar the unprecedented scale of the COVID-19 vaccination program should necessitate a similarly unprecedented effort in safety monitoring. Shockingly, as explained below, this does not appear to be the case.

Approaches to Surveillance for Adverse Events

The approaches to the surveillance for adverse events of vaccines can be divided into two main categories: adverse events of special interest (AESIs) and organ systems-based surveys (see Figure 1). Both approaches rely on a variety of passive and active vaccine safety monitoring systems. An overview of the major types is provided in Table 1.

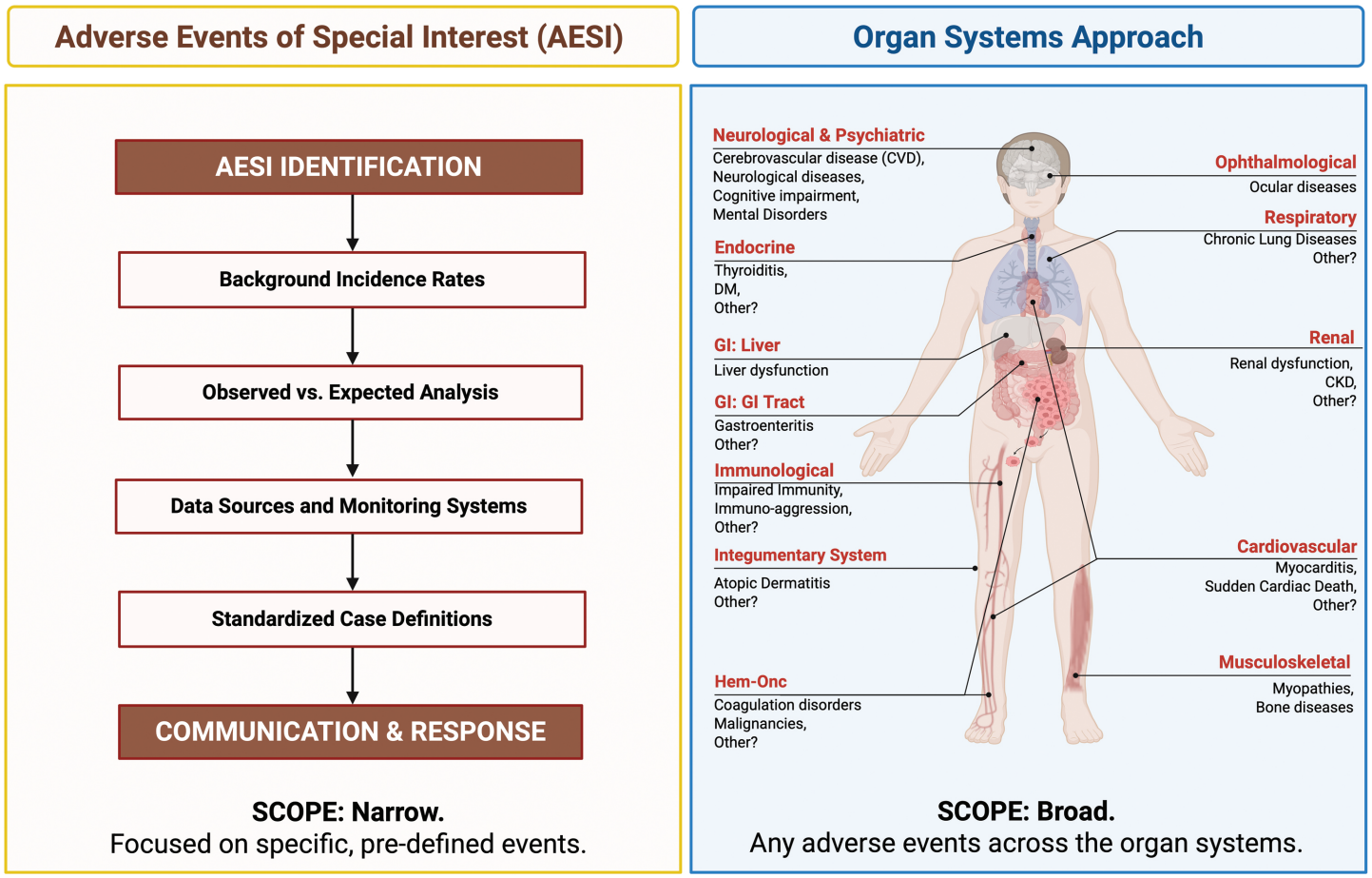

Figure 1. Approaches to surveillance for adverse events of vaccines

Adverse Events of Special Interest (AESI) Model

The principles of surveillance for vaccine adverse effects using the adverse events of special interest (AESI) method involve several key components (see Figure 1):

1. **Identification of AESI:** AESIs are pre-specified medical conditions that are of particular concern due to their potential association with vaccination. These conditions are selected based on their severity, biological plausibility, and previous evidence of association with vaccines. For example, Guillain-Barré syndrome, myocarditis, and thrombosis with thrombocytopenia syndrome have been identified as AESIs for COVID-19 vaccines.[29]
2. **Background Incidence Rates:** Establishing background incidence rates of AESIs is crucial for contextualizing observed events post-vaccination. This involves calculating the expected rates of these conditions in the general population without vaccination, stratified by age, sex, and other relevant factors.[30]
3. **Observed vs. Expected Analysis:** Surveillance systems compare the observed rates of AESIs following vaccination to the expected background rates. This observed-to-expected (OE) ratio helps identify potential safety signals. An OE ratio with a lower bound of the 95% confidence interval greater than 1.5 is often considered a signal warranting further investigation.[29]
4. **Data Sources and Monitoring Systems:** Multiple data sources are utilized for AESI surveillance, including spontaneous reporting systems like VAERS, active surveillance systems like the Vaccine Safety Datalink (VSD), and international collaborations such as the Global Vaccine Data Network (GVDN). These systems enable rapid detection and evaluation of potential safety signals.[31]
5. **Standardized Case Definitions:** Using standardized case definitions for AESIs ensures consistency and comparability across different studies and surveillance systems. This standardization is essential for accurate signal detection and risk assessment.[32]
6. **Communication and Response:** Effective communication strategies are necessary to inform medical personnel and the public about potential risks and the overall benefit-risk profile of vaccines. Prompt and transparent communication helps maintain public trust in vaccination programs.[32]

The AESI method offers several advantages such as efficiency and cost effectiveness. However, its major flaw is related to its very narrow scope. This method is simply very poorly suited to detect novel, unexpected, or stealthy presenting complications of vaccine. AESI appeared to be a sufficiently robust for the traditional well-known types of vaccines. However, it is not the best choice for a novel vaccine based upon technology that had never been widely tested.

Table 1. Overview of Major COVID-19 Vaccine Safety Monitoring Systems

System Type	Examples	Data Source	Key Features	Primary Role	Limitations
Passive Surveillance	VAERS (US)[21] EudraVigilance (EU)[22]	Spontaneous reports (public, medical staff, manufacturers)	Accepts all reports regardless of causality; Early warning system	Signal detection	Under/over-reporting bias; Incomplete data; Cannot establish causality; No denominator for rate calculation (except special circumstances)[21]
Active Surveillance (Population-Based)	VSD (US)[23] GVDN (global)[24]	Electronic Health Records (EHR) from large populations	Near real-time analysis; Defined populations; Calculates rates	Signal refinement; Hypothesis testing; Causality assessment; Rate estimation	Relies on coded data accuracy; Potential for residual confounding; Access to data may be restricted
Active Surveillance (Individual-Based)	V-safe (US)[25]	Self-reported health check-ins via smartphone	Active solicitation of symptoms; Near real-time data collection	Monitoring common reactions; Early signal detection; Safety assessment in specific groups (pregnancy)	Self-report bias; Participation bias; Primarily focused on common, short-term reactions
Specialized Registries/Studies	NBDPS[26] BD-STEPS[26]	Specific issues (birth defects)	Focused data collection on specific outcomes and populations	Safety assessment in specific groups	May have smaller sample sizes than large EHR systems; Specific focus limits generalizability
Clinical Case Review	CISA[27]	Complex AEFI cases referred for expert review	In-depth clinical assessment	Understanding mechanisms of complex AEFIs; Individual causality assessment	Limited number of cases; Not population-based
Real World Data Based	BEST[28]	Large-scale claims data and EHR	Access to data sources with a short data lag; On-demand sophisticated analytic capabilities	Assurance of the safety and effectiveness of biologic products including vaccines	Uncertain data completeness and accuracy due to reliance on administrative (not scientific or medical) documentation; Possible selection bias (mainly patients with commercial health insurances)

Abbreviations: VAERS: Vaccine Adverse Event Reporting System; VSD: Vaccine Safety Datalink; GVDN: Global Vaccine Data Network; V-Safe: Vaccine Safe; NBDPS: National Birth Defects Prevention Study, BD-STEPS: Birth Defects Study To Evaluate Pregnancy exposures; CISA: Clinical Immunization Safety Assessment; BEST: Biologics Effectiveness and Safety System; AEFI: Adverse Event Following Immunization; EHR: Electronic Health Records

Organ Systems Approach (OSA)

The moniker and its abbreviation "Organ Systems Approach (OSA)" is not officially used in the literature. However, it will be used here to denote the multifaceted approach based upon monitoring potential complications across all organ systems. This is achieved through several key systems:

- **Vaccine Adverse Event Reporting System (VAERS):** Co-managed by the CDC and FDA, VAERS is a passive surveillance system that collects reports of adverse events following vaccination from medical personnel and facilities, manufacturers, and the public. It serves as an early warning system to detect potential safety issues but cannot generally assess causality.[21]
- **Vaccine Safety Datalink (VSD):** A collaboration between the CDC and multiple healthcare organizations, VSD conducts active surveillance and epidemiologic research. It uses electronic health records to monitor vaccine safety and can perform detailed studies to test hypotheses and assess causality.[23]
- **Clinical Immunization Safety Assessment (CISA) Project:** This project involves the CDC and several medical research centers. It provides expert consultation and conducts clinical research on vaccine-associated health risks, offering in-depth clinical assessments of adverse events.[27]
- **Biologics Effectiveness and Safety (BEST) System:** Managed by the FDA, BEST uses large-scale claims data and electronic

health records to rapidly detect and evaluate adverse events, enabling detailed safety studies.[28]

The CDC and FDA play pivotal roles in managing these systems. They collectively ensure robust post-licensure monitoring of vaccine safety, allowing for the detection and investigation of even rare and stealthy adverse events. This approach has a very broad scope and appears to be best suited for the surveillance of side effects related to novel vaccines such as those based upon mRNA platform.

Implications of choosing AESI over OSA

It is surprising that the surveillance of adverse effects of COVID-19 vaccines has been based on the adverse events of special interest (AESI) method rather than on the organ systems approach (OSA). This counterintuitive strategy is typically being explained by giving the following key reasons:

- **Predefined Safety Signals:** AESIs are predefined based on known or suspected risks from clinical trials, historical vaccine data, and early post-marketing surveillance. This targeted approach allows for more efficient and effective monitoring of specific, potentially serious adverse events that have a higher likelihood of being causally related to the vaccine. For example, myocarditis and pericarditis following mRNA vaccines and thrombosis with thrombocytopenia syndrome (TTS) following adenoviral vector vaccines were identified as AESIs based on early data.[33]
- **Resource Allocation:** Monitoring all potential complications across all organ systems would be resource-intensive and may dilute the focus from detecting and managing the most critical and plausible risks. By concentrating on AESIs, health authorities can allocate resources more effectively to detect, investigate, and respond to significant safety signals.[34]
- **Regulatory and Public Health Priorities:** Regulatory agencies like the European Medicines Agency (EMA) and the U.S. Centers for Disease Control and Prevention (CDC) have prioritized AESIs to ensure rapid identification and management of serious adverse events. Assuming that regulatory agencies are considered to be credible by the public, this approach helps maintain public trust.[35]
- **Observed-to-Expected Analyses:** AESIs are often monitored using observed-to-expected (OE) analyses, which compare the incidence of these events in vaccinated populations to historical rates. This method is particularly effective for identifying rare but serious adverse events, as demonstrated in studies that identified increased risks of Guillain-Barré syndrome and cerebral venous sinus thrombosis following certain COVID-19 vaccines.[29]

The above explanations are not persuasive because they do not address the major problem of AESI related to its very narrow scope. In fact, one can argue that overreliance on this method can guarantee that virtually none of the endocrine complications of COVID-19 vaccine will be detected. The question of why anyone would be satisfied with this approach remains unanswered.

Endocrinology: a Clinical and Scientific Conundrum

The other reason that endocrine side effects of COVID-19 vaccinations are more likely to be overlooked than other adverse reactions is related to the paradoxical nature of endocrinology. There is perhaps no other medical subspecialty that seems to be so ostensibly obvious and yet so elusive. As a branch of clinical medicine, endocrinology can be at the same time alluringly promising and dismally disappointing. Scientifically, endocrinology can be initially perceived as a straightforward and logical discipline, only to reveal itself to be an convoluted arcanum, filled with contradictions and paradoxes.[36,37] Both the art and science of endocrinology are *unjustly underestimated* by many and *inappropriately overestimated* by others.[38,39]

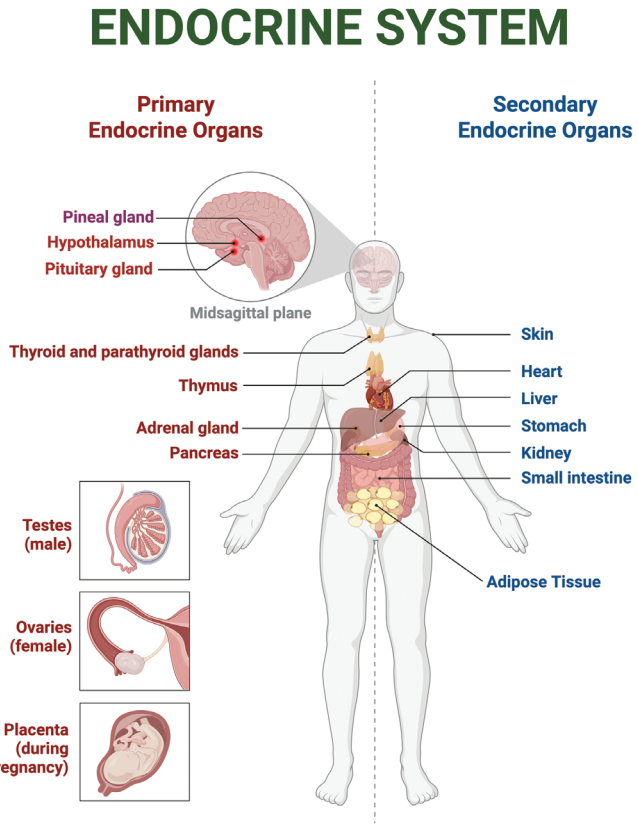

Figure 2. The endocrine system

Endocrinology encompasses the study of the physiology and pathology of the endocrine system (see Figure 2) and metabolism. It represents a vast and fundamentally important area of medicine, addressing the intricate hormonal regulation that underpins every aspect of physiology. Its scope extends from common conditions like diabetes, thyroid disease, and osteoporosis to rare and immensely complex disorders affecting normal growth in the young and aging in the old.

Endocrine dysfunction affects the regulation of essential life functions such as hunger, thirst, digestion, reproduction, bone health, functionality of muscles, and integrity of skin. All aspects of metabolism including anabolism, catabolism, and energy conversion are under endocrine control. Consequently, chronic dysregulation of endocrine processes causes debilitating and ultimately fatal diseases affecting the cardiovascular, neurological, pulmonary, gastrointestinal, renal, and immune systems.

The complexity of endocrine disorders, combined with their nonspecific symptoms and prevalent misconceptions, often results in public confusion and even diagnostic errors by physicians lacking formal training in endocrinology. Dr. Philip Felig, a distinguished academic endocrinologist, has provided the following insightful summary of this paradoxical situation [emphasis added]:

The variable nature of the clinical presentations of many endocrine disorders may result in their going unrecognized for prolonged periods. **By contrast, there is a tendency (both in the general population and in the medical community) to attribute an endocrine basis to common complaints even when evidence is lacking**. For example, hypoglycemia is often invoked to explain weakness and depression, obesity is frequently attributed to a "slow metabolism," …. While each of these symptoms may in fact be due to an endocrine-metabolic disorder, the diagnosis should rest not on the nature of the symptom but on rigorous clinical and laboratory evaluation.[40]

Many patients with chronic endocrine disorders still struggle with understanding the complex nature of their long-lasting conditions. It is still challenging to them to grasp the details of endocrine dynamic tests. If such experienced patients have difficulty assessing the severity of their disease, new patients are obviously likely to perceive their newly developing endocrinopathies as mild and inconsequential. Thus, they may also overlook the link between emergence of their endocrine conditions and COVID-19 vaccination. Similarly, even physicians who are vaccine skeptics but not endocrinologists by training may easily miss the diagnosis of the endocrine adverse effects of vaccination in their patients. And so, the "silent killer" of endocrine side effects of vaccination may be hiding in plain sight.[41]

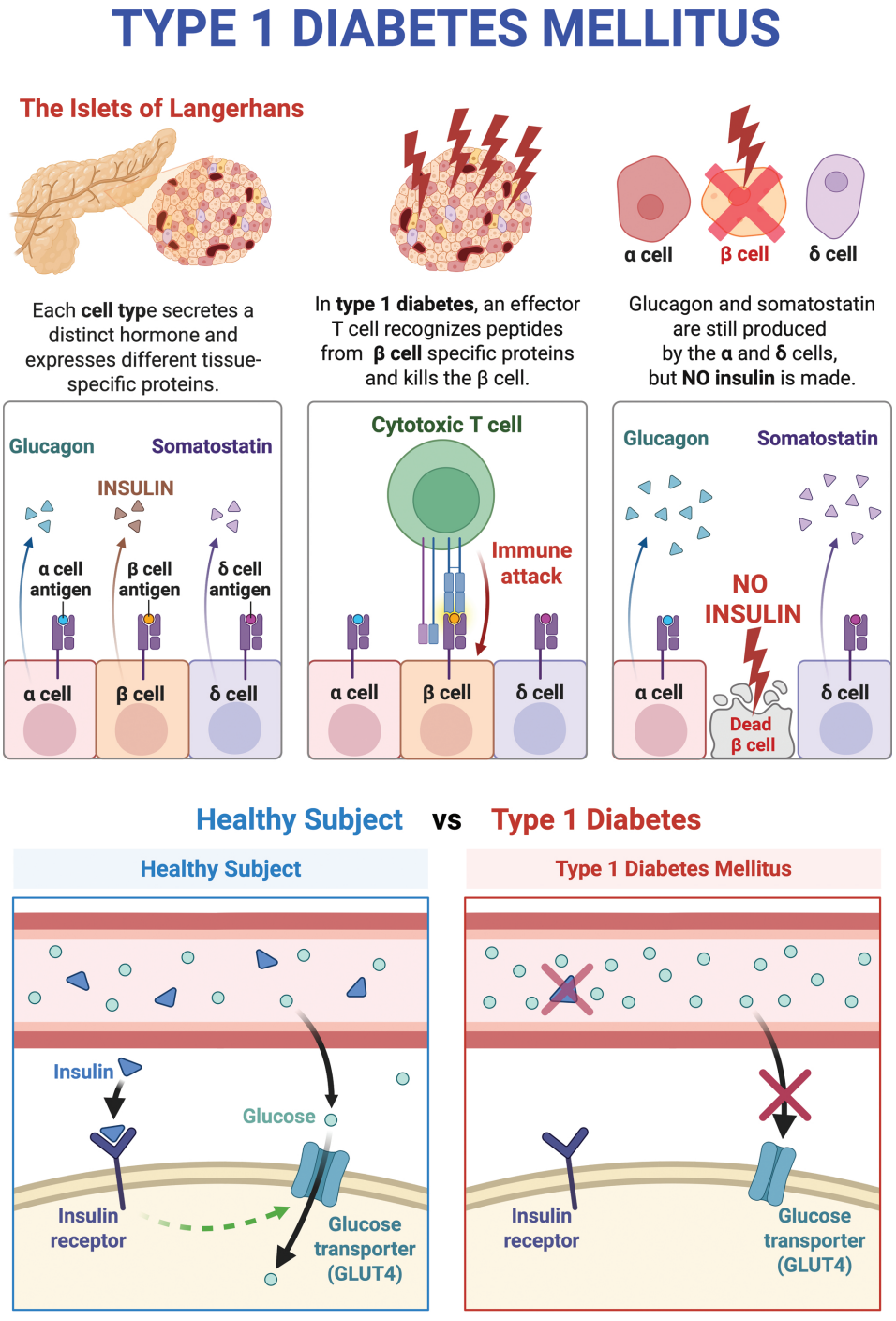

Figure 3. Etiology of diabetes mellitus type 1

Endocrine Adverse Effects of COVID-19 Vaccine: Positive and Negative Evidence

While the potential endocrine adverse events related to COVID-19 vaccine have been receiving much less attention than other types of side effects, a few brave authors have mustered the courage to publish case reports and reviews on this subject.[41,42-53] It has been long recognized that induction of autoimmunity is a potential mechanism involved in causing side effects of the COVID-19 vaccine.[54] As illustrated in Figures 3 and 4, the etiology of two most common endocrinopathies, type 1 diabetes mellitus and Graves disease, involves well-known autoimmune pathomechanisms. It is therefore not surprising that those two endocrine conditions have been discussed most frequently as putative adverse effects of COVID-19 vaccine.[41,45-52] However, some investigators pointed out the existence of compelling evidence that COVID-19 vaccine may be implicated in causing also pituitary and adrenal disease.[42,44]

Mainstream medicine has responded to the above publications by stating that while these potential endocrine adverse effects have been reported, the current research does not support a strong causal relationship between COVID-19 mRNA vaccines and these endocrine disorders.[55] The leading argument of officialdom was that current large-scale, AESI-based vaccine safety surveillance has not identified significant endocrinological complications as "leading concerns" (i.e. they were not classified as AESI), and therefore they cannot be causally linked to COVID-19 vaccination.[29] By choosing such an explanation, officialdom has used the clear negative evidence as their "counter-measure of choice" in order to "obliterate"

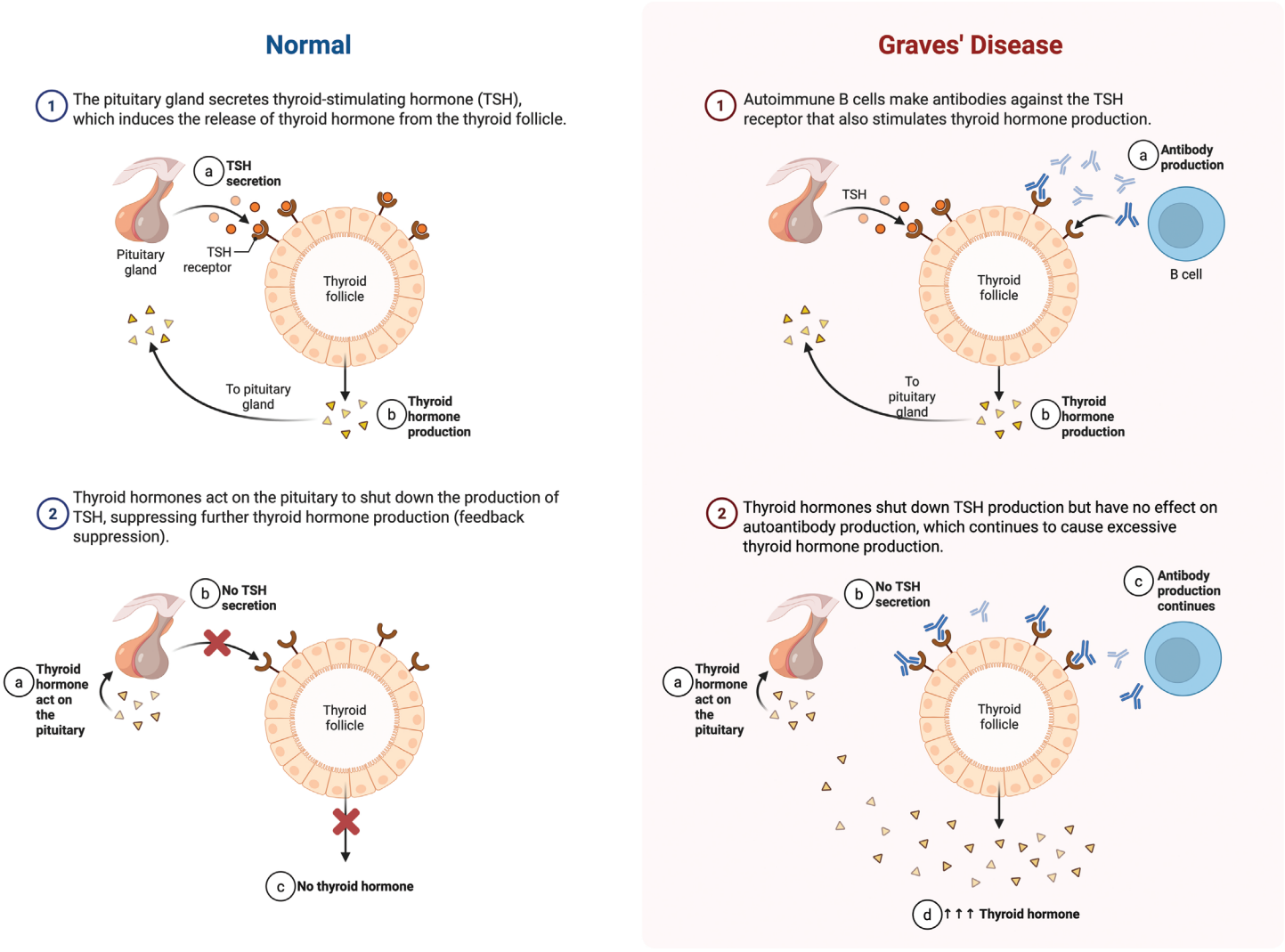

Figure 4. Etiology of Graves disease

the large body of positive evidence that was presented by the vaccine-skeptical authors.

Conclusions

Based upon positive and negative evidence, there is a strong possibility that COVID-19 vaccines may be associated with significant endocrine side effects, which may present clear and present danger to countless patients who have been immunized with the novel mRNA vaccine. There may be mild and barely noticeable symptoms and signs. However, when not discovered early and treated they result in substantial morbidity and mortality.

Unlike other much more apparent side effects, these elusive conditions are being overlooked not only by biased mainstream researchers but also by the vaccine-skeptical public. The main two reasons are the overreliance of authorities on cheap but ineffective surveillance methodology and the stealthy nature of endocrine pathologies.

A potential disaster is likely to be unfolding surreptitiously. Scientists, clinicians, and members of the general public should do their best to persuade their political representatives that the problem of endocrine complications of COVID-19 vaccine needs to be addressed promptly, and clinicians need to have a high index of suspicion for this problem in their patients.

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