



## Opinion

# Seven Deadly Sins of the Immune System

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Citation: Rijkers GT, van Overveld FJ (2021) Seven Deadly Sins of the Immune System. J Vaccines Immunol 6: 165. DOI: 10.29011/2575-789X.000165

Received Date: 14 December, 2021; Accepted Date: 23 December, 2021; Published Date: 27 December, 2021

## Introduction

The function of the immune system is to defend the body against infections. It does this by recognizing, attacking and eliminating potentially infectious micro-organisms in an antigen specific way. To that end, T- and B-lymphocytes are equipped with specific antigen receptors. Each lymphocyte (in fact: each clone of lymphocytes) expresses an antigen receptor with a single, preformed antigen receptor. The repertoire of the immune system is complete, meaning that for every antigen from the microbial and non-microbial environment, a specific antigen receptor is available. The implication of this is that T- and B-lymphocytes have millions, perhaps even billions of different antigen receptors. With the deciphering of the human genome it became crystal clear that the huge diversity of the human immune system cannot be linear encoded by the mere 1000 or so genes of the immune system. The underlying mechanism for creating this immense diversity (the Generator Of Diversity, abbreviated as GOD) is the recombination of a limited set of gene segments, supplemented with random addition and removal of nucleotides. With such a complex molecular machinery, even the generator of diversity can make mistakes and things may go wrong. How, where, and when can the immune system go wrong? Too much (immunoproliferative diseases), too little (immune deficiencies), too late (also immunodeficiencies), too active (autoimmune, allergy) all are ways in which the immune system can go wrong [1].

How, where and when can man go wrong. What is right and what is wrong in worldly life is laid down in sets of laws, rules and regulations, including the penalties for those who break those laws, rules and regulations. For the spiritual and religious life comparable regulations are in place, with corresponding penalties that can even extend into the afterlife. As a guide for their disciples, the Christian church installed an intricate system of daily and deadly sins, and commandments. The seven deadly sins are communicated to and imprinted in spoken words and scriptures. In order to maximize their impact, the seven deadly sins are also symbolized in works of art such as in Dante Alighieri's *Divina Commedia* [2] and the table painting entitled "The Seven Deadly Sins and the Four Lost Things" by Jheronimus Bosch (Figure 1). This painting is exhibited in the Prado museum in Madrid, and all Spanish experts agree that it is a genuine Bosch painting, with his signature on it [3]. Because of major style differences with other paintings of Bosch and the species of wood used (poplar, while all other Bosch' paintings are made on oak), there is some doubt, especially among specialists from The Netherlands [4]. It could be from the school of Jheronimus Bosch, so biologically speaking a form of mimicry. For surviving attacks by predators, mimicry is a good thing. For the immune system, molecular mimicry between microbial and human protein sequences forms a challenge, and can easily lead to a number of deadly sins, as will be discussed below.



**Figure 1:** Central part of the painting “The seven deadly sins” by (the workshop of?) Jheronimus Bosch (approximately 1500), Museo Prado, Madrid, Spain. [https://commons.wikimedia.org/wiki/File:Hieronymus\\_Bosch- The\\_Seven\\_Deadly\\_Sins\\_and\\_the\\_Four\\_Last\\_Things.JPG](https://commons.wikimedia.org/wiki/File:Hieronymus_Bosch- The_Seven_Deadly_Sins_and_the_Four_Last_Things.JPG) Assessed December 14, 2021.

In this opinion paper we will attempt to relate the seven deadly sins (pride, lust, sloth, gluttony, greed, envy, and wrath) to specific conditions when the immune system goes wrong. Where possible, we will try point out virtues, or immunotherapeutic interventions, which can prevent or correct a deadly sin of the immune system.

## The Seven Deadly Sins of The Immune System

### Pride

Pride, although a deadly sin, can have a positive as well as a negative connotation. Pride describes the feeling of being proud of something accomplished. This feeling of respect could even be expected to be shared by others. In philosophy and social psychology, pride is regarded as a secondary emotion which requires the development of a sense of self [5]. A further requirement is the conceptual distinction between pride and happiness and joy. In the Jheronimus Bosch painting, the pride (superbia) panel shows a woman, with her back to the viewer, admiring her reflection in a mirror, but the mirror is held up by a demon. Thus pride would be a dangerously corrupt sense of self. In that context, autoimmune diseases would be the consequence of pride in the immune system. The inborn or acquired defects in the perception of “self” leads to autoimmune diseases. An example of an autoimmune disease is the one caused by the defective expression of the Autoimmune Regulator (AIRE) gene. This in turn prevents thymic transcription of tissue specific self- antigens resulting in severe autoimmune disease [6].

### Lust

Lust (luxuria) is by itself an important driver for becoming active (lust for life, lust for work). Lust as a craving is a deadly sin and includes lust for sexuality, lust for money or the lust for power. It also can take a mundane form in the lust for food (which is distinct from the need for food). Lust can be considered the psychological force which produces an intense wanting for something or a circumstance which would fulfill the emotion. In the depiction of lust by Bosch, two couples enjoy a picnic in a pink tent, with two clowns entertaining them. It illustrates both lust for sexuality (the couple in the background and the sadomasochistic lust of the clowns) as well as lust for food of the couple in the foreground.

If lust is the force producing the intense wanting for something, that lust would be the built-in (innate) sin of each and every individual lymphocyte. Each lymphocyte is equipped with a unique set of antigen receptors which can only be triggered through interaction with their corresponding antigen [7]. The lust of every lymphocyte thus is to come into contact with its corresponding antigen and subsequently become activated.

### Sloth

Sloth (acedia) in Middle English was named accidie, meaning “without care” [8]. The term was used for monks who became indifferent to their duties, but also in a more general way for the loss of affection, boredom, and apathy. Sloth by Bosch is shown as a lazy man, who dozes in front of his fireplace. Faith, disguised as a nun, appears in his dream and reminds him to say his prayers. The lazy man lacks any interest and is not stimulated at all by triggers from the environment. Good examples of sloth in the immune system are the immunodeficiencies which result from defects in signal transduction mechanisms (i.e. not being stimulated by triggers) [9,10]. Probably the best example of sloth within the immune system is the so-called lazy leukocyte syndrome (characterized by recurrent infections, stomatitis, quantitative and qualitative defects in neutrophils and neutrophil motility) based on a deficiency of an actin-interacting protein [11,12].

### Gluttony

Gluttony (gula in Latin) is shown a drunkard drinking from a bottle, and a clearly overweight man eating with greed, while an obese boy, maybe the son, begs him for some food. As stated by Francine Prose, gluttony is the only sin whose effects are visible, written on the body [13]. The trigger for gluttony, seeing or smelling of food, sometimes even just thinking of food, leads to uncontrollable intake of food, i.e. an uncontrolled response [14]. From that perspective, (food) allergy would be the gluttony of the immune system. Exposure to minute quantities of food (cow’s milk, peanut) induces an uncontrollable and exaggerated response [15]. This exposure to allergens can be deliberate or accidental, the latter case when prepacked food isn’t properly labeled [16].

## Greed

Greed (avaricia) can be described as the desire to acquire or possess more than one would need. It can occur when there is a lack of control of the desire to “need” or “want”. For Jheronimus Bosch it was the greed displayed by the judiciary who inspired him to depict a lawsuit in which the judge who pretends to listen sympathetically to one party, accepts a bribe from the opposing party. Lymphoid malignancies have the tendency to acquire and occupy ecological niches in bone marrow and other body sites, displacing the resident, non-malignant cells [17]. Because of the highly active metabolic state, malignant cells also used a disproportionate amount of energy [18]. The same kind of behavior also is displayed by other malignancies.

## Envy

Envy (invidia) occurs when a person lacks another’s superior quality, achievement, or possession and either desires it or wishes that the other lacked it” [19]. Envy is depicted by Bosch in a scene in which a couple is standing in their doorway while casting envious looks at an obvious rich man with a hawk on his hand and a servant to carry his luggage. There could be a genetic component in envy [20], because their daughter is flirting with a man standing outside her window, but her eyes are focused on his purse. There also are two dogs, ready to fight for one bone, a situation which can result in envy in any one of them. During every humoral immune response, due to somatic hypermutation, affinity maturation of antigen receptors on B lymphocytes takes place [21]. The B lymphocytes (the dogs) with the highest affinity receptors will bind and be activated by the antigen (the bone). B lymphocytes with lower affinity antigen receptors will not be able to bind antigen and ultimately will die. Envy could be the cause of death.

## Wrath

Wrath (Ira) is defined as the uncontrolled feelings of anger, rage and hatred. Wrath is illustrated in a fight between two drunken peasants. A woman standing in the middle is trying to stop it. Whether she had played a causative role in the event is unknown and left to the imagination of the viewer. For the immune system, wrath would be expressed in chronic inflammatory conditions such as rheumatoid arthritis and the inflammatory bowel diseases [22,23]. The uncontrolled raging inflammation characteristic of severe COVID-19 is another example [24].

## Discussion

The order in which the seven deadly sins are listed is not important: all are deadly sins meaning that if such a sin was committed and not confessed, the consequence would be the same: you end up in hell. In the table painting *The Seven Deadly Sins*, the circular arrangement also illustrates that all deadly sins are of equal

severity. Still, pride (superbia) is considered to be the number one deadly sin. The reason is that the other deadly sins could all be the ultimate consequence of pride. Apart from the seven deadly sins discussed above, there are two additional so-called historic deadly sins. The first one is acedia, meaning without care. It is a form of apathy, depression, and melancholy. There is a persistent belief that the spleen is the organ where melancholy, and thus acedia would reside [25,26]. From that perspective splenectomy, apart from relieving the clinical symptoms of idiopathic thrombocytopenic purpura and sickle cell anemia, could have an additional beneficial effect [27]. Limited experimental evidence in mice suggests otherwise: splenectomy would increase depressive behavior rather than relieve it [28]. The second historic sin, vainglory (vanagloria) is defined as unjustified boasting. The term is a combination of glory, which is not a sin, and vanity, which is. In the opinion of Pope Gregory, vainglory is a form of pride [29]. Thomas of Aquino considered it the progenitor of envy [30].

## Other Sins of The Immune System

The list of the “classical” deadly sins has been updated by the Vatican in 2008 and now includes also seven “modern” deadly sins, or, as Gianfranco Girotti put it in an interview with *l’Osservatore Roma*: social sins in this age of globalization [31]. They include genetic modification, experiments on the person, environmental pollution, taking or selling illegal drugs, social injustice, causing poverty, and financial greed. Of these additional modern sins, the immune system wouldn’t have to confess anything, apart of course from one major sin: genetic modification. It is this very principle of genetic recombination and modification that enables the immune system to build its repertoire [32]. Without it, the immune system wouldn’t function, mankind wouldn’t exist, and no one would be there to confess or to confess to. Bless our sins.

## Conclusions and Future Prospects

It has been suggested that serotonin dysfunction in the brain forms the biological basis for the seven deadly sins committed by humans [33]. Because serotonin also is an important regulator of the immune system [34,35] it would be attractive to postulate that this molecule could be involved in the immunological diseases discussed above. Sloth can be expressed as neglect. In psychology, the term immune neglect is being used to describe an affective disorder [36,37]. It should be pointed out that the immune system has nothing to do with this condition and therefore it cannot be considered a deadly sin in the context of this analysis. There are two other sins of the immune system which cannot be categorized as deadly sins. The first is the so-called antigenic sin [38,39]. After primary contact with a given micro-organism, say a virus, the dominant immune response will be directed against the dominant epitopes. Upon a secondary exposure, the response still will be mainly targeted at the same epitope, even if the virus has drifted



to express other major epitopes. This phenomenon is the antigenic sin. For the host, the consequence of this sin can be deadly. The second is “thou shalt not kill”. This sin is committed on a daily basis by many different cells and molecules of the immune system, including cytotoxic T-lymphocytes [40] and complement proteins [41,42]. Natural killer cells are programmed to kill, not their neighbors, but invading or tumor cells [43]. Thou shalt not kill, however, is one (the 6th) of the Ten Commandments, not to be confused with the deadly sins.

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