Review of: "Christ Bearing the Cross: the original antigenic sin of the immune system and its potential role in emerging diseases"

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The provocative title and the nice analogy with the Bible original sin immediately attract attention to the subject of the paper by Ger Rijkers and Frans J. van Overveld. The authors present several examples showing that immune response (antibodies) generated with the help of memory cells, which had been formed in the course of previous infections (original antigenic sin, OAS), can be both helpful (protective) and harmful (pathogenic) by either neutralizing the newly emerging infection or facilitating it by antibody-dependent enhancement (ADE). It appears that in most cases, it is difficult to distinguish OAS from ADE if the outcome is negative and, contrarily, if the outcome is positive, OAS should be regarded as not a sin but a virtue. I can add here an example that at the end of 50-ies, when all our family was sick with severe influenza, the only person who remained healthy was my grandfather who survived Spanish influenza in 1918.

The concepts of both OAS and ADE were developed quite long ago and have attracted fresh attention with the emergence of Covid-19. SARS-Cov-2 infection, which affected millions of people all over the world, allowed performing a unique experiment when people were vaccinated with different types of vaccines, possessed experience of both infections and vaccinations, as well as infections with various virus strains. The results of this experiment are still to be analyzed and discussed; however, some facts have become already evident.

First of all, cross-reactivity with previous common coronaviruses appeared to be not so important; therefore, in this case OAS seems not to play a significant role. Second, the outcome of vaccinations appeared to be quite individual: in some people the antibodies were protective, while others were infected several times in spite of vaccinations. Moreover, it becomes evident now that SARS-Cov-2-specific antibodies can be the reason of long-covid or post-covid complications, which appear weeks and months after recovery from acute infection. In our animal experiments, mice immunized with 674-685 fragment of SARS-Cov-2 S-protein demonstrated a dramatic impairment of episodic memory and similar result was obtained if intact animals were injected with immunoglobulins purified from the sera of immunized mice [1]. Moreover, the antibodies of such specificity have been found in the blood of people who experienced Covid-19 2 to 6 months ago; many of them complained for the memory problems…

Returning to the paper of Ger Rijkers and Frans J. van Overveld, I would like to say that the problem they touch is beyond OAS: we see now that the antibodies formed either in response to current infection or as a memory of previous infection/vaccination can be both protective and pathogenic. This idea is well formulated in the paper of Rothman [2]

describing immune response to denge virus (cited by Ger Rijkers and Frans J. van Overveld as (5)): “Depending on the specific epitope targeted and the antibody avidity and concentration, denge virus-specific antibodies can inhibit viral infection (neutralization) or enhance the uptake of virions into cells bearing immunoglobulin receptors (ADE)”. For this it should be added that the epitope specificity of antibodies formed in response to certain antigen is individual for persons possessing different allogeneic forms of MHC II and, therefore, activating T lymphocytes of non-identical specificity. The presence of pre-existing memory T and B cells, induced by the prior infection, can alter the kinetics and specificity of the immune response - this is the essence of OAS. However, the OAS is only a special case of a much wider phenomenon – multiple, both useful and harmful effects of antibodies formed against certain antigen/infection. I completely agree with the authors that this phenomenon should be studied in more details. It is especially important for post-covid patients and for those vaccinated with RNA vaccines, because constant expression of SARS-Cov-2 S-protein stimulates prolonged antibody production that can exert non-desirable effects.

By the way, this is due to the Bible original sin that we can analyze and discuss the things above…

[1] Lykhmus O, Kalashnyk O, Koval L, Krynina O, Komisarenko S, Skok M. Immunization with 674-685 fragment of SARS-Cov-2 spike protein induces neuroinflammation and impairs episodic memory of mice. Biochem Biophys Res Commun. 2022;622:57-63.

[2] Rothman AL. Immunity to dengue virus: a tale of original antigenic sin and tropical cytokine storms. Nat Rev Immunol 2011; 11: 532-43.