

## Psoriasis: A Sequela of Streptococcal Infection Similar to Acute Rheumatic Fever

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### Abstract

We propose that psoriasis is a sequela of streptococcal infection similar to acute rheumatic fever (ARF). This hypothesis arises from many different lines of evidence: a markedly elevated serum anti-streptococcal antibody is present in plaque psoriasis. However, cultures are routinely negative in psoriasis because the Group A *Streptococcus pyogenes* “hides” inside cells and inside biofilms and is thereby unculturable. The activation of either arm of the immune system is likely related to whether internalization or biofilm formation is predominant. With internalization, we postulate it is the adaptive immune system and with biofilm formation, the innate system. Lastly, prolonged treatment with anti-GAS antibiotics is effective in psoriasis as in ARF.

### Description

Acute rheumatic fever (ARF) is considered a prototypical sequela of streptococcal pharyngitis [1]. It has clinical manifestations in the joints, heart, and skin as well as other organs. In the heart and, especially in the mitral valve, the consequences of this disease are very destructive and result from antigen-antibody reactions [2]. This disease, however, has become almost non-existent, save for occasional outbreaks [3]. This is due to the treatment of the preceding pharyngitis with antibiotics (particularly penicillin or penicillin derivatives); it is also due to the continued treatment of ARF with a daily dose of penicillin.

We propose psoriasis is also a sequela of streptococcal infection similar to ARF. It has similar clinical findings [4] and a similar response to penicillin [5]. There are many lines of evidence to support this hypothesis: the first is epidemiologic-if there is no group A *Streptococcus pyogenes* (GAS) in the environment, there is no psoriasis. This is true above certain latitude in northern Europe as well as certain Pacific islands including the largest, Australia. (The indigenous Aborigines had no psoriasis prior to the arrival of the English prisoners due to the lack of GAS in the environment.) The prevalence of GAS increased with decreasing latitude with a resulting increase in the prevalence of psoriasis [6]. This gradually decreased towards the equator.

The next line of evidence is the presence of GAS itself: in guttate psoriasis [7] (psoriasis with many small scaling lesions), patients have a positive throat culture or a positive anti-streptolysin O (ASO) titer. The addition of penicillin is useful in the treatment of this variety of psoriasis.

In contrast to guttate psoriasis, the presence of GAS in plaque psoriasis has been obscured by the fact that the organism cannot be cultured, nor is it accompanied by an elevated ASO titer. Two factors lead to this reality including internalization [8], (Figure 1) and formation of biofilms (Figure 2) [9]. The GAS thus “hides” in the tonsillar epithelial cells or in biofilms, only to reappear when the organisms leave the cells and recolonize [10]. With internalization, this

may occur as long as a year after entry; and, with biofilms, it occurs only on the rare occasion when “exporter” cells leave [11]. These exporter cells can rapidly form a new biofilm (There is then a very narrow “window” for culturability) [12]. Consequently, these organisms truly create a chronic infection with little evidence of their presence.

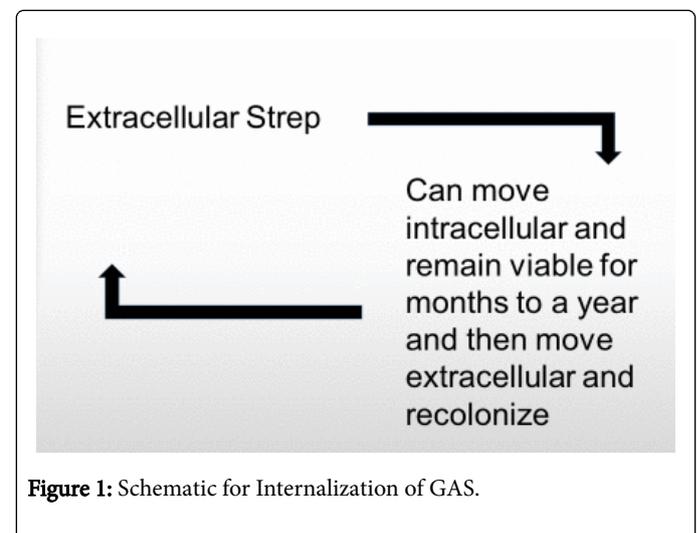
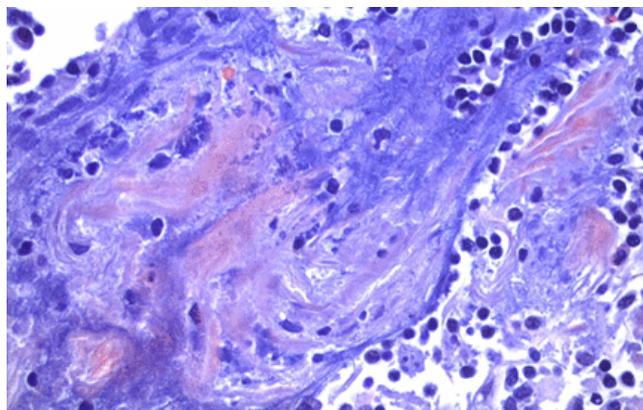


Figure 1: Schematic for Internalization of GAS.

### The Next Line of Evidence Comes from Treatment

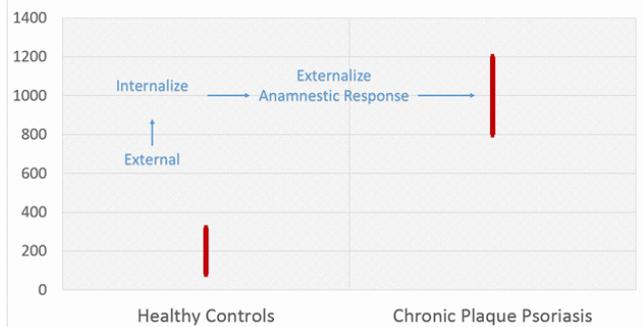
If plaque psoriasis is treated with continuing doses of penicillin, it resolves [13]. Penicillin likely kills the GAS being “externalized” before allowing them to react with the immune system. In like manner, it would kill the “exporter” cells as they leave the biofilm. Similar to ARF, the treatment needs to be continued for a long time. Surgical treatment has also been shown to ameliorate psoriasis [14]. This becomes a viable option especially when the psoriasis is accompanied by chronic tonsillitis or an elevated ASO titer. Similar to penicillin, clearing of the

psoriasis may not occur for many months, as it takes that amount of time for the serum antibody to decay [15].

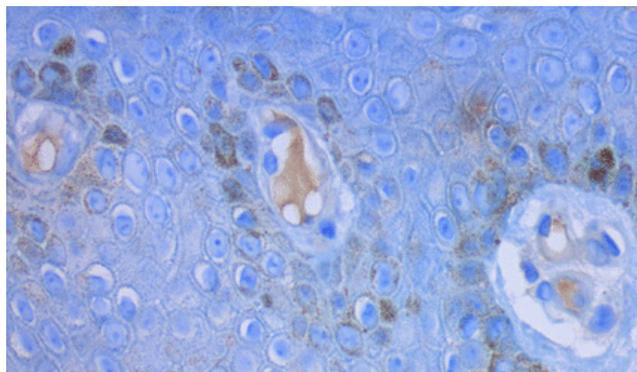


**Figure 2:** Tonsillar tissue from chronic tonsillitis in psoriasis. Congo red positive staining confirms the presence of amyloid which forms the infrastructure of biofilms. 40X.

The serum antibody versus GAS forms the next line of evidence. In plaque psoriasis, the anti-streptococcal IgG is markedly elevated compared to controls [16]. When the graph displaying this finding is examined, it is obvious that 60% of the patients had markedly elevated antibodies, “dragging” the entire group to the significant level seen. The remainder was in the “control” range. When one considers the behavior of the internalized GAS, a possible answer becomes apparent: the bacterial cells externalize and the antibody has an anamnestic response leading to the markedly higher level found (Figure 3). The remainder of the patients in whom the GAS is in the biofilms, conceivably activate the innate immune system as in other diseases [17]. This would lead to the Toll-like receptor 2 that has been found in the dermal capillaries (Figure 4). There it can lead to the development of the psoriatic lesions by known pathways, most notably MyD88→NFκB→TNFα [18].



**Figure 3:** Combination of Figure 1 and adaptation of graph from reference 16; demonstrates how IgG could be markedly elevated in plaque psoriasis patients.



**Figure 4:** Biopsy of psoriatic plaque stained with CD 282 (TLR 2). Positive staining is noted in the lumens of the upper dermal capillaries and in the basal layer of the epidermis (control location in the epidermis). 40X.

Compared to the innate immune system working primarily with TNFα, the adaptive immune system has many more weapons at its disposal: complement, alternate complement, killer T cells and many cytokines. Related to the elevated IgG, this would most likely lead to the development of the destructive psoriatic arthritis, chronic metabolic syndrome, renal disease, and uveitis noted in several patients. It would also be the ultimate comparator for psoriasis as related to ARF.

The antigen in the skin is yet to be determined as is the impact of the gene (one of the PSORS genes) [19]. It is likely to be via molecular mimicry as is the situation in ARF. Even more obscure are the antigens for the many varieties of psoriasis, such as pustular and erythrodermic.

The impact of the biologic medications on psoriasis has been dramatic. Those medications act very late in the cascade of events from the initial GAS infection to the psoriatic plaque. While very effective, these agents must be continued because they are not addressing the source of the inflammatory response. Perhaps, if the patient could tolerate it, the ideal treatment would be a biologic medication and penicillin plus/minus a biofilm disperser. The biologic predictably would cause remission and then could be discontinued after 10-12 months while the penicillin was continued. It was shown that the penicillin could even be discontinued after two years in many patients [13]. Presumably, these are the patients with internalization of the GAS; those with the biofilms would, in all probability, need the additional agents.

Thus, similar to ARF, psoriasis leads to involvement of other organs. Psoriasis is very destructive in the in the joints, while ARF is most destructive in the cardiac tissue. Moreover, psoriasis differs from ARF in that it will cause renal involvement similar to glomerulonephritis while ARF does not [20]. As previously postulated, this tissue destruction is very likely due to the adaptive immune system with involvement of an antibody. Consequently, with the involvement of the adaptive immune system, tissue destruction occurs much more extensively and with much greater alacrity leading to disabling disease [17,21].

## Summary

We have shown how epidemiology, microbiology, physiology, immunology, clinical findings and treatment all play a role in the hypothesis that *Streptococcus* is most important in the etiology of psoriasis. We have also shown how it is not the presence of the organisms, or the process of internalization, or the biofilm production that actually leads to the disease. It is the immune system, in both its arms, innate and adaptive, which causes the disease. In nearly every regard then, it is similar to rheumatic fever, and we believe it should also be included as a sequela of streptococcal infection.

Genetics plays an important role, probably as the first (or second) hit in the double-hit phenomenon, and the streptococcus represents the environmental "hit". This can be seen when there is acute or chronic pharyngitis without the development of psoriasis because the patient lacks the gene.

Penicillin and azithromycin (both excellent anti-streptococcal drugs) have been shown to eradicate the psoriasis, and we have theorized why they must be continued for long intervals. Also, in many patients, the addition of a biofilm dispersing agent may be necessary.

All the foregoing should help in understanding of this cutaneous disease with systemic findings, and should firmly place it alongside rheumatic fever and glomerulonephritis as a sequela of streptococcus.

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