Psoriasis is one of the most common skin diseases affecting about 2-3% of the caucasian population. Its clinical presentation is the formation of red scaled plaques on the skin. The main pathological features of psoriatic plaque comprise of skin inflammation, disturbances of keratinocyte proliferation and maturation and angiogenesis. Although the precise precipitating mechanism of psoriasis has not been discovered yet, the key element in psoriasis initiation is T- lymphocyte population. Nevertheless, other inflammatory cells (e.g. neutrophils, macrophages) as well as activated endothelium play a role in its pathogenesis. Indeed, one of the first histological changes in the affected skin is leukocyte infiltration. The so called trafficking of inflammatory cells to the skin is tightly regulated process guided by cytokines especially chemokines. Angiogenesis is a process of new blood vessel growth from preexisted vessel bed. Vessels in the most of the tissues of adult individual remain in a state of quiescence. The rate of endothelial cell turnover is relatively slow (1-2 years). However in cases of physiological or pathological requirements, a new vessel formation can be initiated by the mechanism called angiogenic switch. One of the pathological conditions associated with angiogenesis is formation of psoriatic plaques. Treatment for psoriasis that would cure the disease once and for all is presently not known. Current therapeutic strategies are focused on instigating remission. One of the oldest effective albeit empirical treatments is Goeckerman´s therapy (GT). It is a combination of topical application of coal tar ointment with subsequent UV irradiation. Although its mechanisms of action are not fully elucidated as of yet, one of its hallmarks is marked immunosuppression. The aim of this study was to elucidate the effect of GT on various markers of inflammation and angiogenesis in the patients with psoriasis and thus help to further extend understanding of its mechanisms and targets of action. Both adult and pediatric psoriasis patients in whom psoriasis was diagnosed and who were treated by GT at the Department of Dermatology and Venereology, University Hospital in Hradec Kralove, were enrolled to our investigation which was approved by the Ethics Committee of University Hospital. Disease activity and treatment efficacy were justified by standardized PASI score as assessed by referring dermatologist. Samples of venous blood were taken from patients before therapy and at the date of dismission from the hospital ward.

PTX3 and CRP: The aim of the first study was to evaluate the influence of Goeckerman's therapy of psoriasis on levels of two pentraxins: long pentraxin PTX3 and C reactive protein in 49 patients with chronic plaque psoriasis. Both pentraxins are presumed to be markers of activated local (PTX3) and systemic (CRP) inflammatory response. CRP was assessed by immunonephelometry on IMMAGE 800 (Beckman, USA). PTX3 was detected using sandwich ELISA detection set (Alexis Biochemicals, Switzerland). The serum levels of both parameters (expressed as average ± 1 SD) were significantly diminished after GT. The level of PTX3 dropped from 1.92 ± 0.72 ng/ml before GT to 1.66 ± 0.58 ng/ml after GT ($p = 0.0396$) and the level of CRP fell from 4.64 ± 3.93 mg/l to 1.66 ± 0.58 mg/l ($p < 0.0001$). Compared to healthy controls, the serum levels of both parameters before GT were significantly higher than those found in healthy blood donors and remained significantly increased after GT. Increased serum concentrations of pentraxin 3 and CRP are alleviated by GT in patients with psoriasis.

Chemokines: Chemokines in psoriasis are considered to reflect increased inflammatory cell trafficking to the site of developing psoriasis plaque that contributes to histological feature of lesional leukocyte infiltration. In addition, either antiangiogeneic or proangiogenic properties were observed in some chemokines. The aim of this study was to evaluate the influence of Goeckerman´s therapy of psoriasis on the levels of proangiogenic chemokines ENA-78 (CXCL5, Epithelial Cell Derived Neutrophil Attractant-78), GRO alpha (CXCL1, Growth-Related Oncogene), IL-8 (CXCL8, Interleukin-8), MCP-1 (CCL2, Monocyte Chemotactic (Chemoattractant) Protein 1) and RANTES (CCL5, Regulated on Activation of

Normal T Cell Expressed and Secreted) in peripheral blood of 22 children´s patients with psoriasis. 22 otherwise healthy children serve as a control group. The serum levels of chemokines were determined by commercial membrane protein array technique (RayBiotech, USA). Efficacy of Goeckerman´s therapy was delineated by PASI score. Disease activity was significantly diminished by Goeckerman´s therapy ($p < 0.001$). Serum levels of GRO alpha and MCP-1 in patients before GT were significantly higher than those measured in healthy blood donors (GRO alpha: $p = 0.0128$ and MCP-1: $p = 0.0003$). Serum levels of GRO alpha, MCP-1 and RANTES were significantly diminished by GT (GRO alpha: $p = 0.002$, MCP-1: $p = 0.048$ and RANTES: $p = 0.0131$). Compared to the healthy controls, serum level of MCP-1 remained significantly increased in psoriasis patients after GT ($p < 0.0001$). In conclusion, we found that the GT of psoriasis influenced the serum levels of proinflammatory and proangiogenic chemokines, especially GRO alpha, MCP-1 and RANTES. It could be the cause for decreased proangiogenic activity which is described after GT of psoriasis.

VEGF, bFGF: VEGF is a principal angiogenic factor responsible for angiogenesis initiation thus representing the turning on of the angiogenic switch. bFGF has a synergistic effect with VEGF, but its main role seems to maintain angiogenic process once it is initiated. The aim of this study was to evaluate the influence of GT of psoriasis on angiogenic activity by comparing serum levels of vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) in 44 patients with psoriasis in peripheral blood samples collected before and after therapy. Forty otherwise healthy blood donors serve as a control group. The efficacy of GT was delineated by psoriasis area and severity index (PASI). The disease activity was significantly diminished by GT ($p < 0.001$). The serum levels of both VEGF and bFGF were significantly correlated to PASI value in patients before the treatment by GT. The serum levels of VEGF (329.4 ± 125.5 pg/ml) and bFGF (10.2 ± 5.04 pg/ml) in patients before GT were significantly higher than those measured in healthy blood donors (VEGF 236.4 ± 55.9 pg/ml, bFGF 7.3 ± 3.7 pg/ml). The serum levels of both VEGF and bFGF were significantly diminished by GT. The level of VEGF dropped from 329.4 ± 125.5 pg/ml before GT to 278.5 ± 109.9 pg/ml after GT ($p = 0.0042$) and the level of bFGF fell from 10.2 ± 5.04 to 7.78 ± 4.5 pg/ml ($p = 0.019$). Comparing to healthy controls, the serum level of bFGF in psoriasis patients was normalized ($p = 0.5723$) after GT. In contrast, the serum level of VEGF remained significantly increased in psoriasis patients after GT in comparison to healthy blood donors ($p = 0.0319$). In conclusion, we found that the angiogenic potential which is abnormally increased in patients with psoriasis is significantly alleviated by GT.

Endoglin: The aim of the last study was to evaluate the influence of GT of psoriasis on serum levels of soluble endoglin (sCD105). Endoglin (CD105) is a transmembrane co-receptor for TGF beta that is preferentially expressed on activated and proliferating endothelial cells. It is considered a marker of angiogenesis. The soluble form of endoglin is considered to be shed by enzymatic splicing of the surface molecule. It is thought to play an antagonistic role in angiogenic signaling as shown in pathophysiology of preeklampsia where its elevated levels precede the onset of the disease and are correlated with its severity. A higher lesional expression of endoglin and lower expression in non lesional skin was demonstrated in psoriatic patients when compared to the skin of control normal population. As of yet there was no paper on the levels of soluble endoglin in psoriasis. The disease activity was significantly alleviated by GT (PASI score of 19.22 ± 7.49 before therapy lowered to 8.85 ± 6.29 after therapy; $p < 0.001$). Serum levels of soluble endoglin (sCD105) in patients with chronic psoriasis were significantly lowered after GT. From 7.85 ± 2.26 ng/ml to 7.01 ± 1.71 ng/ml ($p = 0.0002$). The levels of sCD105 before GT were significantly higher than those of healthy controls (4.85 ± 0.95 ng/ml) ($p < 0.001$) and remained higher even after therapy ($p < 0.001$). However, there was no correlation found between levels of sCD105 (be it before or after therapy) and disease activity (as expressed by PASI scoring).

Conclusion: We can conclude that GT influences pathophysiological processes involved in psoriasis progression. Changes in markers of both inflammation and angiogenesis were observed. Finding of a specific treatment focused on psoriasis initiation mechanisms and leading to the complete cure (without further exacerbation) might not be achieved in the near future. Current therapeutic strategies are targeting effector mechanisms of psoriasis with the goal to achieve remission and/or to prevent new exacerbation. Reassessing the effect of these classical therapies on various (newly discovered) pathophysiological disease mechanisms can elucidate disease pathways and help to find possible targets for future drug development. Our findings with GT and inflammation and angiogenesis markers represent such effort.