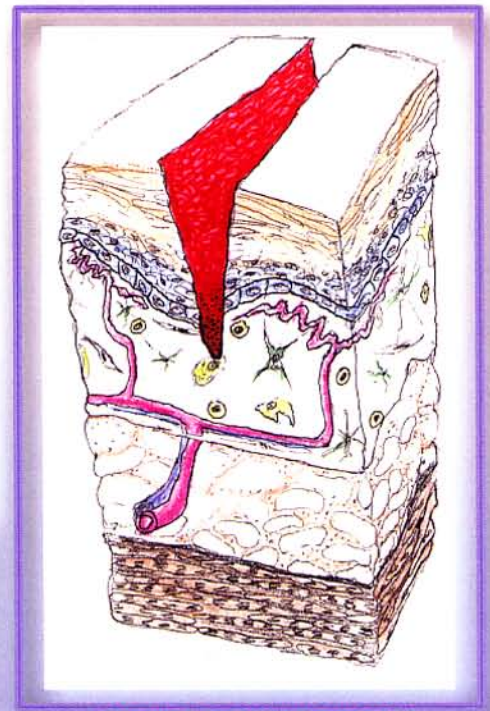


Normal Skin

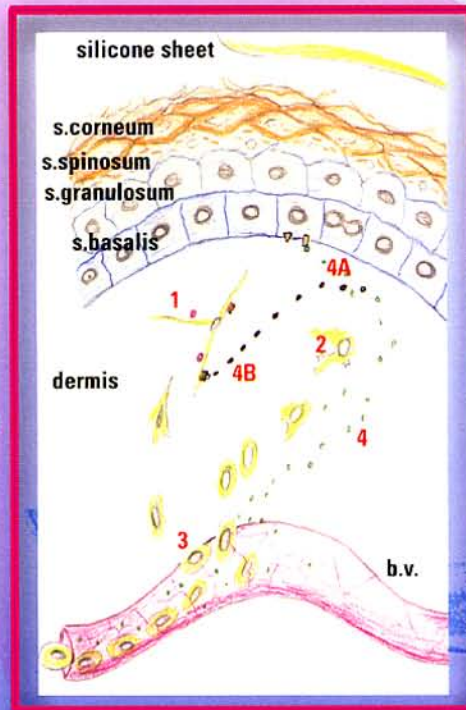


BARRIER LOST, CALCIUM RELEASE
THROMBOSPONDIN-1 TGF- β -1 Injury

SILICON MOBILIZES CD36 TO DERMIS
HYALURONON CLEAVED
MACROPHAGE ACTIVATION BALANCE PLASMONOGEN

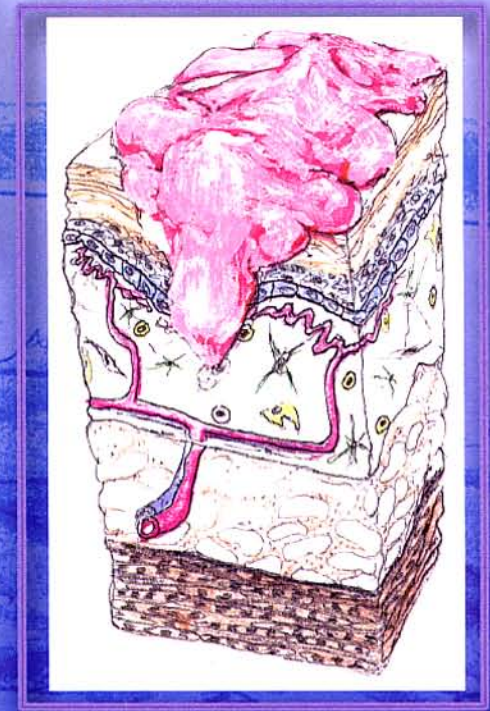


Rejuveness Silicone Sheet



- 1 dermal dendrocyte with scavenger receptors
- 2 cd68 macrophages
- 3 migrating precursors
- 4 thrombospondin-1
- 4A SR-BI rec on basal cells
- 4B oxLDL from injury

TEWL POOR BLOOD SUPPLY CD36 IN EPIDERMIS INACTIVE
MACROPHAGE IMBALANCED PLASMONOGEN



Keloid Formation

Rejuveness[®]
PURE SILICONE SHEETING

Silicone Sheeting; Beneath the Surface

TARGETING UNDERLYING CAUSES OF KELOID AND HYPERTROPHIC SCARS

Healing of the skin is a deceptively complex process that involves multiple interactions of intracellular cascades, intercellular signaling with growth factors, injury signals and other cytokines, extracellular matrix dynamics, as well as the proliferation, migration and differentiation of numerous cell types. Problematic healing sequelae seen in keloid and hypertrophic scarring (HS) is a daunting problem, both as a basic science issue as well as a clinical entity.

Although there are significant gaps in our understanding of the mechanisms involved in problem scarring, recent *in vivo* and *in vitro* studies point to key roles in cells bearing the CD36, CD44, cell surface receptors and thrombospondin-1. These are nodal points for adhesive cell interactions, and the migratory cycle of cells, lipids, and plasminogen/ plasmin system in the dermis and epidermis during the healing and scarring process.

Recent studies with the application of silicone sheeting over keloid and hypertrophic scar tissue suggest that the dramatic positive effects of silicone sheeting therapy involves the distribution of CD36 through the dermis leading to normalization of macrophage activity. The way silicone sheeting resolves keloid and HS by inducing cascade action of surface receptors, fibroblast and microphages may be indirect.

◆ KELOID AND HYPERTROPHIC SCAR (HS) PHYSIOLOGY ◆

Keloid and HS are fibroproliferative disorders which seem to remain in the early wound healing stages with symptoms of redness, itchiness, swelling as well as a TEWL (Trans Epidermal Water Loss) four times higher than normal scars². On the cellular level keloid and HS patho-physiology could be characterized by the predominance of adhesive activity with a four fold increase in the rate of fibronectin biosynthesis³, high Thrombospondin-1 levels associated with imbalanced urokinase plasminogen levels and high TGF-B1¹. These have all been indicated in chronic inflammatory states leading to decreased fibrinolysis and excessive fibrin deposition⁴. Misplaced and elevated counts of myofibroblast cells⁶, decreased hyaluronan (CD44)⁷ along with high levels of CD36 remain in the upper dermis and lower epidermis⁸. Fibroblast in keloids are active on the outer edge of the scar expanding boundary⁹ and are marked by abundant rough endoplasmic reticulum¹⁰ with an imbalance of plasminogen in cell media and on cell surface¹.

◆ CD36 AND CD68 NORMALIZATION ◆

In a recent combined clinical/immunohistochemical study, ten keloids underwent surgical excision and ten keloids underwent surgical excision and silicone sheeting application for three months¹¹. Complete remission was observed in 60% of the silicone sheeting sites with four partial recurrences. The sites without silicone sheeting

had one remission but nine keloids returned. Immunophenotypic analysis revealed high levels of ten immune-cell infiltrates in the excised keloids. The silicone sheeting infiltrate clearly showed decreased levels in all immunophenotypic cell types, except CD36- and CD68-positive cells. There were marked increases of CD68+ macrophages and CD36 dermal dendrocytes in the excised lesion covered with silicone sheeting.

The results showed support for the hypothesis that *in situ* mechanisms are involved in the development of pathological scars. Of considerable interest is that the CD36+ and CD68+ cells were evenly distributed throughout the dermis, reflecting a more normal pattern and macrophage stimulation. These findings strongly suggest that silicone sheeting induces normalization of both the levels of immunotypic markers as well as distribution of cells bearing these markers. This implies that silicone sheeting induces a dynamic normalization of cyclic migration of CD36 and CD68 cells between deeper areas of the dermis where they activate macrophages leading to plasminogen normalization and fibrinolysis¹². CD36 also enables macrophage catabolism of oxidized lipid clusters and take up of cholesterol for lamellar body formation, ultimately leading to stratum corneum barrier repair and TEWL normalization¹³. This hypothesis is supported by the theory that prolonged reepithelialization could be leading to keloid and HS formation and that stratum corneum repair initiates a "stop" paracrine signal to the dermis in wound repair⁵.

◆ MACROPHAGE ACTIVATION REGULATING PLASMINOGEN ◆

Hyaluronan regulates dermal condensation and facilitates cell movement¹⁴. Decreased amounts of hyaluronan in keloid and HS with increased amounts in the epidermis correspond to a four fold increase in epidermal water holding capacity over normal scars². The separate fetal origins of dermal and epidermal hyaluronan have been singled out why humans heal by scarring and not regeneration to begin with¹⁵. More importantly, the macrophage production of plasminogen activator (uPA) and plasminogen activator inhibitor (uPA-1) which some researchers see as nodal points for adhesive activity and overproduction of TGF-B-1 in keloids¹ seems to be hyaluronan molecule size dependent¹⁷. The combination of properly metabolized hyaluronan and activated macrophages in the dermis is thought to balance plasminogen production leading to keloid and HS resolution. Silicone sheeting could be stimulating macrophages directly or indirectly through CD36 migration from epidermis to dermis as well as inducing properly cleaved hyaluronan. These parameters will enable activated macrophages to balance urokinase plasminogen levels in the extracellular matrix¹⁸ which may play a role in the regulatory mechanisms of keloid formation¹⁷.

◆ FUTURE RESEARCH ◆

Silicone sheeting has been designated as only one of two management options supported by evidence-based results¹⁹. Emerging models that target dynamic changes in the expression and distribution of CD36 and urokinase plasminogen activity should provide novel and useful approaches to the management of problem scarring.

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