Of equal importance in the total picture of collagen metabolism is the complex process of collagen degradation.

Normally, the collagen in our connective tissues turns over at a very slow and controlled rate of growth.

However, after injury, collagen synthesis and remodelling continue at the wound site for some time, in an effort to achieve the original collagen ultra structure.

The body is constantly trying to remodel the scar collagen to achieve the original collagen ultra structure that was present before the injury.

Collagen degradation requires the activity of a family of enzymes called matrix metalloproteinases or MMPs, which are collagenases.

These are synthesised and released by various cells including fibroblasts, macrophages, neutrophils, osteoclasts and tumour cells.

The Rowett Institute in the UK is currently researching the role of collagen metabolism in fibrotic conditions. They suggest that

"Fibrotic lesions may be caused by the build-up in the tissue of collagen with the `wrong' type of cross linking. The tissue-specificity of collagen crosslinking appears to be controlled by the enzyme Telopeptide lysyl hydroxylase." ([i])

Fibrinolysis:

Once the tissue repair is complete, fibrinolysis removes the clot or thrombus from the injured tissue.

The fibrinolytic pathway is initiated by plasminogen, which is a proenzyme that forms plasmin. Tissue plasminogen activators are found in most tissues, and include *tissue plasminogen activator* -- tPA and *urokinase* .

The latter has been used in attempts to break down epidural scar tissue. Plasminogen activator is also a product of macrophages.

The level of tissue activator in the plasma is normally low, but can be increased by exercise and stress.

Triggering of fibrinolysis occur when the plasminogen activator, plasminogen, and fibrin are all in close proximity. Both plasminogen and its activator bind strongly to fibrin as the clot forms.

This close association prevents inhibition of plasmin activity by inhibitor, and allows proteolysis of the fibrin to proceed after the production of lys-plasminogen.

Plasmin inhibitors (*antiplasmins*), which can control plasmin activity include: 1-antitrypsin, 2-antiplasmin, C1 inhibitor, antithrombin III.

Plasmin attacks fibrin at a number of different sites, at least 50, reducing its size and forming

many fragments, some of which retain the capacity to polymerize, thus competing with fibrinogen for thrombin and acting as inhibitors of clot formation.

This may prevent the clot being removed before the tissue is repaired.

Dullerud et al. ([ii]) looked at 78 patients who had undergone a previous laminectomy.

No evidence of scar formation was seen in 19 patients, a small amount was seen in 36 patients, a moderate amount in 17 patients, and a large amount was observed in 6 patients.

More extensive surgery was associated with greater scarring. Fibrinolytic factors tissue plasminogen activator antigen and tissue plasminogen activity were evaluated pre-operatively.

It was found that low values were associated with a poor clinical outcome and greater scarring.

The authors concluded:

"The amount of scar formation after lumbar discectomy seems to be related to the clinical outcome, the size of the surgical exposure, and some fibrinolytic factors."

As we shall see, this concurs with the hypothesis of Jayson, who suggested that a fibrinolytic defect might be responsible for the scarring in arachnoiditis.

Hypertrophic Scarring:

? Overproduction of all components of extracellular matrix

? The normally fine basket weave pattern of collagen in skin is replaced with nodules containing large filaments from fibroblasts

Research:

Growth factors, such as TGF-β are being investigated with respect to their influence on wound healing.

Beanes et al. recently published an article on the central role of TGF-β in skin repair and scar formation. ([iii])

In the American National Cancer Institute, work is in progress on the role of TGF-β in wound healing, fibrosis and carcinogenesis. TGF-beta plays an important role in wound healing and is both released from degranulating platelets at the time of tissue injury and produced by fibroblasts and inflammatory cells migrating into a wound site.

Numerous studies have shown that systemic or topical TGF-beta can restore normal healing in models of impaired healing.

One of the associated ?downstream' proteins, Smad3 is also being investigated, especially in relation to the effect of loss of Smad3 in radiation injury and secondary fibrosis.

Smad3 appears to be protective against radiation-induced damage, and selective inhibition of Smad3 activation may be beneficial in wound healing and protective against fibrosis.

The Molecular Neuroscience Research Group at the University of Birmingham (UK), have looked at TGF-β in deposition of scar tissue in lesioned spinal cord. ([iv])

They have also investigated fibroblast growth factor, comparing scarring and non-scarring models of CNS injury ([v]).

Tumour necrosis factor alpha has been found to inhibit Type I collagen synthesis ([vi]).

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[i] http://www.rowett.ac.uk/factsheets/Resources/6.%20S.%20Robbins.pdf

[ii] Dullerud R, Graver V, Haakonsen M, Haaland AK, Loeb M, Magnaes B. *Spine.* 1998 Jul 1; 23(13):1464-9. Influence of fibrinolytic factors on scar formation after lumbar discectomy. A magnetic resonance imaging follow-up study with clinical correlation performed 7 years after surgery.

[iii] Beanes SR, Dang C, Soo C, Ting K *Exp. Rev. Mol. Med*. 2003 (5) DOI: 10.1017/S1462399403005817 Skin repair and scar formation: the central role of TGF-β .
[iv] Lagord, C., Berry, M. & Logan, A. *Molecular and Cellular Neuroscience* 2002; 20: 69-92 Expression of TGF beta 2 but not TGF beta 1 correlates with the deposition of scar tissue in the lesioned spinal cord.

[v] Smith, C, Berry, M Clarke W and Logan, A. *European Journal of Neuroscience* 2001; 13(3):443-458. Differential expression of fibroblast growth factor-2 (FGF-2) and FGF receptor 1 (FGFR1) in a scarring and non-scarring model of CNS injury. European Journal of Neuroscience 13(3):443-458.

[vi] Greenwel P, Tanaka S, Penkov D, Zhang W, Olive M, Moll J,Vinson C, Di Liberto M, Ramirez F *Mol Cell Biol*. 2000 February; 20 (3): 912-918 Tumor Necrosis Factor Alpha Inhibits Type I Collagen Synthesis through Repressive CCAAT/Enhancer-Binding Proteins