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- HYPERTROPHIC SCARRING
- UW BURN INJURY REHABILITATION MODEL SYSTEM

FUNDING

International Association of Firefighters

National Institute on Disability and Rehabilitation Research

- Department of Education

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Laboratory Topics

We reported last year that we have now clarified the histological anatomy of the cones of skin (Fig.1) in normal uninjured skin, burn-injured skin, mature and hypertrophic scars, fetal skin, rat, rabbit, and pig skin and that we hope to use these structures as a window to further our understanding of hypertrophic scarring. We have also reported on our investigation of the female, red Duroc pig and found it to be a promising animal model of hypertrophic scarring (Fig. 2). In 2002, we received funding from the National Institute on Disability and Rehabilitation Research, Department of Education (NIDRR) and the Washington State Council of Fire Fighters Burn Foundation (WSCFFBF) to conduct further studies of these with three specific aims, which are summarized below. Drs. Gibran, Cole and Isik are significantly involved in these activities. The Visiting Scientists listed above have also played major roles within these projects.

Broad Long Term Objective: To understand the cause of hypertrophic scarring after burns, with the intent of reducing or eliminating this devastating outcome and thereby greatly improving rehabilitation.

Hypertrophic scarring is perhaps the most significant negative outcome of a burn injury. Scarring affects one's quality of life through disfigurement, which in turn, can lead to lowered self-esteem, social isolation, prejudicial societal reactions and job discrimination. Scarring also has profound rehabilitation consequences including loss of function, impairment, disability, and difficulties pursuing recreational and vocational pursuits. Children, young adults and people with pigmented skin are particularly vulnerable to scarring. There is essentially no known early treatment, leaving

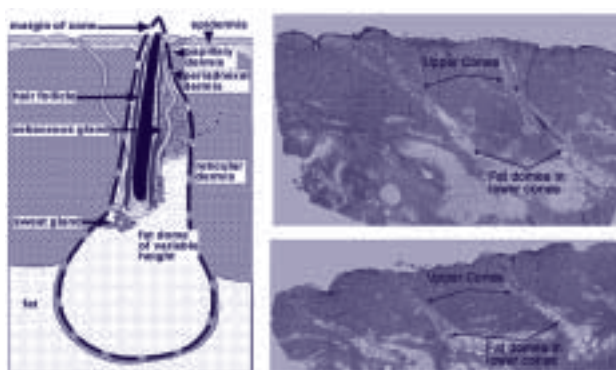


FIGURE 1: The Cones of Skin, Schematic and in vivo

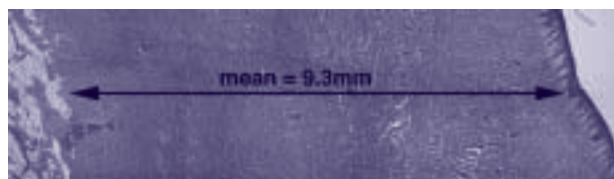


FIGURE 2: Thick Scar in Female, Red Duroc Pig

the only option to be reconstructive plastic surgery. It is clear that new, prospective approaches to this devastating problem, which allow us to intervene before permanent scarring occur, are necessary. In fact, the impact of scarring is so profound that until steps are taken to greatly reduce or eliminate scarring all together, efforts to enhance rehabilitation of burn survivors will remain palliative at best.

Hypertrophic scars are hard, raised, red, itchy, tender, and contracted. They are ugly and uncomfortable and may regress, but never totally go away (Fig. 3). Histologically, increased fibroblasts, collagen and other extracellular proteins characterize hypertrophic scars.

Hundreds of studies of collagen and fibroblasts in human, hypertrophic scar have been done over the past twenty years, but the pathophysiology of hypertrophic

scarring remains unknown. One fundamental reason is the lack of an animal model, which means that human tissue must be used for all laboratory studies. Human tissue cannot be obtained in a systematic and orderly fashion and at best is obtained only on a convenience basis. This severely hampers any laboratory studies.

Hypothesis: Scarring in the female, red Duroc pig is a model of human, hypertrophic scarring and can be used to verify that the cones of skin are related to hypertrophic scarring and to determine the etiology of hypertrophic scarring.

Specific Aim 1: To confirm that cutaneous scar in the female, red Duroc pig is similar to human, hypertrophic, cutaneous scar.

One reason for our lack of understanding of hypertrophic scarring is that tissue for study has historically been obtained from humans undergoing scar revision. This has been necessary since there is no useful animal model. This means that tissues are obtained on a convenience basis without order or control, which prevents systematic study of the hypertrophic scarring process. Nearly 30 years ago, Silverstein, Goodwin, Raulston, and Pruitt reported that deep donor sites in 12/12 female, red Duroc pigs healed with hypertrophic scarring (Hypertrophic scar in the experimental animal. The ultrastructure of collagen. J.J. Longacre. Springfield, IL, Thomas). No manuscripts either confirming or disproving this model have since appeared in the literature.

Because the acquisition of human, burned tissue in a systematic and controlled fashion is so difficult, and our understanding of hypertrophic scarring is limited, this animal model must be confirmed. We will do this by



FIGURE 3: Hypertrophic Scar

factor one in the scar of the female, red Duroc pig harvested on post-wounding days 0, 7, 14, 21, 28, 60, 90, and 150 to that reported in the literature for human, hypertrophic scar.

Specific Aim 2: To confirm that cutaneous scarring in the female, red Duroc pig and/or human, hypertrophic, cutaneous scarring involve the cones of skin.

A second reason for our lack of understanding of the etiology of hypertrophic scarring is that, in the past, most tissue has been minced and homogenized thereby destroying skin anatomy and homogenizing all cell populations. Thinking that skin architecture and cell location/orientation might be important to understanding the cause of hypertrophic scarring, we reviewed skin anatomy to include the cones. The cones were described in the early 1900s and re-discussed in the mid-1900s with little interest. In fact, most studies of human, hypertrophic scar either ignore the anatomy

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comparing the clinical appearance; histology; immunohistochemical localization of decorin, versican, transforming growth factor beta one, insulin-like growth factor one, and constitutive and inducible nitric oxide synthase; in situ hybridization of decorin and insulin-like growth factor one; and quantification of transforming growth factor beta one and insulin-like growth

totally or mince the tissue thereby destroying the structures.

We recently revisited the cones of skin and re-described the contents that include hair follicles, sebaceous glands, sweat glands, and a fat dome continuous with the hypodermis. More importantly, we demonstrated that these cones are located where hypertrophic

scar occurs and are not present in those anatomic locations where hypertrophic scarring does not occur. Since these structures are anatomically related to hypertrophic scarring and since our understanding of hypertrophic scarring is so minimal, we believe the cones must be examined in relation to hypertrophic scarring. We will test the relationship by in situ hybridization of collagen I and III mRNA and immunohistochemical localization of transforming growth factor and insulin-like growth factor one in tissues from the female, red Duroc pig and humans.

Specific Aim 3: To determine which genes related to wound healing are up or down regulated in the cones in cutaneous scar in the female, red Duroc pig and in human, hypertrophic, cutaneous scar.

Third, if the cones are related to scarring, genes related to scarring should be up or down regulated within or around the cone tissues. Previous studies of hypertrophic scar have utilized tissues minced and homogenized which totally destroyed the cone structure and any observations related to that structure. We will dissect the cones out of the surrounding mass of scar collagen by laser capture microdissection and study cone tissues in isolation utilizing gene arrays to assess gene expression within this cone tissue in tissues from the female, red Duroc pig and humans. We will give special attention to those reported to be related to wound healing, some of which were mentioned earlier, but will also study those not suspected to be significant in this regard.

Model System Topics

UW Burn Injury Rehabilitation Model System

There is very little data available on the long-term outcome of burn injury. In 1993, 1997 and 2002, the National Institute on Disability and Rehabilitation Research (NIDRR) of the Department of Education funded burn model systems in order to obtain related outcome data. The UW Burn Center was awarded funding at all three time points and now we have a fourteen-year history of burn model system research matched only by the Burn Center at UT Southwestern. Current funding is \$300,000 per year for five years. A large portion of this money funds UW personnel that gather and process clinical research data. The model system research conducted at the UW Burn Center at Harborview covers burn care from injury to discharge from outpatient care with particular attention to rehabilitation and outcomes.

Our Model System grant includes six projects managed by five faculty including Drs. Engrav, Gibran,

Patterson, Esselman and Wiechman. The Research Nurse Supervisor is Gretchen Carrougner, RN, MN. Drs. Kowalske, Fauerbach, Herndon and Lezotte are the other NIDRR Burn Rehabilitation Model System PIs.

- *Project 1* is entitled "A New Approach to the Etiology of Hypertrophic Scarring". The general aim for this project is to develop an increased understanding of hypertrophic scarring. To accomplish this objective, this project will focus on confirming that scarring in the red Duroc pig is similar to human hypertrophic scar and that the hypertrophic scarring process involves the cones of the skin.

- *Project 2* is entitled the "Effect of Virtual Reality on Active Range-of-Motion During Physical Therapy". At this institution our team of investigators has originated the use of distraction via immersive virtual reality as an adjunctive non-pharmacologic analgesic. Within this study, we will test the hypothesis that virtual reality will allow patients to tolerate greater stretching during physical therapy compared to no distraction, and that in spite of achieving greater range-of-motion, patients will still experience lower pain levels while in virtual reality.

- *Project 3* is entitled "Determination of Reasons for Distress in Burn-Injured Adults". This study will identify reasons behind a burn survivor's distress at various time-points after hospital discharge. Results of the study will allow us to better devise and implement interventions to improve the quality of life for burn survivors.

- *Project 4* (collaborative) is entitled "Barriers for Return to Work". This project will identify specific barriers to return to work for burn survivors. Recognition of such barriers is the first step in addressing the educational needs of survivors, medical rehabilitation professionals, employers, governmental agencies, and third-party payers.

- *Project 5* (collaborative) is entitled "Acute Stress Disorder Among Burn Survivors". The focus of this project will to evaluate the effectiveness of cognitive-behavioral therapy, relative to a non-directive, supportive therapy control group, and a national comparison sample in reducing the prevalence of post traumatic stress disorder diagnosis and symptom severity. The University of Washington Burn Injury Rehabilitation Model System will participate as part of the national comparison sample.

- *Project 6* is participation in the national burn rehabilitation database. The Burn Center staff listed above play a major role in gathering this data.

The UW Burn Rehabilitation Model System web

page may be viewed at <http://depts.washington.edu/uwnidrr/index.html>.

Selected Clinical Topics Since Last Years Report

Prevalence of Hypertrophic Scarring

Abstract – Hypertrophic scarring after burns remains a major problem and is considered to be “common”. Pressure garments are commonly used as treatment even though there is little sound data that they reduce the prevalence or magnitude of the scarring. In 1999 we began a study of the efficacy of pressure garments on forearm burns. After studying 30 patients, mainly white adults, we found no hypertrophic scar in either those treated with pressure or without.

This prompted us to review the literature on the prevalence of hypertrophic scarring after burns and found only four articles with a relatively small number of patients and only three geographical locations. It became clear that the prevalence of hypertrophic scarring is really unknown. We then did a retrospective study of 110 burn survivors and counted all hypertrophic scars of all sizes and locations in all races and found the prevalence of hypertrophic scarring to be 67% which conflicts with the published reports and our prospective study and suggests that further research is necessary. We concluded that a worldwide, prospective survey is necessary to establish the prevalence of hypertrophic scarring after burns. In this article we are calling for and offering to organize this survey.

Efficacy of Pressure Garment Therapy

Despite marked improvement in mortality statistics for major burn injuries over the past two decades, comparatively little progress has been made in improving

the scarring, which results from healed, burn wounds. Hypertrophic scars are raised, thickened and hard and are often associated with joint contractures and other anatomic disfigurement. They constitute a major source of morbidity for the otherwise “healed” burn patient, leading to significant functional impairment and cosmetic deformity. Of all the factors that hinder return to work after a burn, hypertrophic scarring is clearly among the most problematic.

The routine use of pressure garments has become the worldwide standard of care in treating healed burns, skin grafts, and donor sites. Yet, no controlled studies have been performed that verify the efficacy of such treatment. Pressure therapy is complex, problematic, and expensive. Therefore, its use cannot be justified solely on the basis of case reports, retrospective studies, and anecdotal data. Presently, the decision to prescribe pressure garments is made on the basis of individual/institutional experience and, in some centers, is ordered for most all patients. Other centers never use pressure garments. Clearly, there is a need to determine whether or not pressure therapy is truly efficacious in reducing hypertrophic scarring and the aesthetic and functional consequences of its use.

The project objective is to determine the efficacy of pressure garment therapy in the prevention of hypertrophic scarring in burn scars and skin grafts in burn-injured children and adults. We hypothesize that pressure garment therapy reduces the degree of hypertrophic scarring and will study the outcome with and without pressure on burns of the upper extremity allowed to heal spontaneously. The International Association of Fire Fighters has funded this project. Gretchen Carrougher and Meryl Moore direct this project.

RELATED PUBLICATIONS

1. Bombaro, K.M., Engrav, L.H., Carrougher, G.J., Wiechman, S.A., Faucher, L., Costa, B.A., Heimbach, D.M., Rivara, F.P., Honari, S. What is the Prevalence of Hypertrophic Scarring Following Burns? *Burns*, 2003; 29(4):299-302.

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