IN SITU TISSUE ENGINEERING WITH INTEGRA® - A NEW PARADIGM OF SURGICAL WOUND REPAIR

Marc E. Gottlieb, MD, FACS
Phoenix, AZ

Arimedica version, May, 2005.

Contacts:

Marc E. Gottlieb, MD, FACS
Plastic Surgeon, Phoenix, Arizona

Phone: 602-252-3354
Fax: 602-254-7891

Email: megott@arimedica.com

IN SITU TISSUE ENGINEERING WITH INTEGRA® - A NEW PARADIGM OF SURGICAL WOUND REPAIR

Abstract

The Problem. The paradigms of surgical wound closure are direct repair, grafts, and flaps. The core subject of plastic surgery, these distinct modalities are a sophisticated art that can reliably close any healthy wound. The caveat is that ordinary surgery implicitly depends on competent wound healing. With pathological wounds, those due to vascular, hematological, immunopathic, and other ulcerogenic diseases, these modalities may not work. The operation is threatened if wound healing is retarded, and incisions and donor sites are subject to morbidity from active disease. Disease and risks may limit potential donor tissues, sustain inflammation and lysis, restrict circulation, or make the patient too ill for elaborate procedures.

A Solution. Integra® collagen-chondroitin matrix has ideal properties for managing chronic pathological wounds: a high grade artificial skin; survives disease and conditions where grafts die; performs the coverage duties of flaps without donor sites; minimizes nursing care; suppresses inflammation, wound healing, and scar; induces embryonic dermatogenesis. Risk free to the recipient, it is safe where disease and altered anatomy make conventional closure impossible or unsafe. It's indications, use, results, and conceptual basis make it a distinct fourth paradigm of surgical wound closure: in situ tissue engineering. Understanding when a flap should but cannot be used is to understand when Integra should be used.

The Study. Using a consistent set of indications and management scheme, Integra was used for chronic pathological wounds in 111 patients (158 individual ulcers, 166 instances of exposed anatomical structures, diverse diagnoses). Success rate was: 92% of patients healed; 90% of open structures healed. Inpatient services were nearly eliminated.

Conclusion. Integra is not an alternative to conventional repair, grafts, and flaps. As a method of tissue engineering, it is a new and equal paradigm of care with its own indications and contraindications, and a superior safety and success profile. Repair, grafts, and flaps, which require wound healing competency, are best suited for healthy and acute wounds. For many chronic and pathological wounds, in situ matrix-guided histogenesis is the best method, and surgeons must begin working this into their practices.

THE CONVENTIONAL PARADIGMS OF SURGERY

Surgery of Repair

Topical care in support of natural contraction underlies all wound management. When wound repair surgery is needed, all conventional operations can be reduced to three technical or biological paradigms:

PARADIGM #0: NATURAL CONTRACTION

The body is programmed to heal. If the subject is healthy, a wound will close by the natural process of contraction and epithelialization.

Example: Young healthy man; wrist drained for suppurative synovitis from a wood splinter; healed with basic hygienic care.

PARADIGM #1: SIMPLE REPAIR

Simple repair is the reduction and approximation of wound margins. Physiological wound healing then amalgamates the coapted edges. Most surgery and trauma is closed this way.

Example: Child with a dogbite of the thigh. After a period of preparational care, the wound was closed by simple suture.

Pros:
Technically rapid and simple.
Efficient and economical.
No donor sites.
Preserves future options.
Minimum loss or setback if it fails.

Cons:
Depends on a healthy host and wound.
Tissue may be insufficient to close.
Wound complexity might prevent it.
Wound pathology apt to cause failure.

THE CONVENTIONAL PARADIGMS OF SURGERY

PARADIGM #2: GRAFTS

A graft is a graft because it has no anatomical attachment to the host, no circulation of its own, and cannot live independently away from a recipient wound. Skin grafts are used mainly for convenient wound closure in a healthy host and wound.

Example: Closure of a healthy healing wound of the ankle after revascularization.

Pros: Convenient and pragmatic.
Can be a renewable resource.
Preserves future options.
Minimum loss or setback if it fails.

Cons:
Grafts depend on the recipient wound, so the wound must be healthy and non-pathological.
Grafts do not carry the "machinery" of repair, so the target must be wound healing competent.
Grafts do not survive on an incompetent wound.
Grafts have special technical requirements.
Prone to scar contracture and late complications.
Donor site required.

PARADIGM #3: FLAPS

A flap is a flap because it maintains an anatomical attachment to the host, carrying its own circulation, living independent of the recipient wound. Flaps are used when normal tissue qualities are needed, when the target has exposed structures, and when the target is wound healing incompetent.

Example: Wound healing incompetent hand, and exposed tendons, after adriamycin infiltration; closed with a groin flap.

Pros:
Can transport large volumes of tissue.
Retain original characteristics and mechanics.
Independently initiate and execute wound repair.
Do not depend on the competence of the wound.
Healthy flaps usually trump pathological wounds.

Cons: Significant donor sites.
Many technical caveats and finesse.
Comorbidities and patient risk may prevent flaps.
Systemic pathologies can kill flaps, and systemic wound healing disorders apt to cause failure.

PROBLEMS THAT CANNOT BE SOLVED BY CONVENTIONAL SURGERY

The Nature of Chronic and Pathological Wounds

There is a paramount distinction between:

Healthy wounds

benign, trauma or incidental
acute, without persistent injury

wound healing competent

Healthy wounds can heal by themselves, or with basic surgery (simple repair and grafts)

Pathological wounds

morbid, due to active disease
chronic, continuing active injury

wound healing incompetent

Pathological wounds may require remote flaps of healthy tissue; for some, surgery must be avoided.

A: Chronic venous ulcer, factor V Leiden, obesity in a young man. Flaps are indicated and will heal the wound, but: no local flap is big enough; high risk of free flap donor morbidity; high risk of flap thrombosis.

B: Diabetes, hand atherosclerosis, open tendons and joints. Flaps are indicated and will heal the wound, but: local flaps not big enough; flap failure likely due to vascular disease; no place to hang a free flap.

C: Severe rheumatoid panniculitis, concurrent atherosclerosis. Only free flaps eligible, likely to fail from vasculopathy. Active immunopathy will complicate healing. Flaps nominally indicated, but assured to fail.

D: Severe atherosclerosis. Local flaps will fail. Free flaps at risk. Persistent inflammation and necrosis, despite care, portend failure if a flap is tried. Comorbidities interdict a major procedure.

In these four examples, an option is needed that is both less risky and more likely to succeed.

PROBLEMS THAT CANNOT BE SOLVED BY CONVENTIONAL SURGERY

Reasons why flaps cannot or should not be done, even if indicated for the wound:

Available flaps may not reach the target. • Available flaps not large enough for the target. • Local vascular anatomy precludes good flap design. • Atherosclerosis may prevent anastomosis of a free flap. • Illness and comorbidities make the patient too high risk. • Flaps can sacrifice useful parts and create disabilities. • Failed flaps waste anatomy and limit further options.

Reasons why flaps or any wound surgery will fail, and are thus contraindicated:

Potential flaps are within the zone of injury. • Inflammation and disease can threaten a flap. • Vascular disease can kill a flap. • Hematological disorders can kill a flap. • Connective tissue disorders and wound pathologies will prevent healing or cause progressive ulceration. • Any other disease or disorder causing the pathological wound will cause comparable problems for the repair. • Similar risks for the donor site, enlarging the problem.

Axiom 1: There are three conventional paradigms of wound repair surgery: direct closure, grafts, and flaps.

Axiom 2: These paradigms have a common biological basis: all three depend on the physiological process of reactive wound repair – the post-inflammatory proliferative wound module of fibroplasia and contraction – aka "inflammatory wound healing".

Axiom 3: Simple repairs and grafts succeed when host and target are healthy and wound healing competent.

Axiom 4: When the target is pathological and incompetent to heal, but the host is generally healthy, then repair and grafts will fail, but healthy flaps succeed.

Axiom 5: When systemic illness or wound healing pathologies are the basis of the chronic problem wound, then none of the classic paradigms of surgery will work.

Surgery cures many problems and should be used when appropriate.

For some problem wounds, conventional surgery can solve the problem, but it might be best avoided due to unreasonable risks of failure or risk to the patient.

There are some problem wounds that conventional surgery simply cannot solve.

Flaps, the romantic heroes of reconstructive plastic surgery, have a pivotal role in the closure of complex wounds,

When the stakes are high for successful closure, good flaps get the job done.

. . . BUT . . .

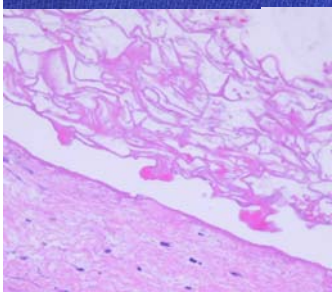
There are times when flaps simply cannot be done or will not survive.

BIOLOGICAL BASIS OF INTEGRA

Integra Artificial Skin: Distinct Biological Behaviors

Integra Artificial Skin arrests inflammation and normal wound repair. Under Integra, a tissue defect ceases to be a physiological wound. Integra induces the process of embryonic histogenesis, resulting in a regenerated tissue comparable to normal dermis, and distinct from scar.

Integra is a Bilaminar Surface Implant



Layer 1 **Collagen-GAG Matrix (CGM)**
(a sponge of type 1 collagen & chondroitin-C)

Layer 2 **Silicone rubber "epidermis"**
(temporary, eventually replaced with autogenous epidermis)

Integra has remarkable properties:

Complete suppression of inflammation.

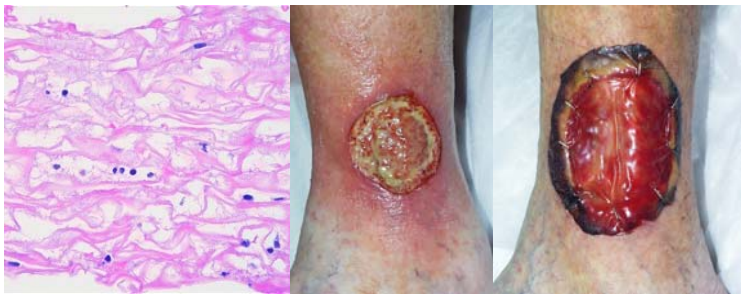
Control of pathological and chaotic wound dynamics.

No inflammation → no wound healing → no scar.

Induces embryonic dermatogenesis.

Acute effects as a high quality artificial skin

Inflammation is consistently eliminated, grossly and histologically. Regenerative cells appear in the matrix, but not inflammatory cells. Inflammation in the host wound never appears. Pathological wound behaviors promptly stabilize. Erythema, pain, and related signs and symptoms cease. Necrosis and ulceration cease.



Inflammation, pathological wound behavior, and normal wound repair all cease.

BIOLOGICAL BASIS OF INTEGRA

Integra Artificial Skin: Distinct Biological Behaviors

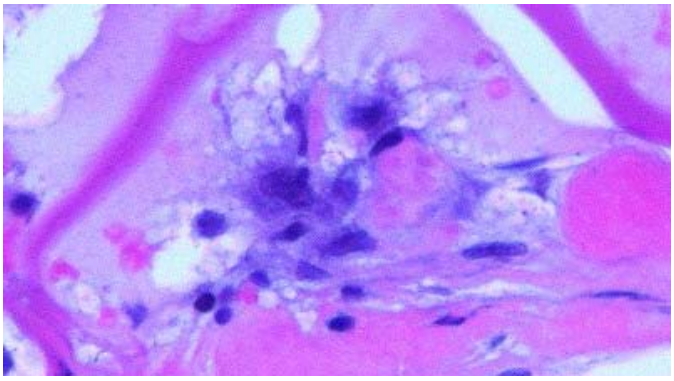
Subacute effects – histogenesis and dermal regeneration

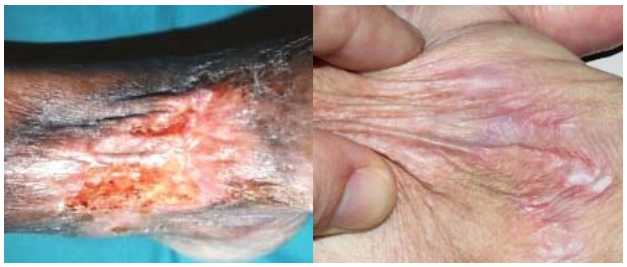
Top row: Note regenerating and healed Integra compared to granulation tissue and scar that occurred in seams between pieces of Integra. Normal wound module is densely vascular. Integra remains pale due to correct vascular density, as occurs embryologically.

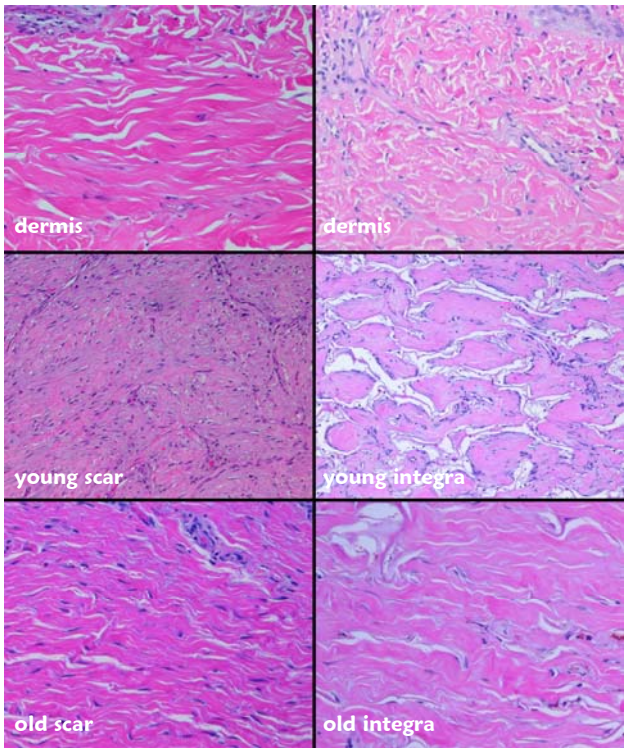
Second row: Normal scar, tightly packed with stiff collagen, compared to regenerated Integra, which is porous, remaining soft and compliant, comparable to dermis and other normal histogenetic tissues.

Bottom group: Normal dermis compared to young and old scar and Integra. While both remodel back to dermis over many years, Integra is comparable to dermis from the outset, histologically and physically.

Below: The large fimbriated cells, "syncytial fibroblasts", are the key to Integra histogenesis. Histologically identical to embryonic dermatoblasts, these cells NEVER appear in a normal post-inflammatory wound.







Integra = dermis, not scar

No wound healing = no scar
Syncytial fibroblasts
Embryonic dermatogenesis

CLINICAL EFFECTS OF INTEGRA

Integra can Survive and Tame Harsh Wound Conditions

By closing defects, and suppressing inflammation and recognition of the wound, Integra eliminates inflammatory stressors on the wound, thereby allowing chaotic dynamics to stabilize in a benign state, permitting pathological wounds the chance to recover and regenerate.

Integra has remarkable properties:

Single device has dual role:

first, it is a high grade acute artificial skin

it then becomes the agent of skin regeneration and reconstruction.

Not alive, so it is tolerant of adverse wound conditions.
"Hides" the wound from the host.
Complete suppression of inflammation.
Control of pathological behavior and chaotic wound dynamics.

No inflammation ➞ no wound healing ➞ no scar.
Embryonic dermatogenesis ➞ dermal equivalent.
No contraction.
Tangential histoconduction.

Recall the reasons why flaps, grafts, and other repairs could not or should not be done, compared to the effects of Integra.

Persistent disease or inflammation prevent repair.
Integra is not alive, so it tolerates harsh conditions. It suppresses residual inflammation.

Local conditions will not support a graft.
Not alive at the outset, it survives where grafts fail.

Flaps not large enough or may not reach the target.
Not autogenous; quantity, procurement irrelevant.

Continued . . . . . .

Example, suppress inflammation. Advanced rheumatoid arthritis, factor V Leiden, and low proteins C & S. Ankle wound refractory to multiple therapies. Complete arrest of inflammation with Integra. The healed reconstruction endured disease flare-up, even as other areas ulcerated (opposite ankle).

CLINICAL EFFECTS OF INTEGRA

Recall the reasons why flaps, grafts, and other repairs could not or should not be done, compared to the effects of Integra.

. . . . . **Continued**

Illness and comorbidities make surgery too risky.
Placing Integra is simple, with no physiological tax.

Flaps can sacrifice useful parts and function.
No autogenous tissue donation.

Failed flaps waste anatomy and limit further options.
No autogenous tissues. No failures, no waste.

Inflammation and disease can threaten a flap.
Because it is not alive, tolerant, and suppresses inflammation, Integra is preferred in these conditions.

Vascular disease can kill a flap.
Circulation-independent, survives where flaps cannot.

Hematological disorders can kill a flap.
Not alive, tolerant of incidental pathology and injury.

Connective tissue disorders and wound pathologies will prevent healing or cause progressive ulceration.
Not only tolerant of incidental pathology and injury, Integra has a potent ability to withstand effects of connective tissue immunopathy and pathology.

Any disorder which caused the pathological wound will cause comparable problems for the repair.
Integra not dependent on normal wound repair physiology – suppresses repair, induces histogenesis.

Similar risks for the donor site, enlarging the problem.
No donor sites, no risk.

Risk of contractures after grafts.
Regenerates dermis, not scar. No contractures.

Example, control pathological behavior. Granulomatous panniculitis of leg, of uncertain etiology. Many failed skin grafts, with persistent inflammation, exudates, and marginal necrosis. Complete arrest of pathology after Integra. Healed reconstruction after epidermal overgrafts.

Example, tangential histoconduction. Open plate and ankle fracture. Standard "textbook care" requires flaps, but multiple free flaps failed. Integra matrix supports horizontal histoconduction, used to here grow new tissue over the open structures. Long term stable healed result, plate still in.

INTEGRA VERSUS CONVENTIONAL SURGERY

Integra: Successful Surgery when other Options Fail

There are problem wounds that conventional surgery cannot solve.
There are times when flaps cannot be done or will not survive.

Then what ?

Understanding when a flap should be used, but cannot be used, is to understand when Integra should be used in lieu of conventional surgery.

In each of these cases, conventional plastic surgery rules dictate a flap to close exposed essential structures, restore function, or salvage limbs. ***In each, caveats of disease and local anatomy militated against flaps***. Because Integra can circumvent most of these exceptions, ***each case had a successful outcome by reconstructing skin with Integra***.

A. Diabetes, hand atherosclerosis; open bone, tendons, joints.
Caveats: Any incision on this hand is prone to pathergy and necrosis (why the hand is this way to begin with). Even if safe to incise, local flaps are not big enough, flap failure is likely due to vascular disease, and there are no recipient vessels for a free flap. The patient cannot afford to lose more of the hand.

B. Scleroderma, vasculopathy; open MP joint, bone, tendons.
Caveats: Any incision on this hand is prone to pathergy and necrosis. Local flaps will not move as expected, due to sclerotic skin. Hand is severely disabled, and cannot afford further loss. Active immunopathy puts wounds and autogenous repair at risk.

Continued on next page . . . . . .

C. Wegener's granulomatosis, severe pulmonary disease, achilles ulcer.
Caveats: Active immunopathy puts wounds and autogenous repair at risk. Patient's general condition prevents any prolonged surgery and anesthesia.

INTEGRA VERSUS CONVENTIONAL SURGERY

Understanding when a flap should be used, but cannot be used, is to understand when Integra should be used in lieu of conventional surgery.

D. Chronic venous ulcer, open tibia, factor V Leiden, obesity in a young man.
Caveats: Skin grafts will fail. Local flaps too small. Latissimus free flap disabling in a young working man. Omentum and rectus abdominis free flaps prone to ventral herniation in an obese patient. High risk of flap thrombosis.

E. Sweet's neutrophilic dermatosis and rheumatoid, chronic thrombocytosis, chronic ankle ulcer, open joint and bone, prior failed skin grafts and free flap.
Caveats: Skin grafts will fail. Local flaps not big enough. Active immunopathy puts wounds and autogenous repair at risk. Free flap at high risk of thrombosis.

F. Aorto-iliac occlusive disease, thigh necrosis after incremental amputations.
Caveats: Any incision on this thigh is prone to pathergy and necrosis. Local flaps and repair will die. Latissimus free flap contraindicated in a wheelchair bound patient, but moot because there is no connection for a free flap.

G. Diabetes, vascular disease, forefoot ulcer, abscess; transtarsal amputation, with open osteotomies and joints.
Caveats: Incisions on this foot prone to necrosis and wound failure. Local flaps are not big enough, and are not safe due to vasculopathy. A free flap is uncertain, and cardiovascular comorbidities make a major procedure unwise. Skin grafts are disallowed over the open joints.

H. Foot necrosis from vascular disease, after successful distal bypass.
Caveats: No local flaps. Skin grafts ineligible over bone and joint. Potential free flap, plugged into the bypass graft, but avoidable prolonged procedure inadvisable due to cardiovascular risks

IN-SITU TISSUE ENGINEERING: A FOURTH INDEPENDENT PARADIGM OF SURGERY

Integra: not an Alternative, but the Indicated Option

In the cases presented, Integra was neither a substitute, an alternative, a capitulation, nor a poor last choice for surgical wound closure. Integra was the preferred option, because it was the most suited modality – superior results with less risk – for the given patients and problems.

Integra is ideally suited to chronic and pathological wounds, as attested by the good outcomes of this recent study of 120 patients in which Integra was used to close the chronic wounds.

In this study, 90% of exposed bones, joints, tendons and organs were successfully closed.

If patients now recognized as poorly selected are excluded (extreme arterial insufficiency, and diabetic plantar ulcers), the success rate for healed wounds was 92%.

Integra for chronic pathological wounds - Outcomes, by diagnosis

Diagnostic category (% of patients per category)	**fully healed**	**> 2/3 healed**	**< 2/3 healed**	**failed**
Macro-arterial	58	8	16	18
Immunopathic	74	16	5	5
Venous / lymphedema	88	---	6	6
Hypercoagulable	86	---	14	0
Mechanical / anatomical	88	12	---	0
Radiation / malignancy	72	28	---	0
Diabetes / neuropathy	0	20	40	40
Unknown	60	20	20	0
Micro-occlusive	100	---	---	0
Trauma / surgery	100	---	---	0
Granulomatous / infectious	50	50	---	0
Adjunct	100	---	---	0
Total	**71**	**10**	**10**	**9**

Gottlieb ME, Furman J: Successful Management and Surgical Closure of Chronic and Pathological Wounds Using Integra®. Journal of Burns & Surgical Wound Care, 3:2, 2004. (journalofburnsandwounds.com).

Gottlieb ME. Management of Complex and pathological Wounds with Integra. In: Lee BY, ed. The Wound Management Manual. New York, McGraw-Hill, 2004: 226-289. (ISBN 0-07-143203-5).

IN-SITU TISSUE ENGINEERING: A FOURTH INDEPENDENT PARADIGM OF SURGERY

Integra: not an Alternative, but the Indicated Option

These good results are accompanied by safety and economy. There is no risk to the patient using Integra, and most chronic wound cases can be managed with outpatient services only.

Integra is a distinct new paradigm of surgical wound closure. Unlike repairs, grafts, and flaps, it is does not depend on normal wound repair. On the contrary, it suppresses normal repair and initiates embryonic histogenesis. It will succeed where the conventional modalities will fail.

Understanding when a flap should be used, but cannot be used, is to understand when Integra should be used in lieu of conventional surgery.

topical care
simple repair - grafts - flaps
in situ tissue engineering

For closing any wound, make choices based on these goals.

keep patient safe
control disease and symptoms
preserve or improve function
preserve or improve lifestyle
heal the wound
do so quickly and efficiently
minimize costs and resources

For pathological wounds, Integra fulfills these goals, and with no risk to the patient.

There are some problem wounds that conventional surgery simply cannot solve.

Flaps remain the heroes of reconstructive plastic surgery.

But for closing problem wounds, Integra is the modern Excalibur.

In-situ tissue engineering

This new paradigm of wound closure most be worked into surgeons' schemas as a preferred option for chronic and pathological wounds.

Integra Dermal Regeneration Template®. Manufactured by Integra Life Sciences, Plainsboro, New Jersey.

Key Points and Summary

Conventional Surgery

Wound repair surgery is based on topical care, plus three classic surgical paradigms: simple repairs, grafts, and flaps.

They have a common biological basis – they all depend on normal physiological post-inflammatory wound repair.

When chronic illness and active disease are creating ulcers, necrosis, and wound failure, and when wound healing is itself inherently sick and pathological, these conventional modes of care will fail.

Integra

Integra Collagen-GAG Matrix (Integra Dermal Regeneration Template) is a surface implant that solves the problem of wound closure for many chronic and pathological wounds.

It is not alive to begin with, so it can endure adverse conditions that autogenous repairs cannot.

It suppresses recognition of injury, inflammation, and inflammatory wound healing. It therefore arrests pathological changes in the tissues to which it is applied. The wound can recover and stabilize.

It also suppresses scar, avoiding the contractures and abnormal biomechanics of conventional wound healing.

It induces embryonic dermatogenesis, and the resulting regenerated tissue has normal non-scarlike qualities.

Key Points and Summary

Integra

Because it is not alive, not autogenous, and does not depend on, and in fact suppresses normal repair, and because it induces embryonic histogenesis, and creates a new tissue from an empty matrix, it is therefore a distinct independent paradigm of wound repair surgery.

It's material and clinical properties give it superior performance and results in closing chronic and pathological wounds.

For many patients and wounds, Integra is not an alternate or secondary treatment, but rather the primary indication.

Understanding when a flap should be used, but cannot be used, is to understand when Integra should be used in lieu of conventional surgery.

Integra's ability to protect a wound, control inflammation, suppress normal wound repair and scar, induce embryonic histogenesis, conduct histogenesis across gaps, withstand future flare-ups of disease, and do so with no risk to the patient is a combination of features unparalleled among surgical and wound products. As a method of in situ tissue engineering, this surgical device is a genuinely new paradigm of wound repair. It is not an alternative to flaps and grafts, but rather an equal option, and all must be selected based on their own merits, indications, and criteria. Integra's biological properties, its safety profile, and its practicality make it the preferred modality for a variety of problems. This is especially true for chronic and pathological wounds, where conventional repair, grafts, and flaps usually fail or are ineligible, but Integra succeeds, oftentimes with a superior final result. Furthermore, Integra succeeds without donor sites nor risk to the patient, and an Integra reconstruction for chronic wounds can be managed almost entirely as an outpatient, with preservation of activity and lifestyle. After 30 years of development and 10 years of clinical use, Integra is no longer a novelty product for burn surgery. It is a versatile surgical tool with unique properties and safety, and Integra should be adopted as a preferred method of closing chronic and pathological wounds.