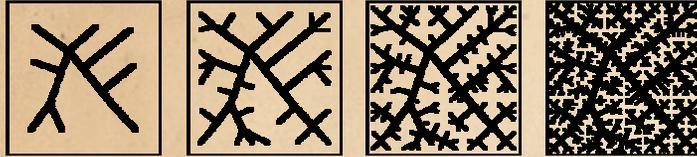


Marc E. Gottlieb, MD, FACS

A Professional Corporation



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In Situ Tissue Engineering with Integra - A New Paradigm of Surgical Wound Repair

Original presentation August 3, 2005, Orlando, FL.

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

Marc E. Gottlieb, MD, FACS Phoenix, AZ

Etherdome of the

*Massachusetts
General Hospital*

October 16th, 1846



*William Thomas
Green Morton*

Gilbert Abbott

*Professor
John Warren*



What would you do?



55 f

fall

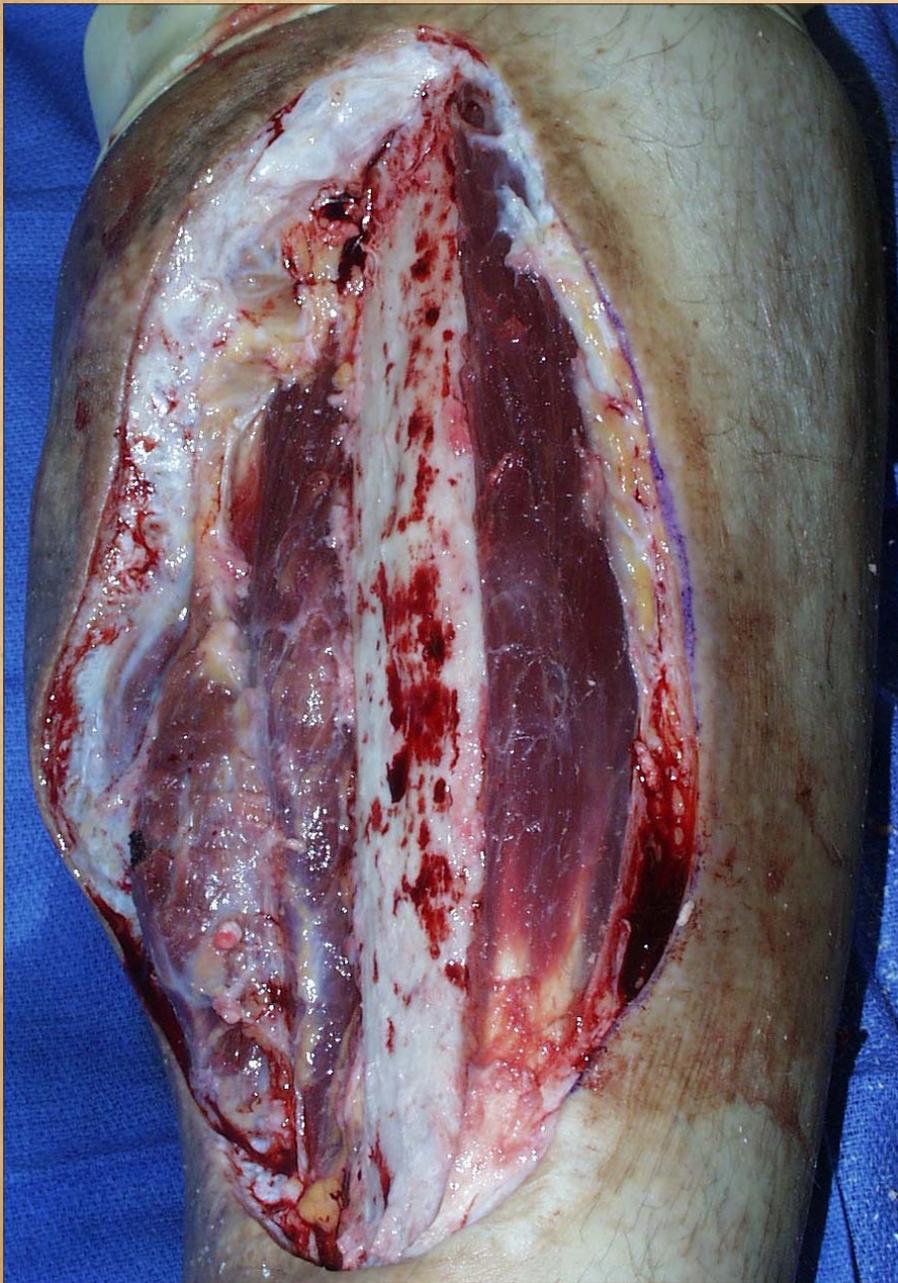
*impact
injury*

*lacerations
and
hematoma*





52 f puncture wound abscess



33 m

*machinery
versus
pedestrian*

*avulsion – degloving
injury*



39 m

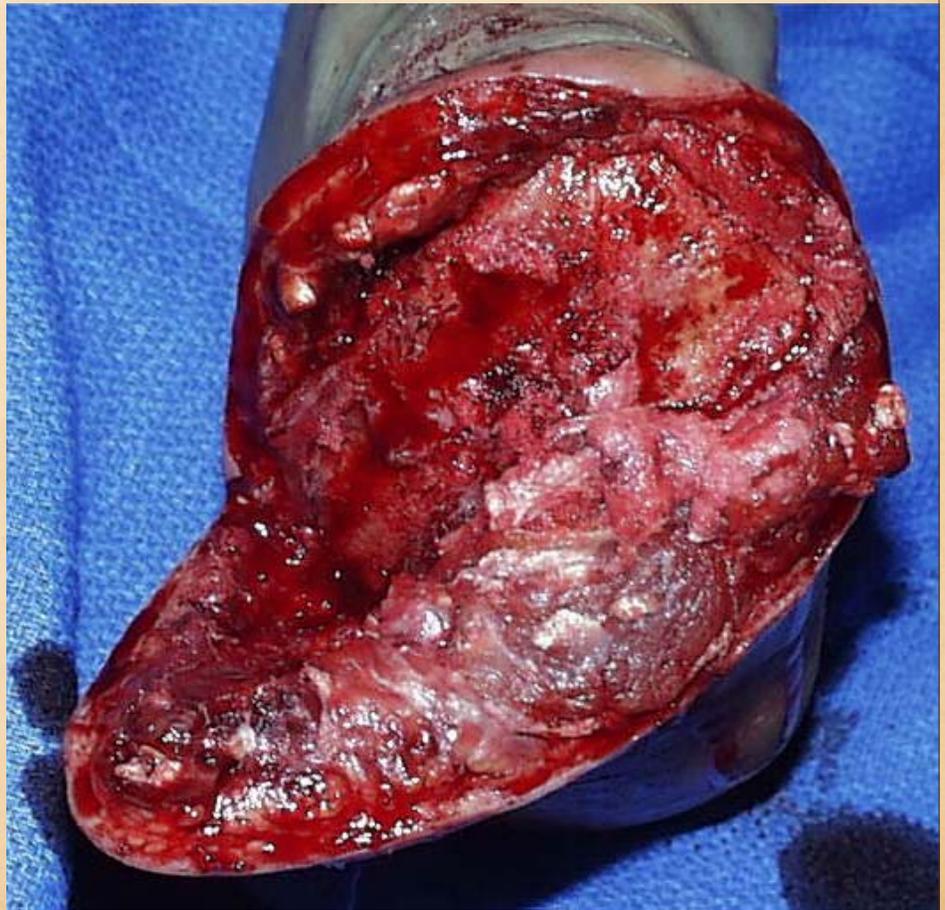
*recurrent
fibrosarcoma
of knee*

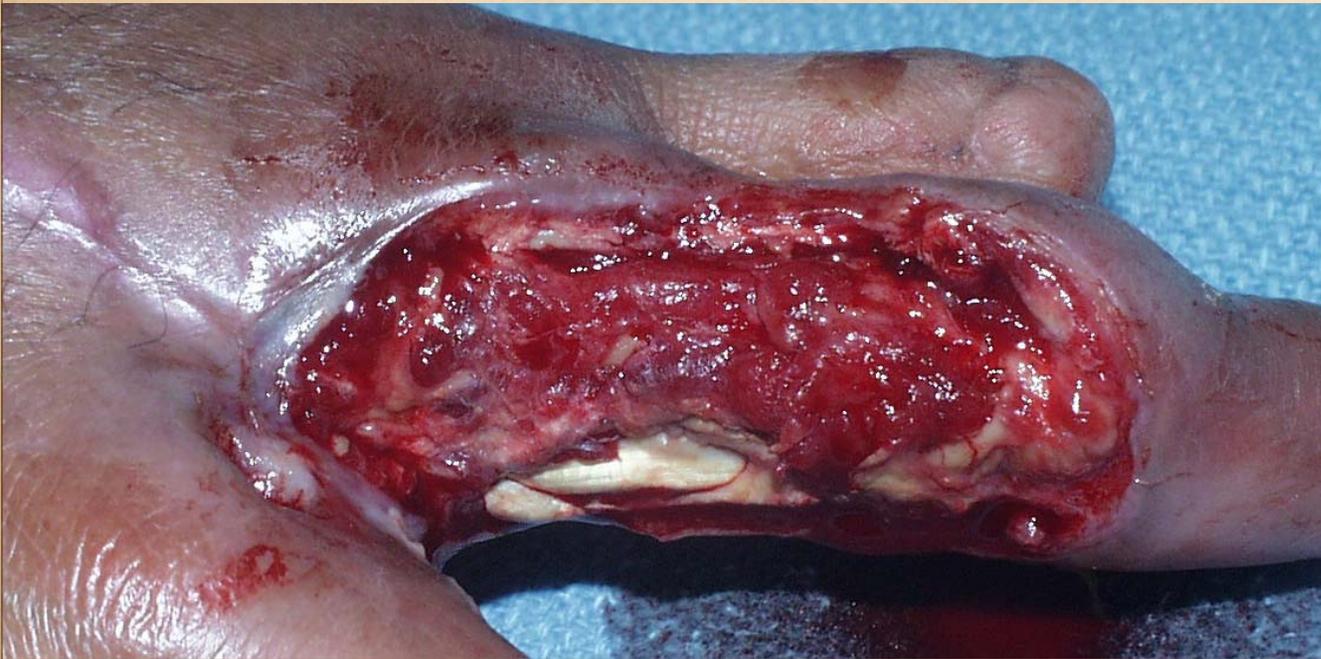
thin flaps

radiation



28 m
traumatic crush of forefoot





42 f

*human
bite
injury*

tenosynovitis



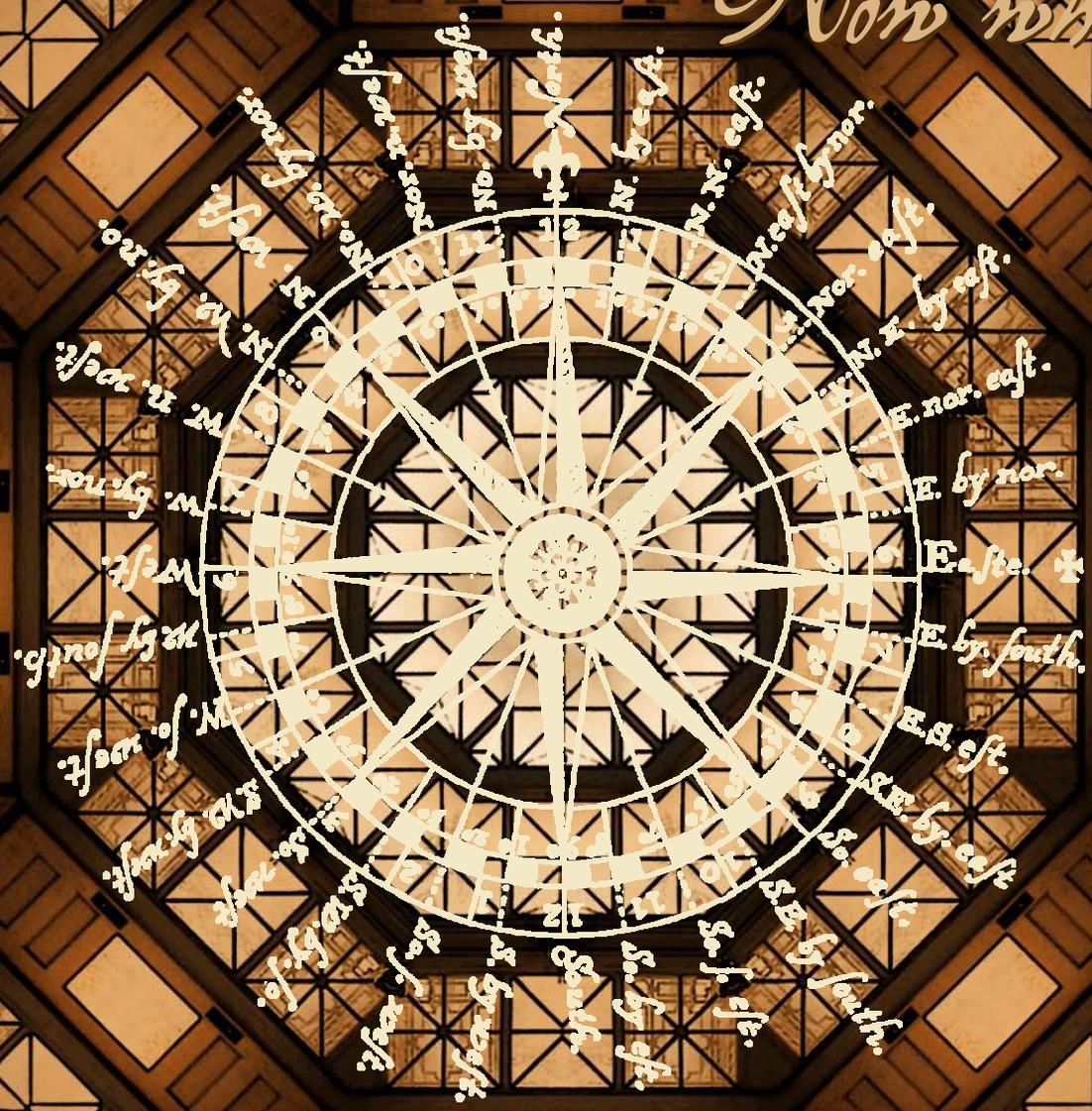
43 m

*motorcycle
injury*

hand abrasion

fractures

Now which way?





65 f

*Wegener's
granulomatosis*

Caveats

Active immunopathy puts wounds
and autogenous repair at risk.

Patient's severe pulmonary
disease prevents any prolonged
surgery and anesthesia.

55 f

fall

impact injury

lacerations, hematoma



67 f

*ischemic
infarction*

Caveats

No local flaps.

Skin grafts ineligible over bone and joint.

Potential free flap, into the bypass graft,
but inadvisable due to cardiovascular risks.

52 f

puncture wound

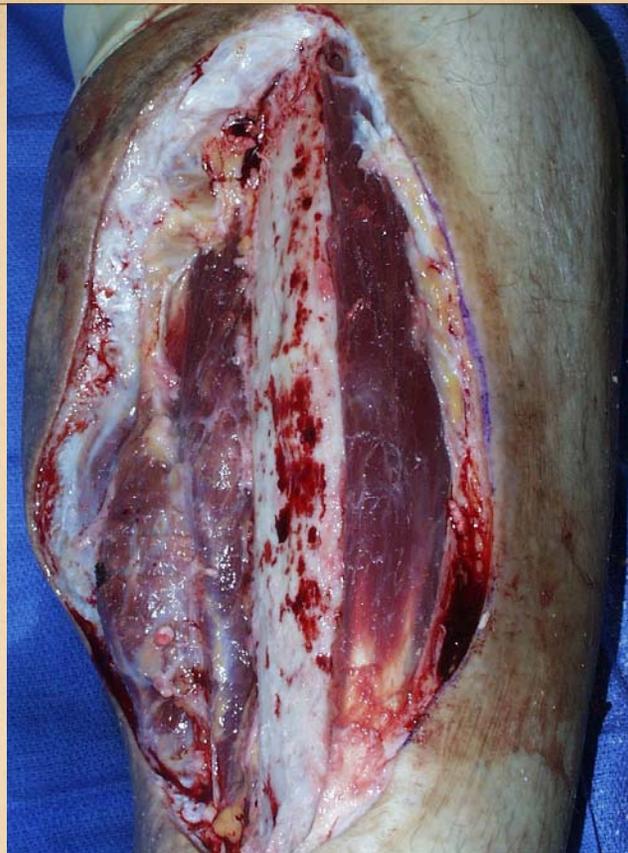
abscess



33 m

*venous
hypertension*

Factor V Leiden



Caveats

Skin grafts have failed. Local flaps too small.
Latissimus f.f. disabling in a working man.
Omentum and rectus abdominis f.f. prone
to ventral herniation in an obese patient.
High risk of any flap thrombosis.



33 m

*machinery versus
pedestrian*

*avulsion –
degloving*



64 m

***aorto-iliac
occlusive disease***

39 m

knee fibrosarcoma

thin flaps

radiation

Caveats

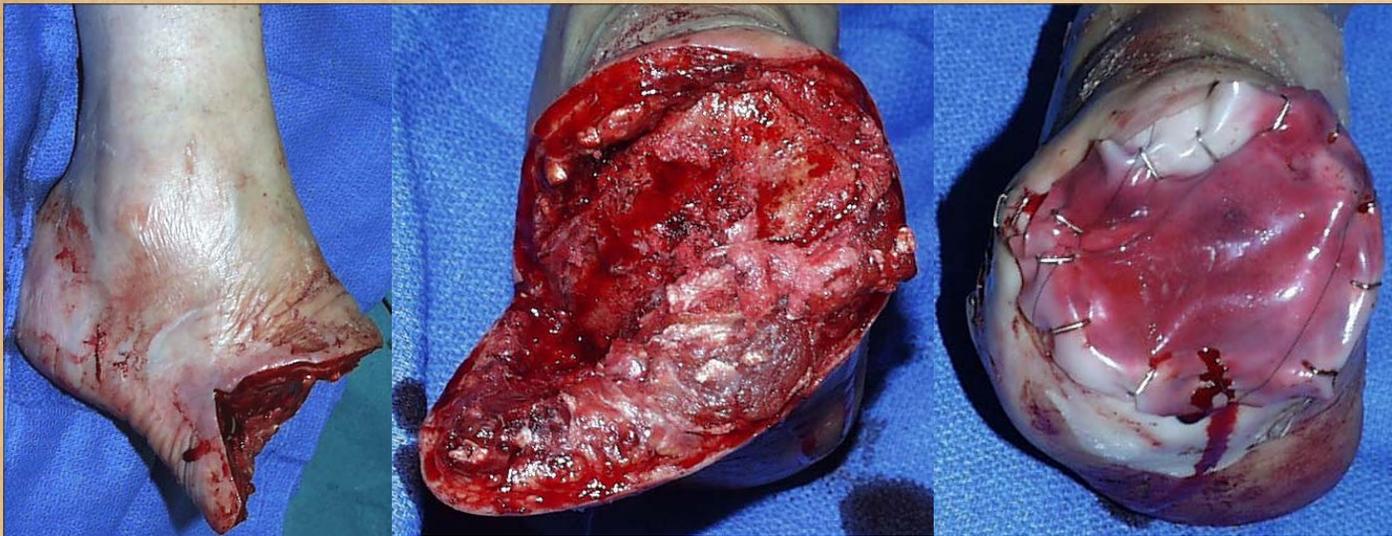
Any incision on this thigh is prone to pathergy and necrosis.

Local flaps and repair will die.

Abdominal flaps (e.g. rectus abdominis) will fail from ischemia

Latissimus free flap contraindicated in a wheelchair bound patient . . .

but moot because there is no connection for a free flap.



*28 m
traumatic
crush
of
forefoot*



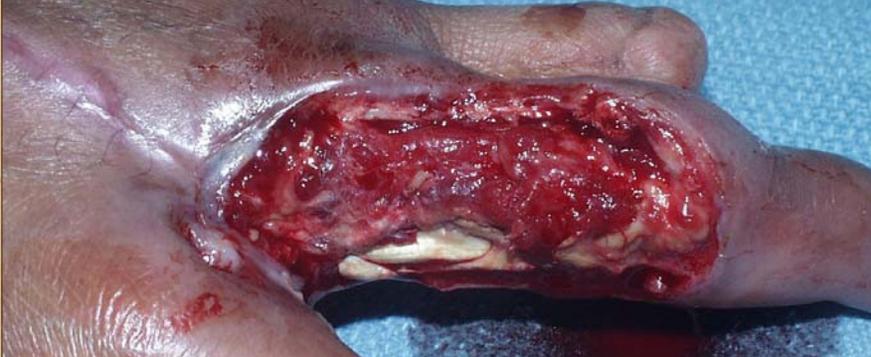
*73 m
embolic necrosis*

Caveats

No local flaps.

Skin grafts ineligible
over bone and joint.

Free flaps precluded by vascular
disease and cardiovascular risks.



Caveats

42 f

diabetes

atherosclerosis

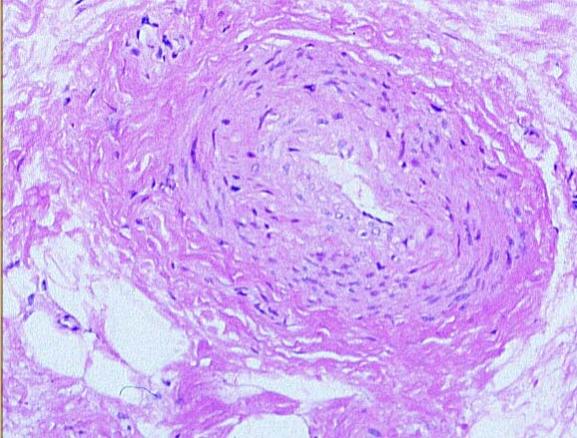
Local flaps are not big enough.
Flap failure likely due to vascular disease.
No recipient vessels for a free flap.

Any incision prone to pathergy and necrosis
(*why the hand is this way to begin with*).
Patient cannot afford to lose more of the hand.

42 f

human bite

tenosynovitis



*43 m
scleroderma
vasculopathy*

*43 m
motorcycle injury
hand abrasion*



Caveats

Any incision prone to pathergy and necrosis.

Flaps will not move properly due to sclerotic skin.

Hand is severely disabled, and cannot afford further loss.

Active immunopathy puts wounds and repair at risk.

INTEGRA VERSUS CONVENTIONAL SURGERY

In each of these cases, conventional plastic surgery rules dictated 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.

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.

Wound Surgery

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: If 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 wound, then none of the classic paradigms of surgery will work.

Clinical Effects of Integra

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 tolerant of adverse wound conditions.

“Hides” the wound from the host.

Complete suppression of inflammation.

Controls pathological behavior & chaotic dynamics.

No inflammation >> no wound healing >> no scar.

Embryonic dermatogenesis >> dermal equivalent.

No contraction.

Tangential histoconduction.

Effects on chronic wounds:

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.

Reasons why flaps, grafts, and other repairs cannot or should not be done.

Persistent disease or inflammation prevent repair.

Local conditions will not support a graft.

Flaps not large enough or may not reach the target.

Local vasculature precludes flap design or execution.

Illness and comorbidities make surgery too risky.

Flaps can sacrifice useful parts and function.

Failed flaps waste anatomy and limit further options.

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 disorder which caused the pathological wound will cause comparable problems for the repair.

Similar risks for the donor site, enlarging the problem.

Risk of contractures after grafts.

Normal repair cannot bridge across voids and alloplastics.

Reasons why Integra can trump the caveats of flaps, grafts, and other repairs.

Not alive; tolerates harsh conditions. Suppresses residual inflammation.

Not alive at the outset - it survives where grafts fail.

Not autogenous; quantity and procurement irrelevant.

Not alive, so it endures ischemia, survives, and is completely safe. ***

Placing Integra is simple, with no physiological tax.

No autogenous tissue donation.

No autogenous tissues. No failures, no waste.

Not alive, tolerant, suppresses inflammation - so preferred in these conditions.

Circulation-independent, survives where flaps cannot.

Not alive, tolerant of incidental pathology and injury.

Tolerant of incidental pathology and injury; potent ability to withstand effects of connective tissue immunopathy and pathology.

Integra not dependent on normal wound repair physiology - suppresses repair, induces histogenesis.

No donor sites, no risk.

Regenerates dermis, not scar. No contractures.

Tangential histoconduction can bridge voids.



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).



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.

About Surgery . . .

**Surgery cures many problems.
It 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.

About Flaps . . .

Flaps are the romantic heroes of reconstructive plastic surgery. They 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.



Sir Flapalot



LE MORTE DE
Flapalot

A FOURTH INDEPENDENT PARADIGM OF SURGERY

In-Situ Tissue Engineering

Integra is a distinct new paradigm of surgical wound closure, in-situ tissue engineering. Unlike repairs, grafts, flaps, it does not depend on normal wound repair. On the contrary, it suppresses normal repair, initiating embryonic histogenesis. It succeeds where conventional modalities fail.

Integra: not an Alternative, the Indicated Option

In the cases presented, Integra was the preferred option, not just because flaps and grafts would not have worked, but also because it was the most suited modality – superior results with less risk.

The Knight of Pathological Wounds

There are many chronic wounds that conventional surgery simply cannot solve. Flaps remain the heroes of reconstructive plastic surgery. But for closing problem pathological wounds, Integra is the modern Excalibur.

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

Integra used to close chronic wounds.

120 patients.

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%**.

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).

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

Give me . . . your wretched refuse . . .



Plastic surgery in the spirit of Emma Lazarus.

Wound repair surgery is based on topical care, plus three classic surgical paradigms: simple repairs, grafts, 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 Collagen-GAG Matrix 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.

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.

Its 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 or tame disease, and do so with no risk to the patient is a set of features unparalleled among surgical and wound products. A method of in situ tissue engineering, Integra is a genuinely new paradigm of wound surgery. Of equal rank to flaps and grafts, its biological properties, safety profile, and practicality make it preferred for many problems. This is especially true for chronic pathological wounds, where conventional repair, grafts, and flaps fail or are ineligible, and Integra succeeds, often with superior results. Furthermore, Integra incurs no donor sites nor risk to the patient, and a reconstruction for a chronic wound can be managed almost entirely as an outpatient, preserving activity and lifestyle. After 10 years of clinical use, Integra is no longer a new 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.



74 f

*Sweet's neutrophilic dermatosis
rheumatoid
chronic thrombocytosis*

Caveats

Prior failed skin grafts and free flap.

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.



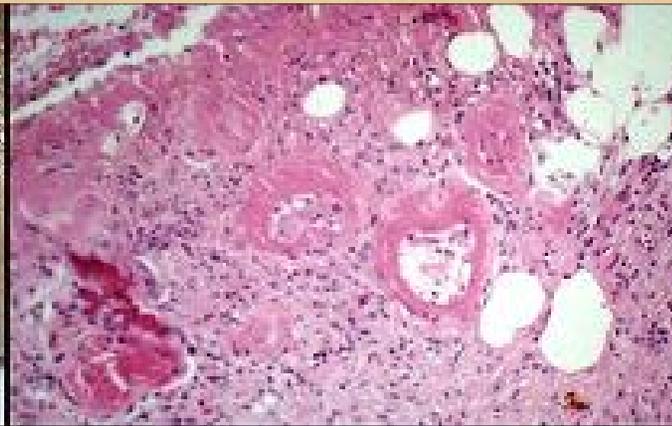
44 f achilles rupture hypercoagulable (anticardiolipin)



58 m intra-arterial injection injury



61 f hypercoagulable (protein S)



69 f



*hyper-
coagulable*

*protein C
cryoglobulins*





53 m

diabetes

atherosclerosis



90 f

*aso /
pvod*



84 f

diabetes

*aso /
pvod*



60 m diabetes, atherosclerosis



74 m diabetes, atherosclerosis



77 f

Sjogren's



50 f

*tibia
fracture*

*hyper-
coagulable
???*

*failed
free flaps*



77 m rheumatoid

No Integra.

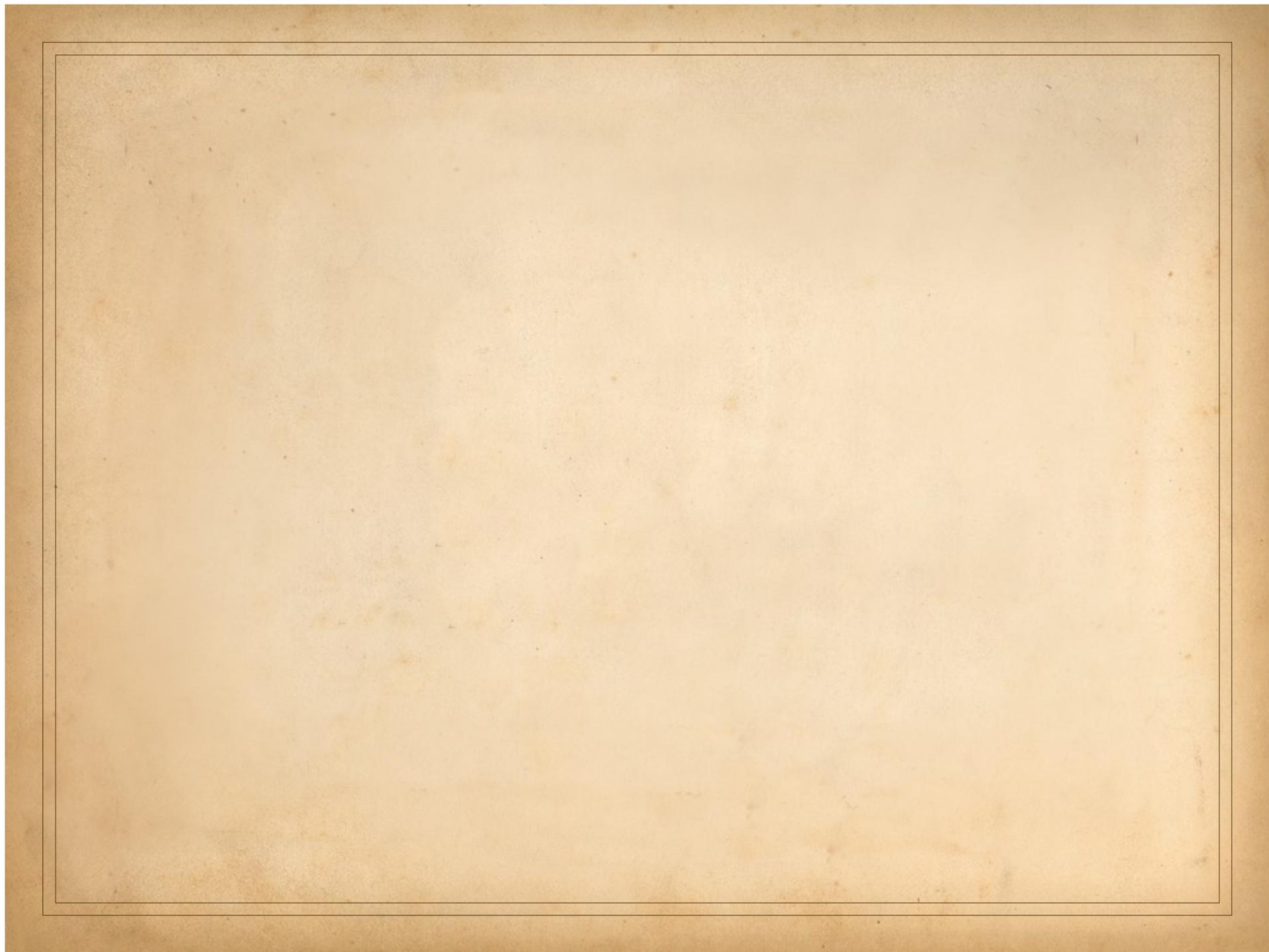
Flaps and grafts.

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

Marc E. Gottlieb, MD, FACS Phoenix, AZ

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

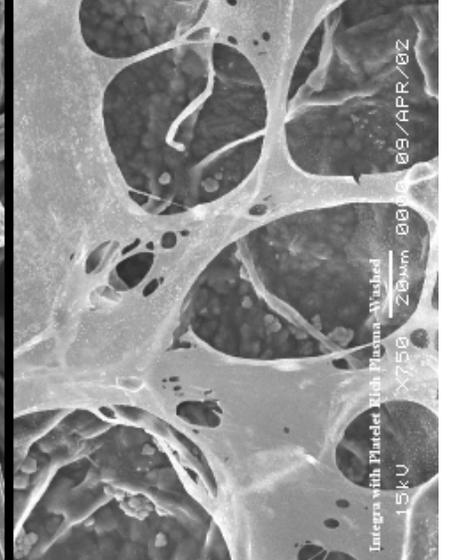
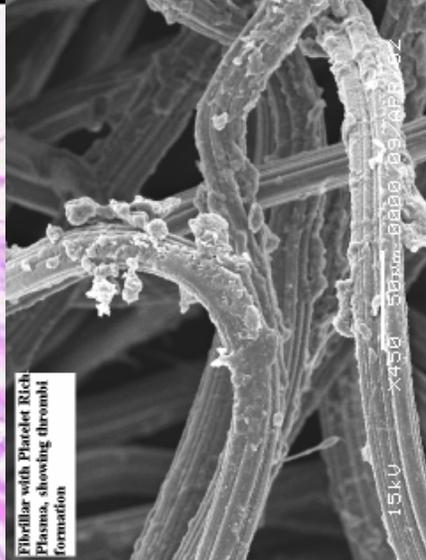
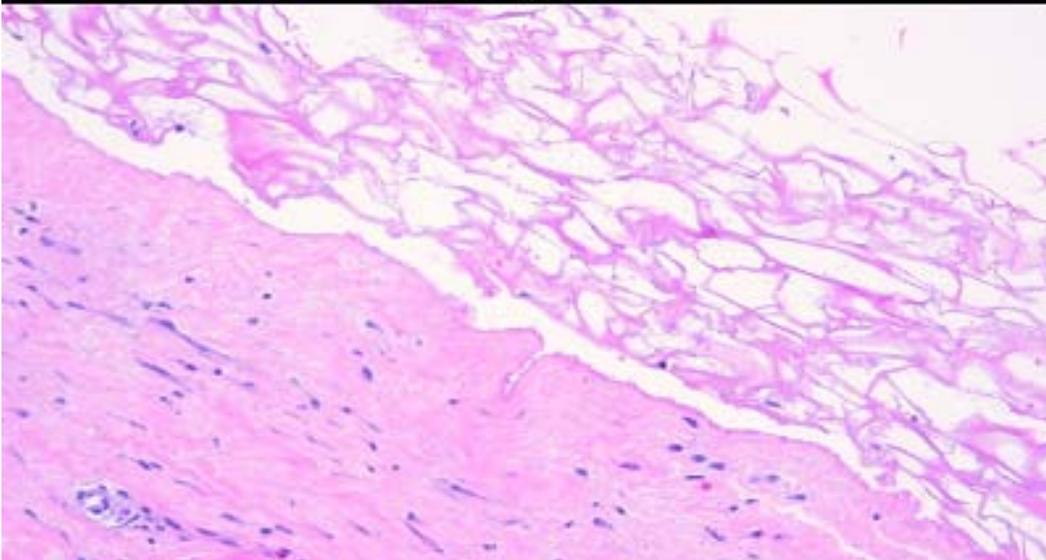
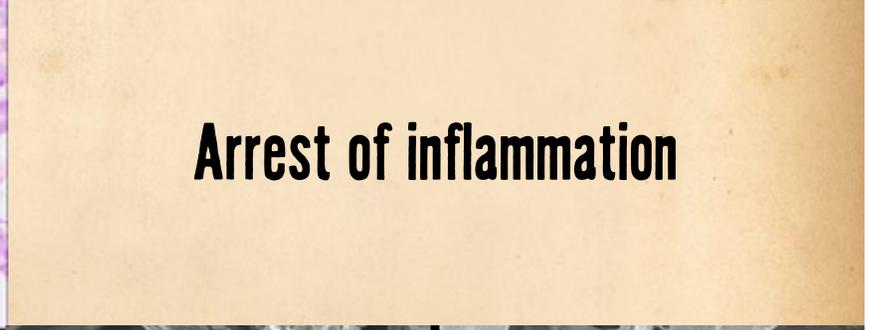
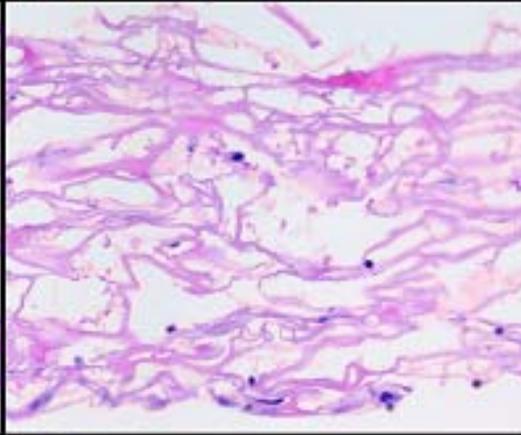
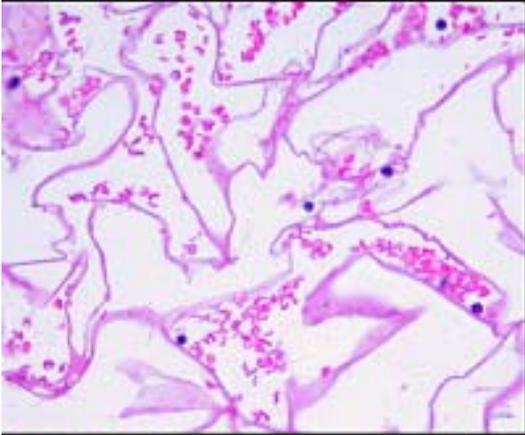
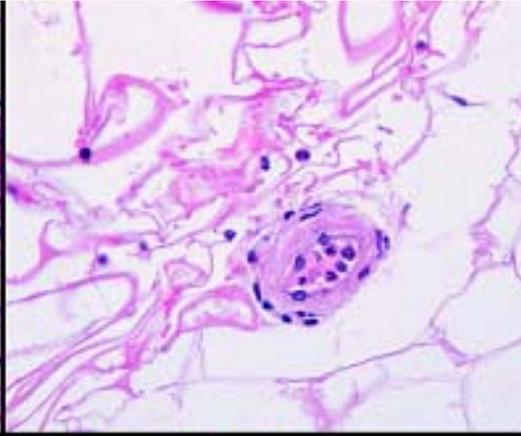
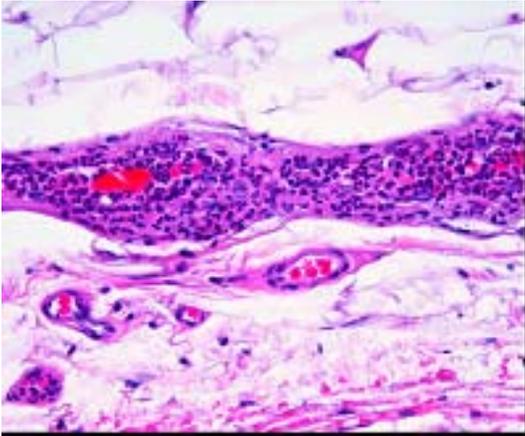
A cure for chronic and pathological wounds.



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

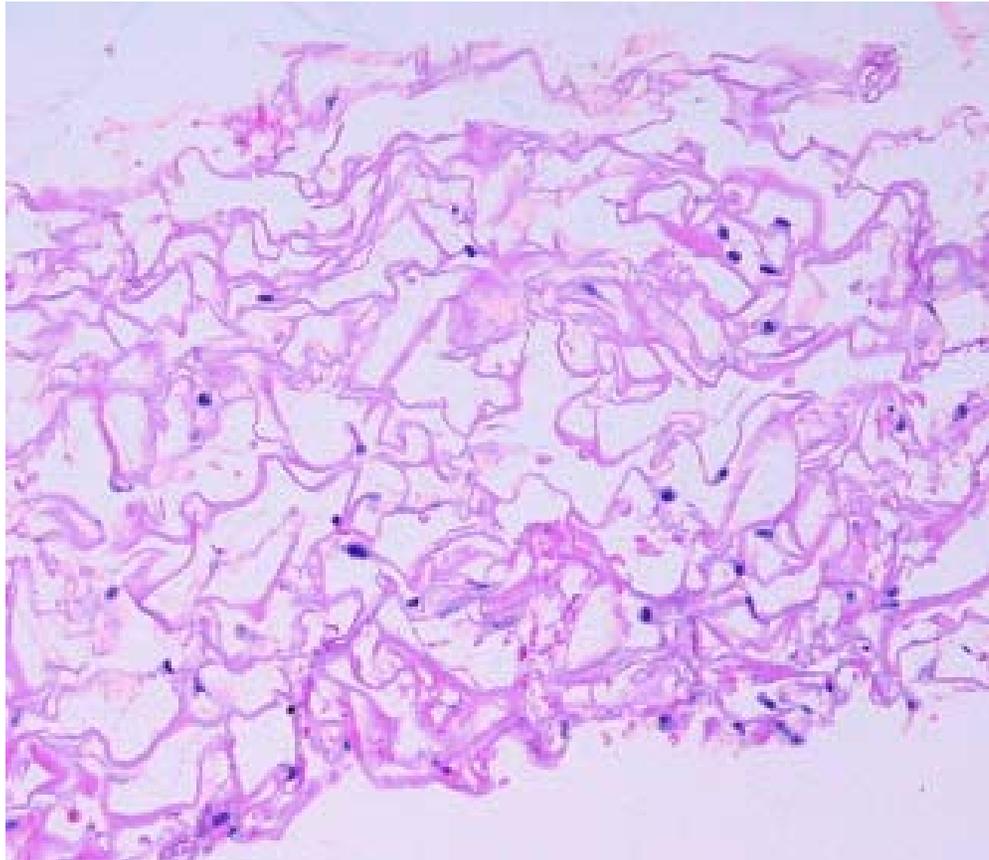
Marc E. Gottlieb, MD, FACS Phoenix, AZ

THE MICROSCOPIC ANATOMY
AND
BIOPHYSICS OF
INTEGRA HISTOGENESIS



Fibrillar with Platelet Rich Plasma, showing thrombi formation

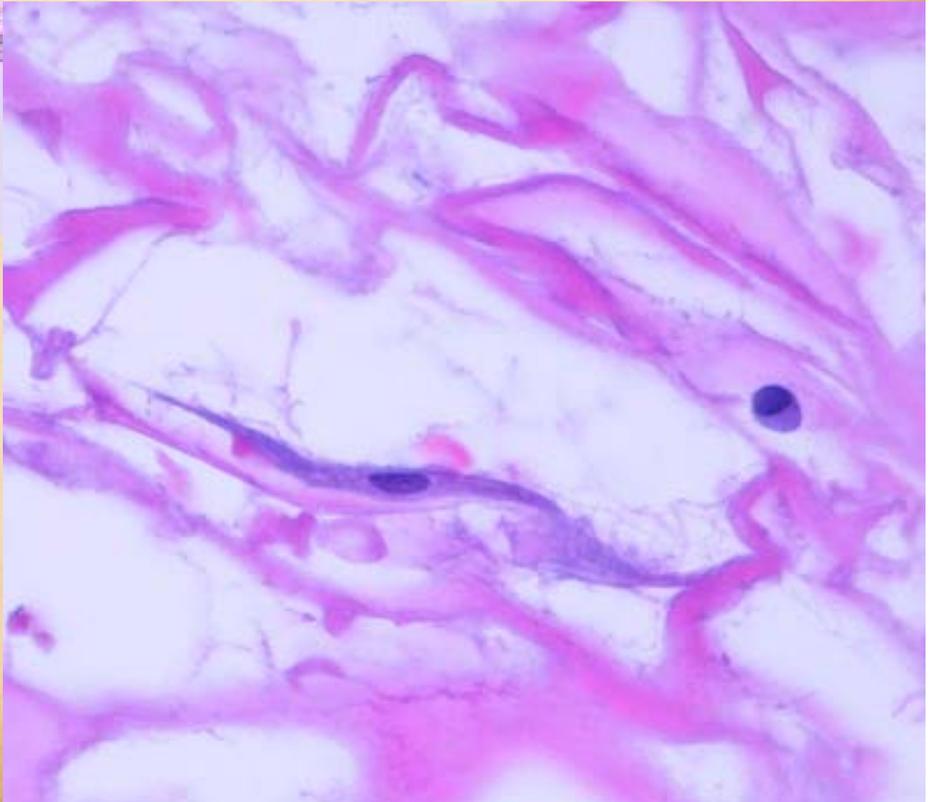
Integra with Platelet Rich Plasma, Washed
15kV x750 20um 0000 09/APR/02

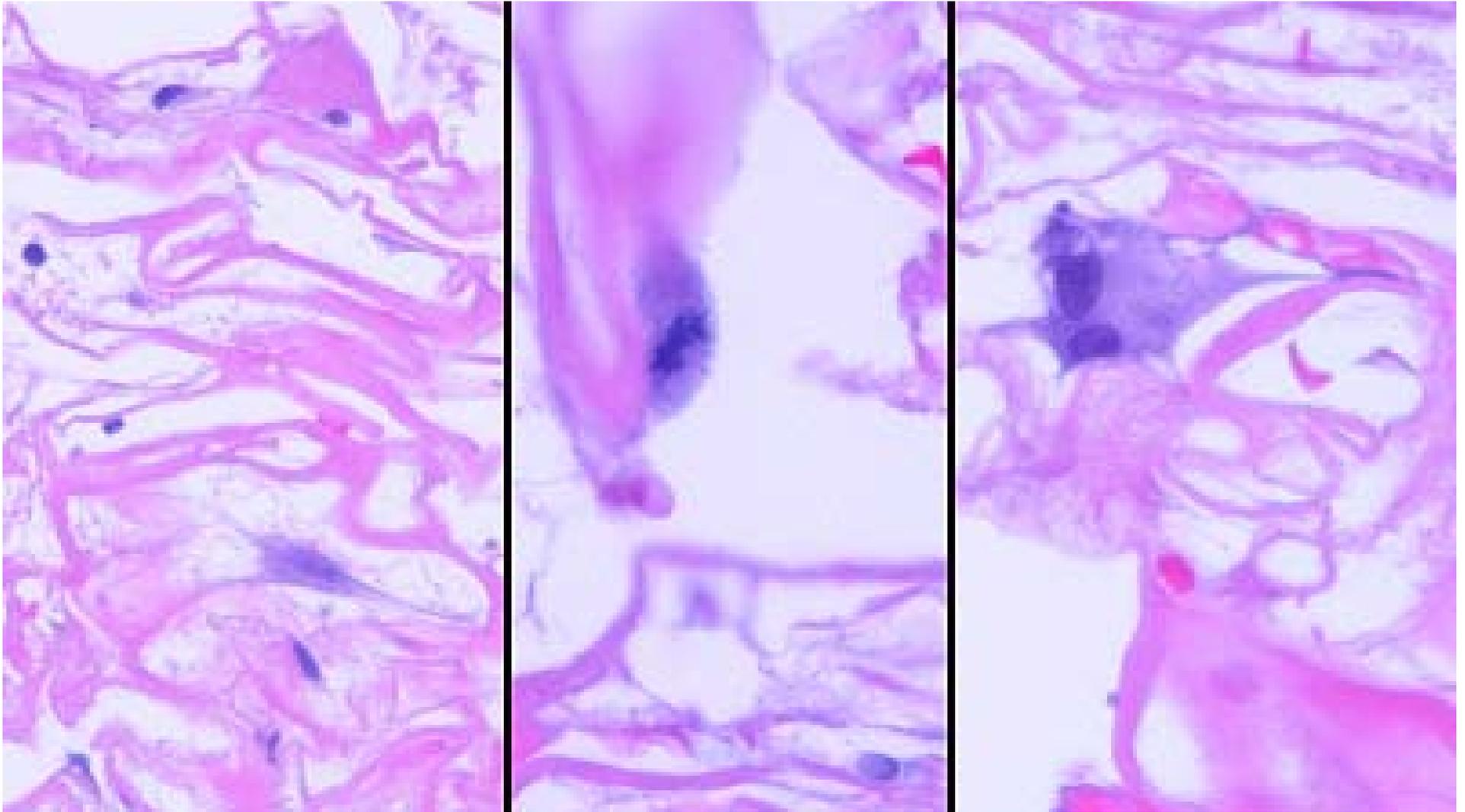


**Recognition of the matrix,
pioneer cells**

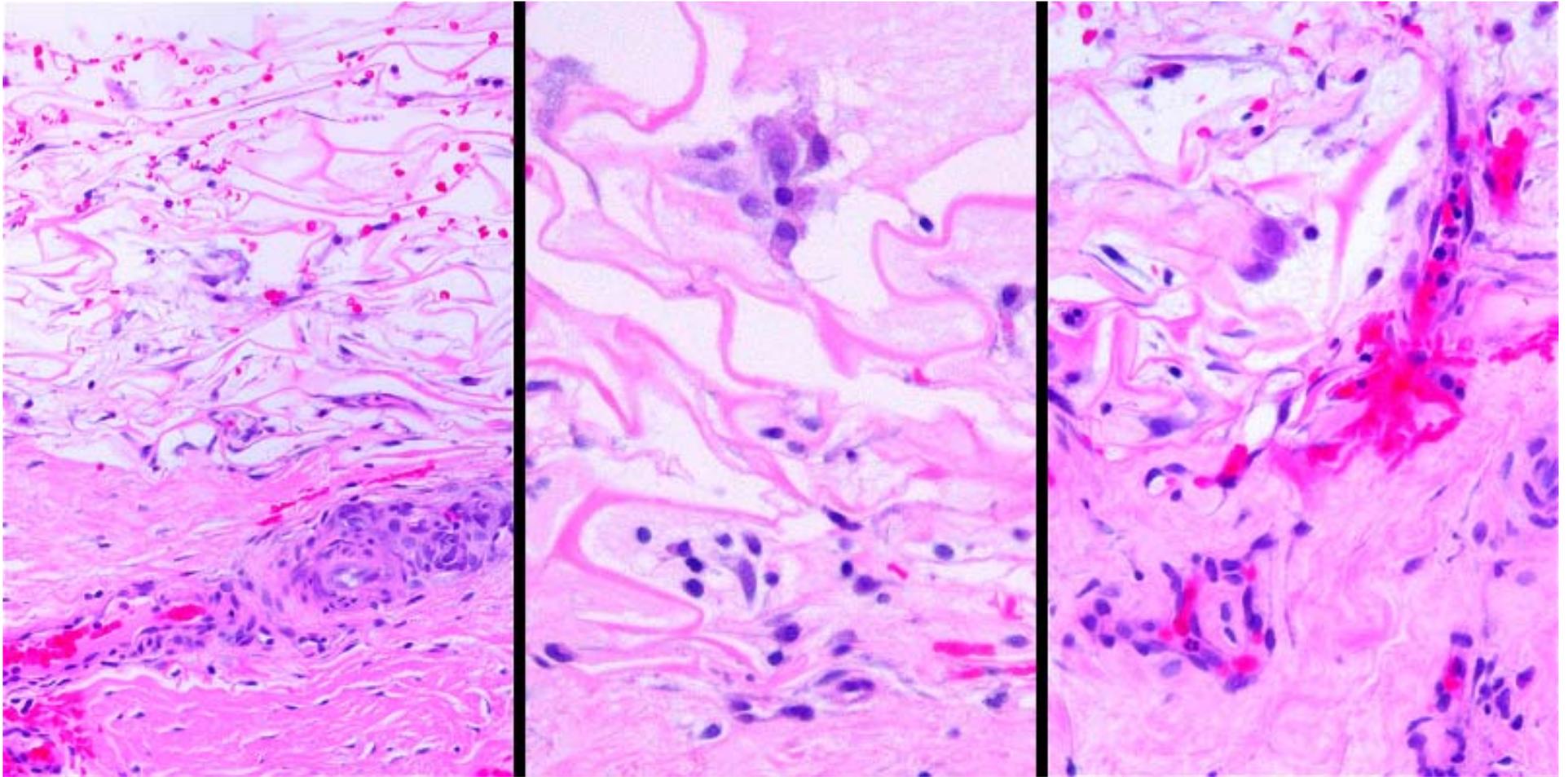


Transition

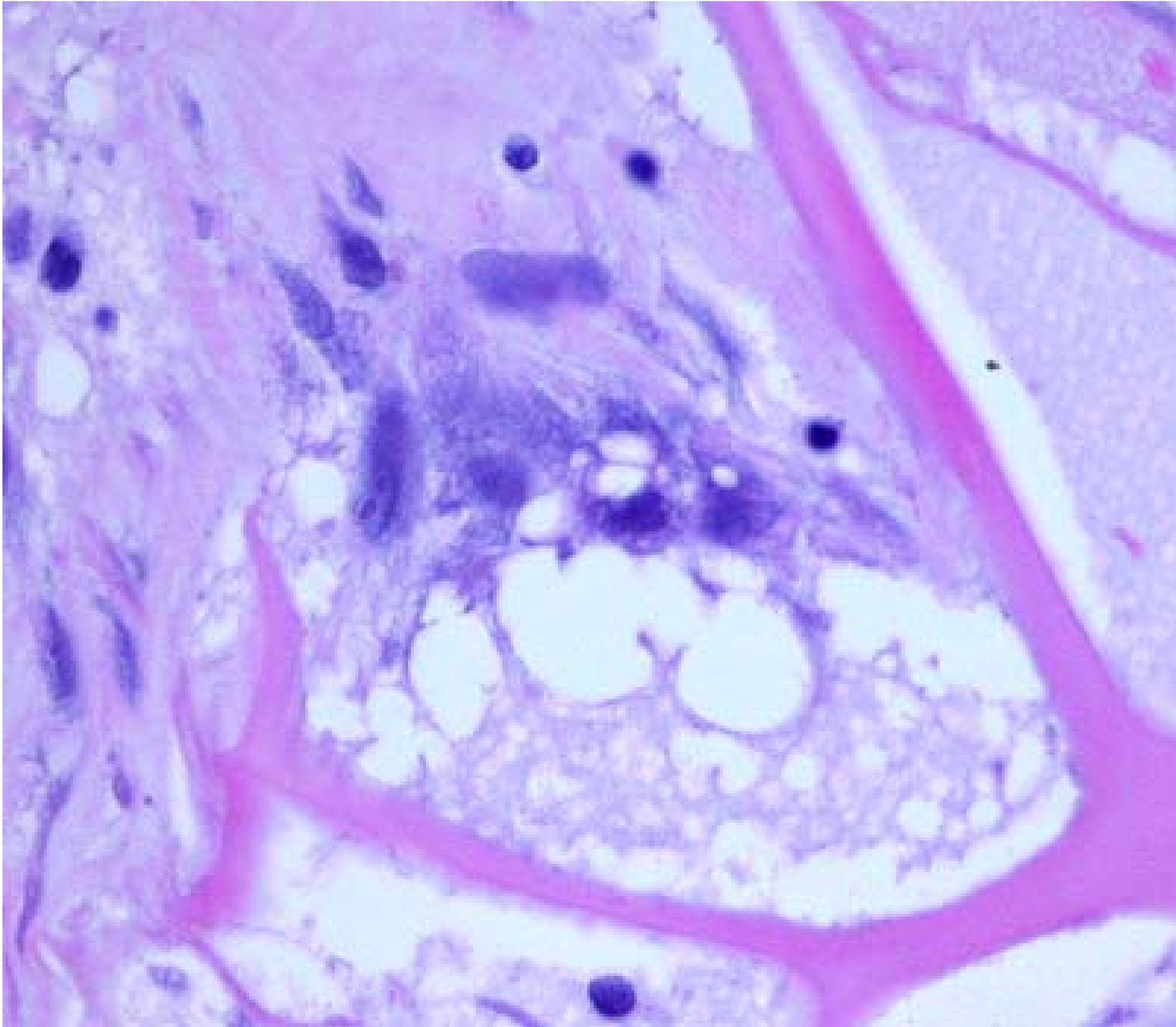




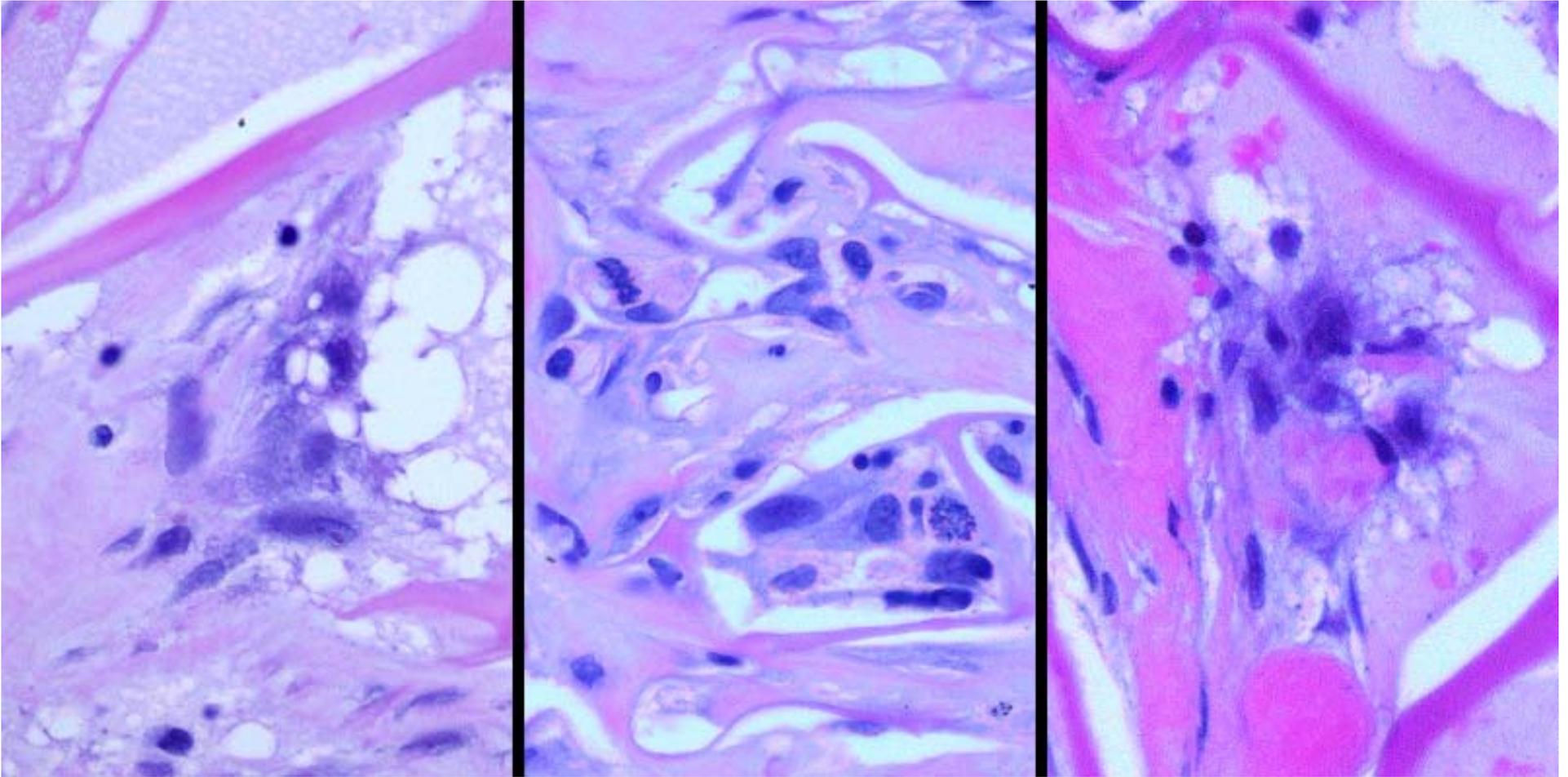
Syncytial transformation



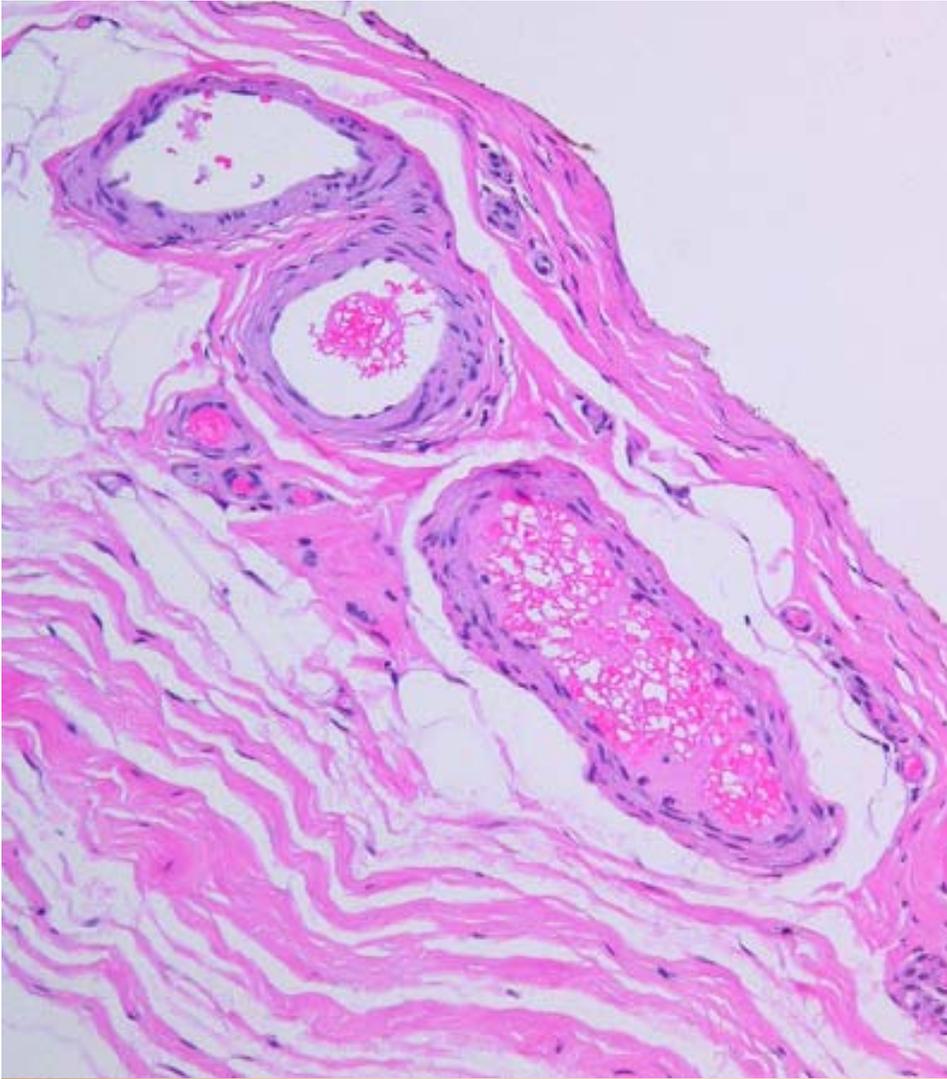
Syncytial transformation



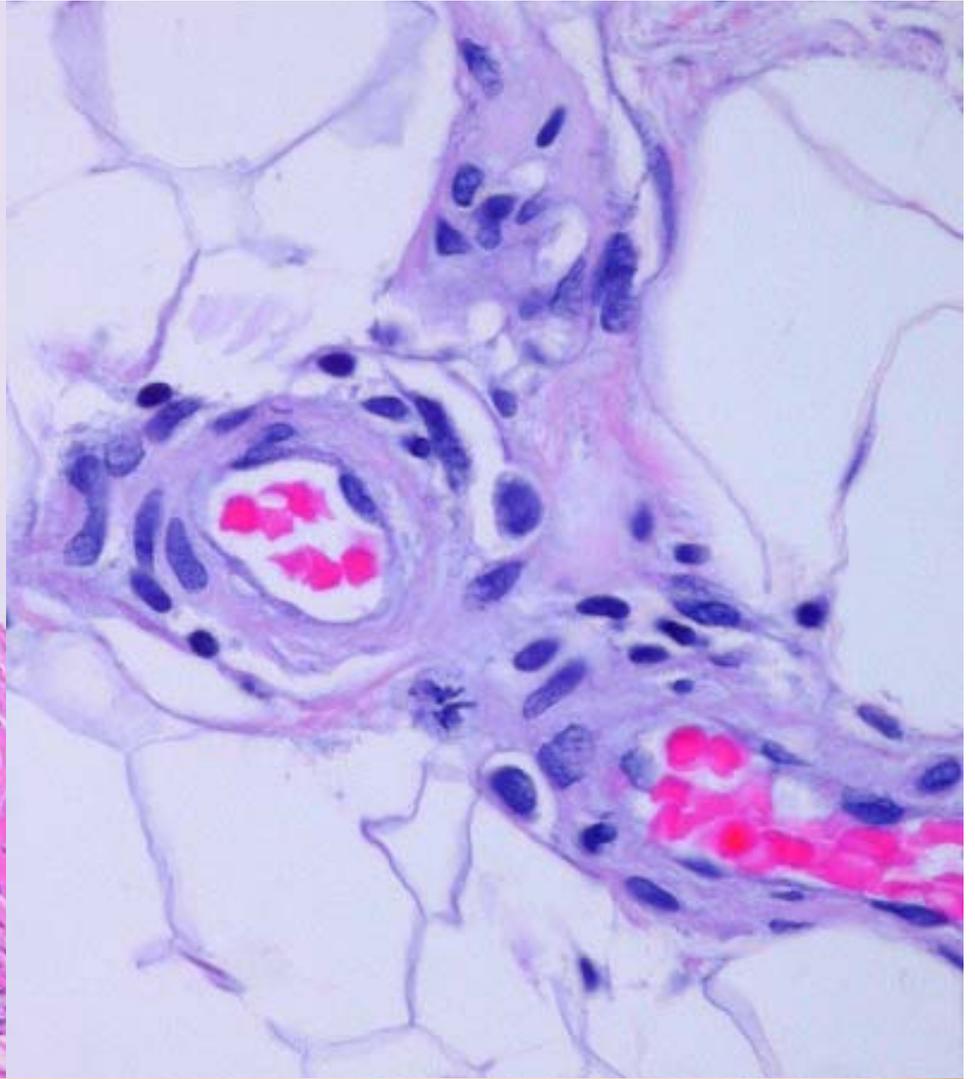
**Syncytial
clusters**



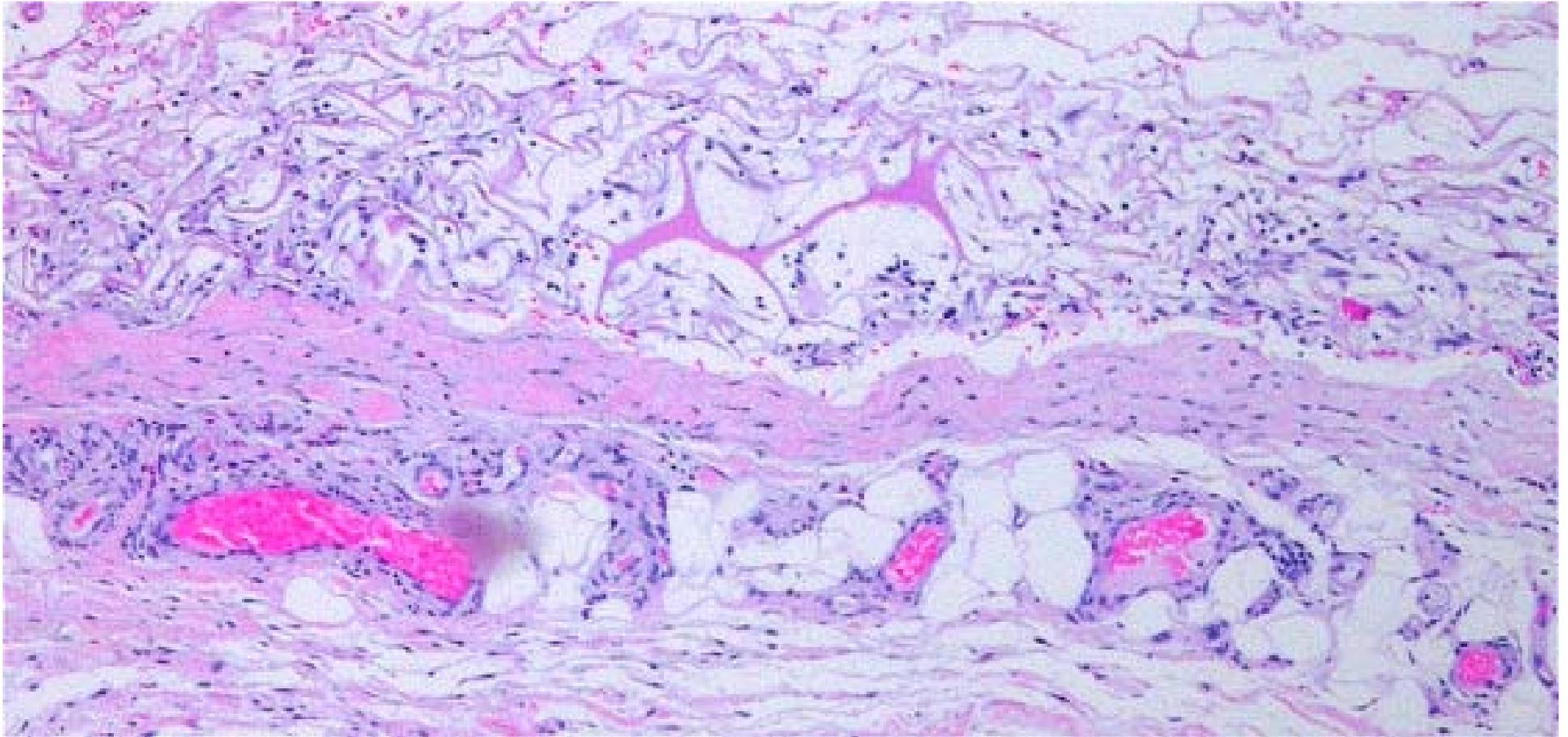
Syncytial clusters



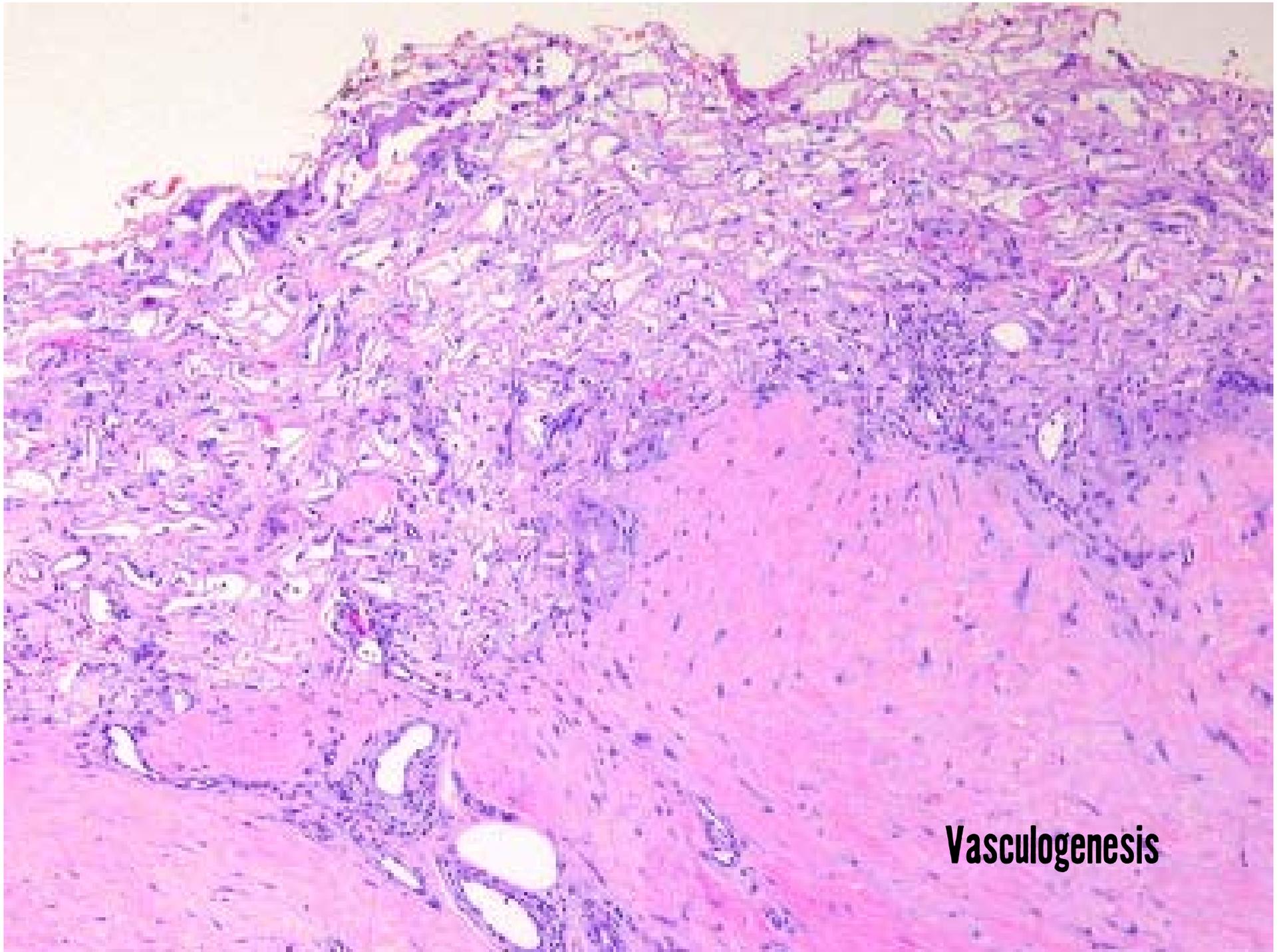
Normal angiocytes prior to Integra



Stimulation of perivascular cells

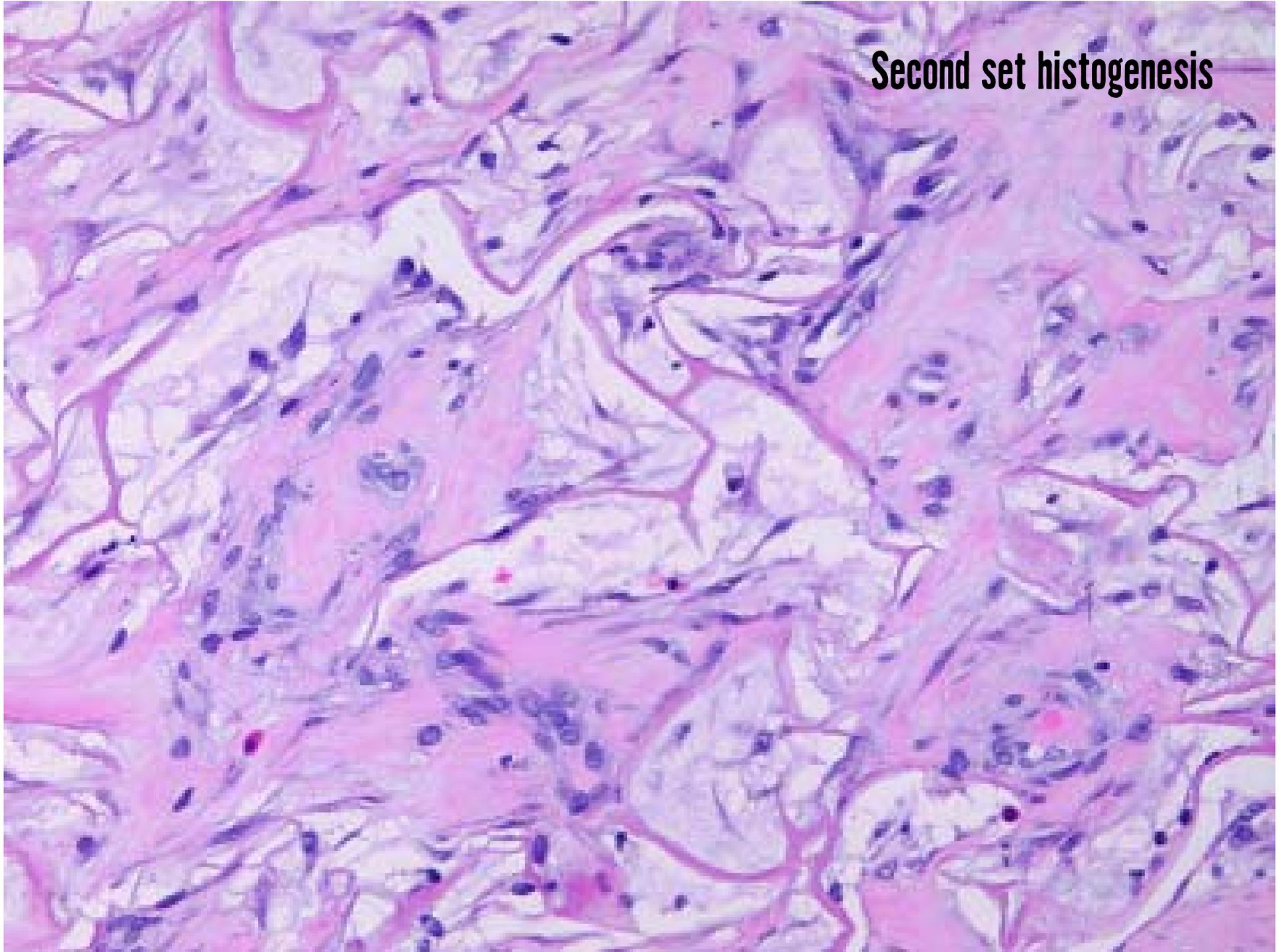


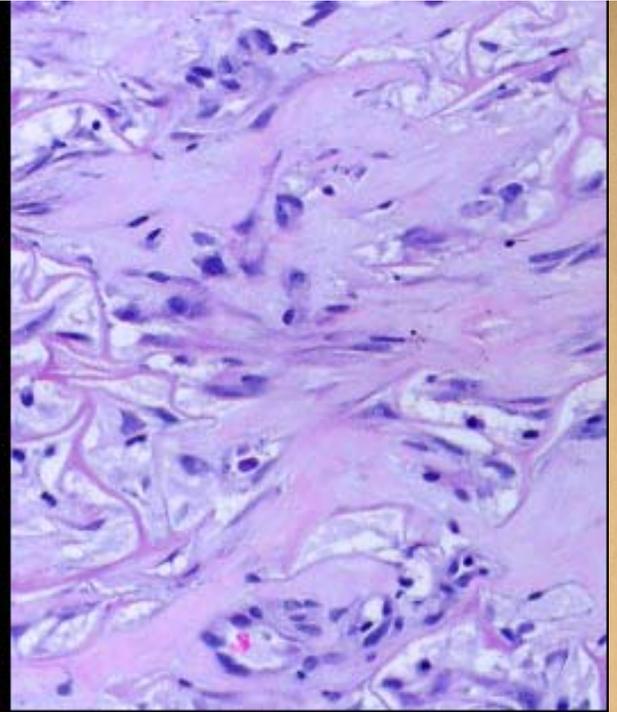
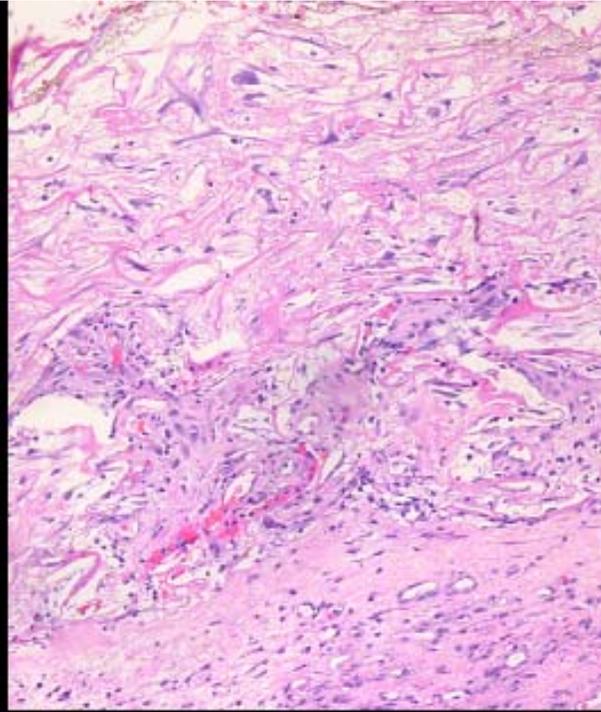
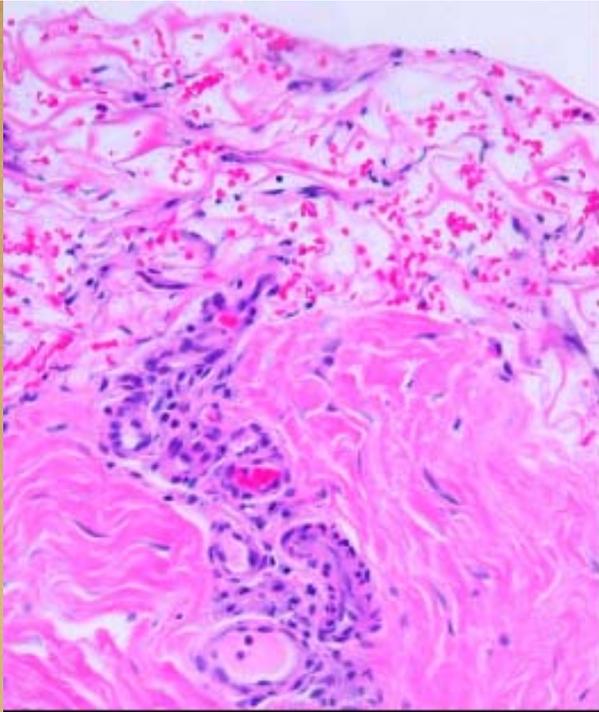
Entrainment of perivascular cells



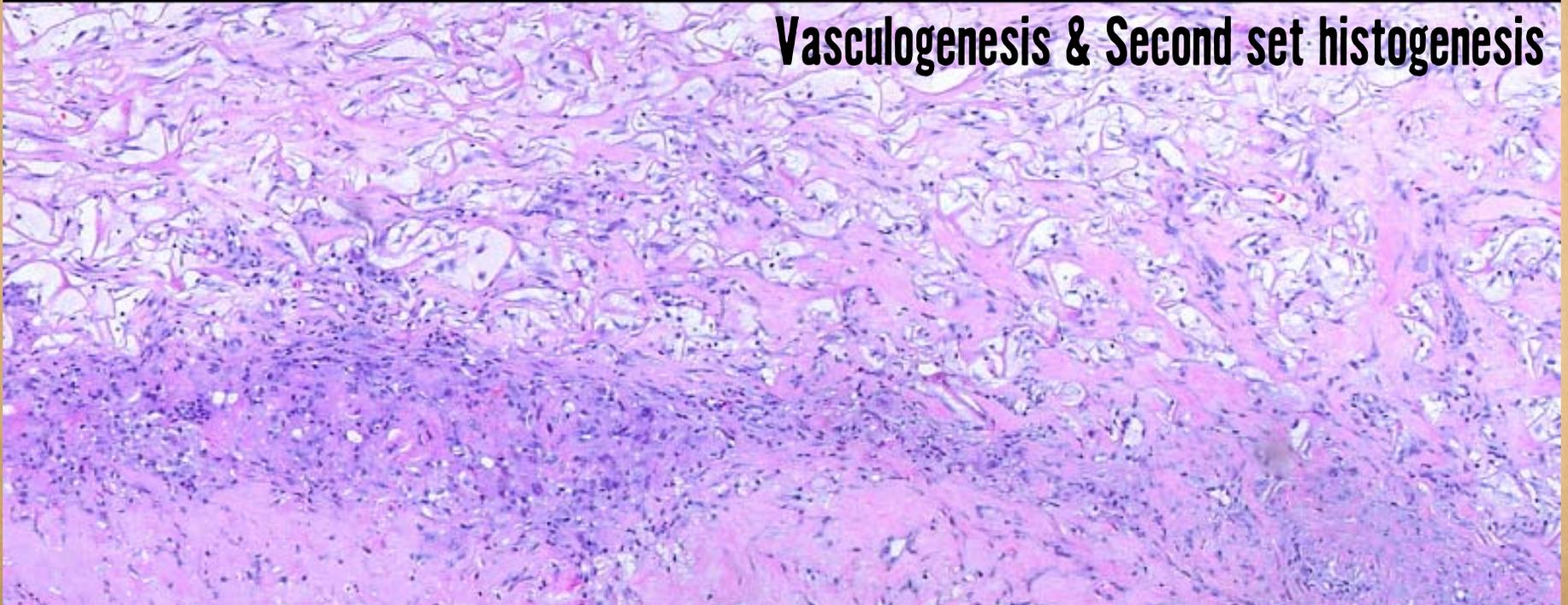
Vasculogenesis

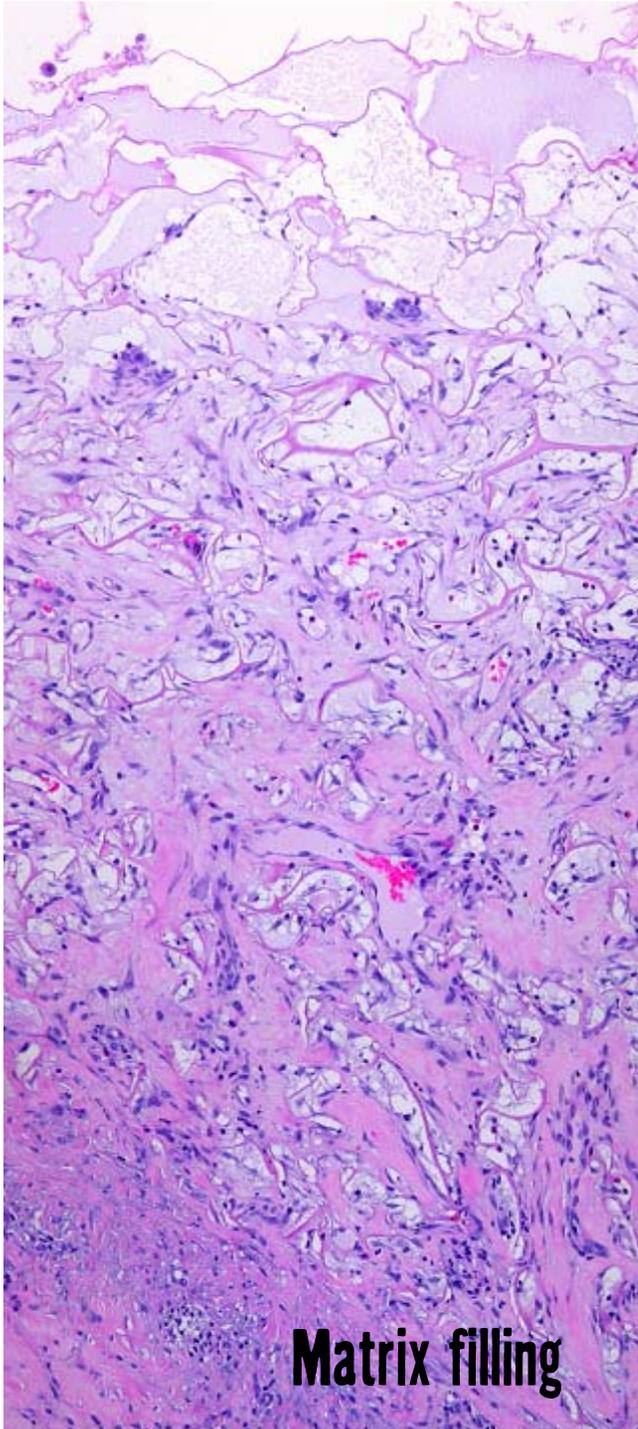
Second set histogenesis



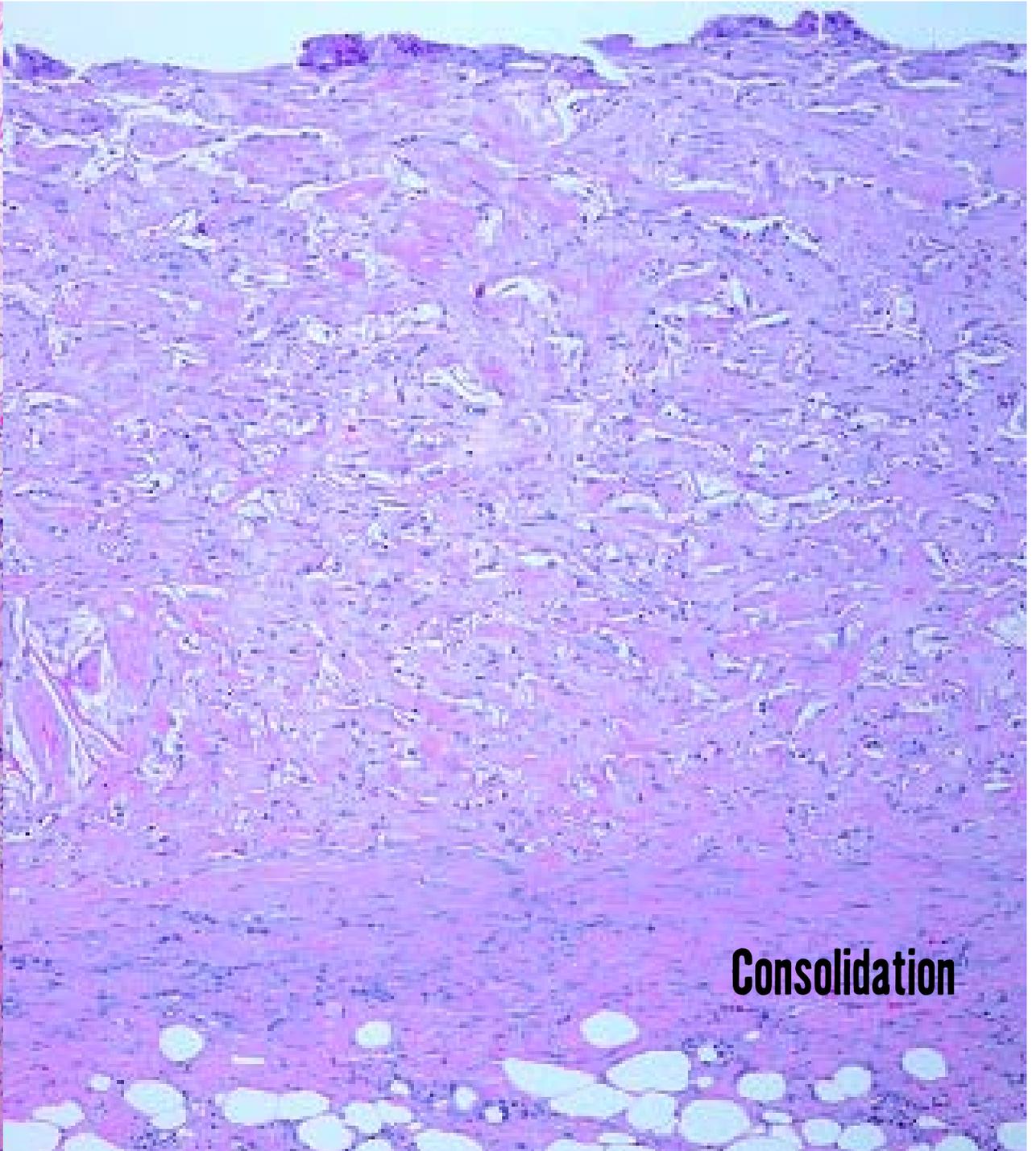


Vasculogenesis & Second set histogenesis

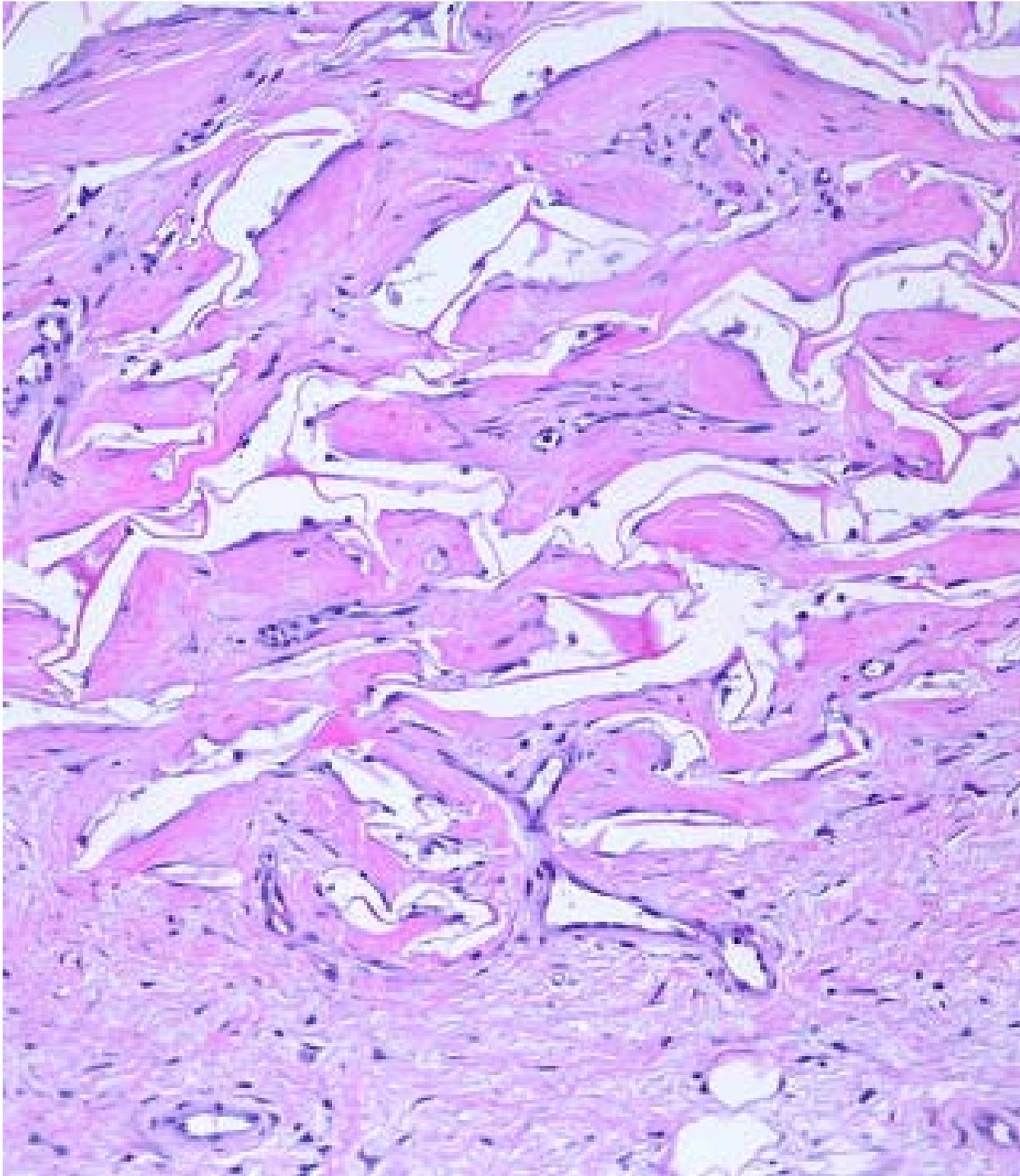




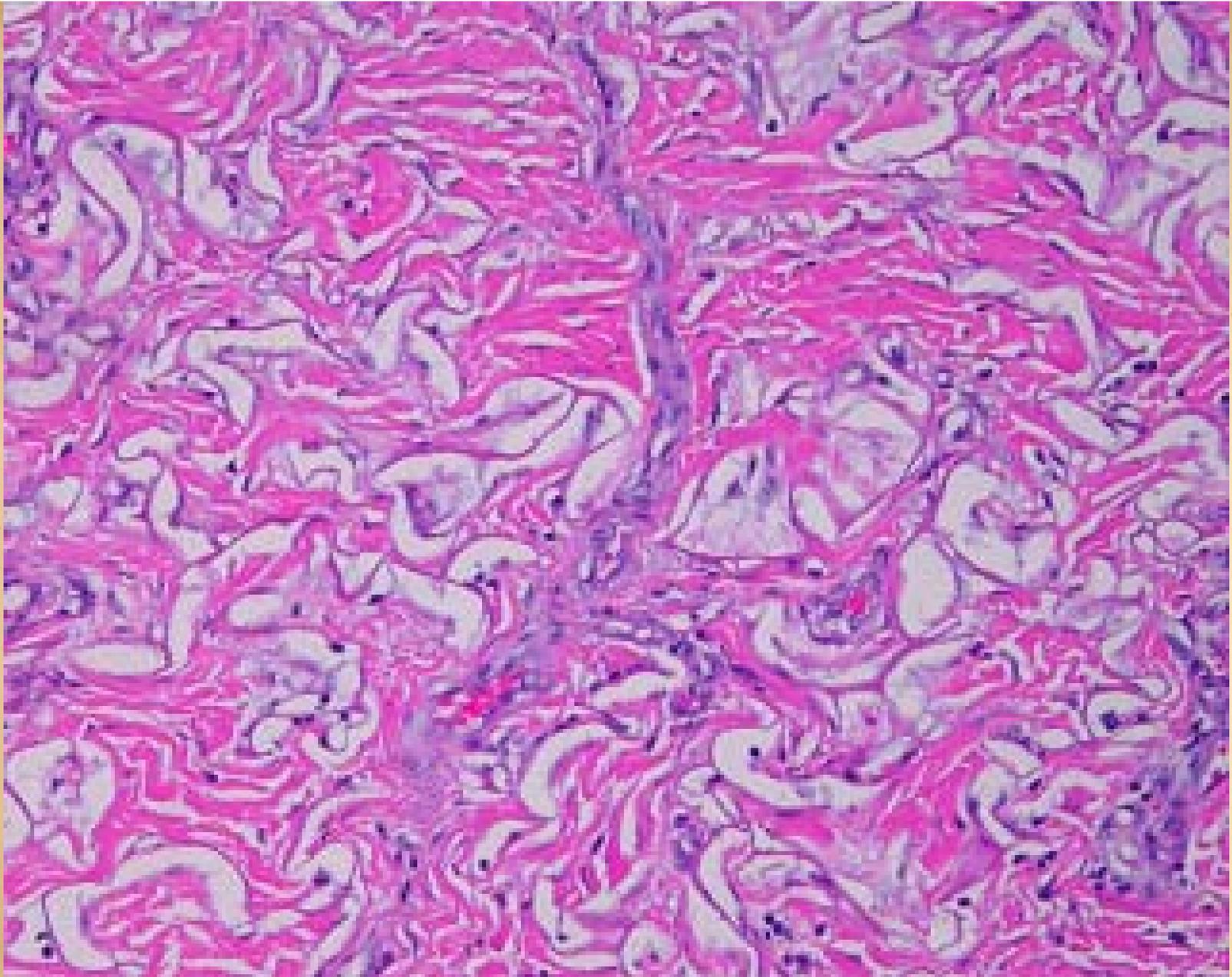
Matrix filling



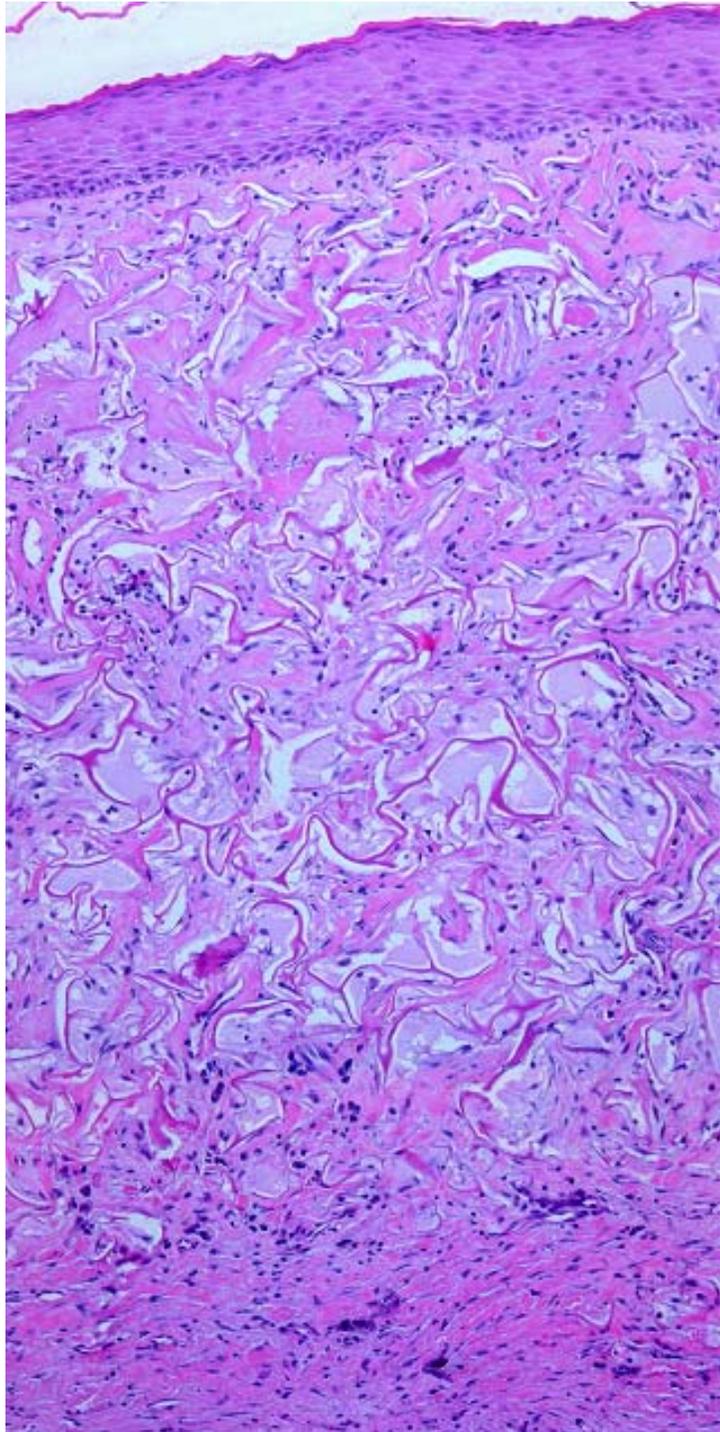
Consolidation



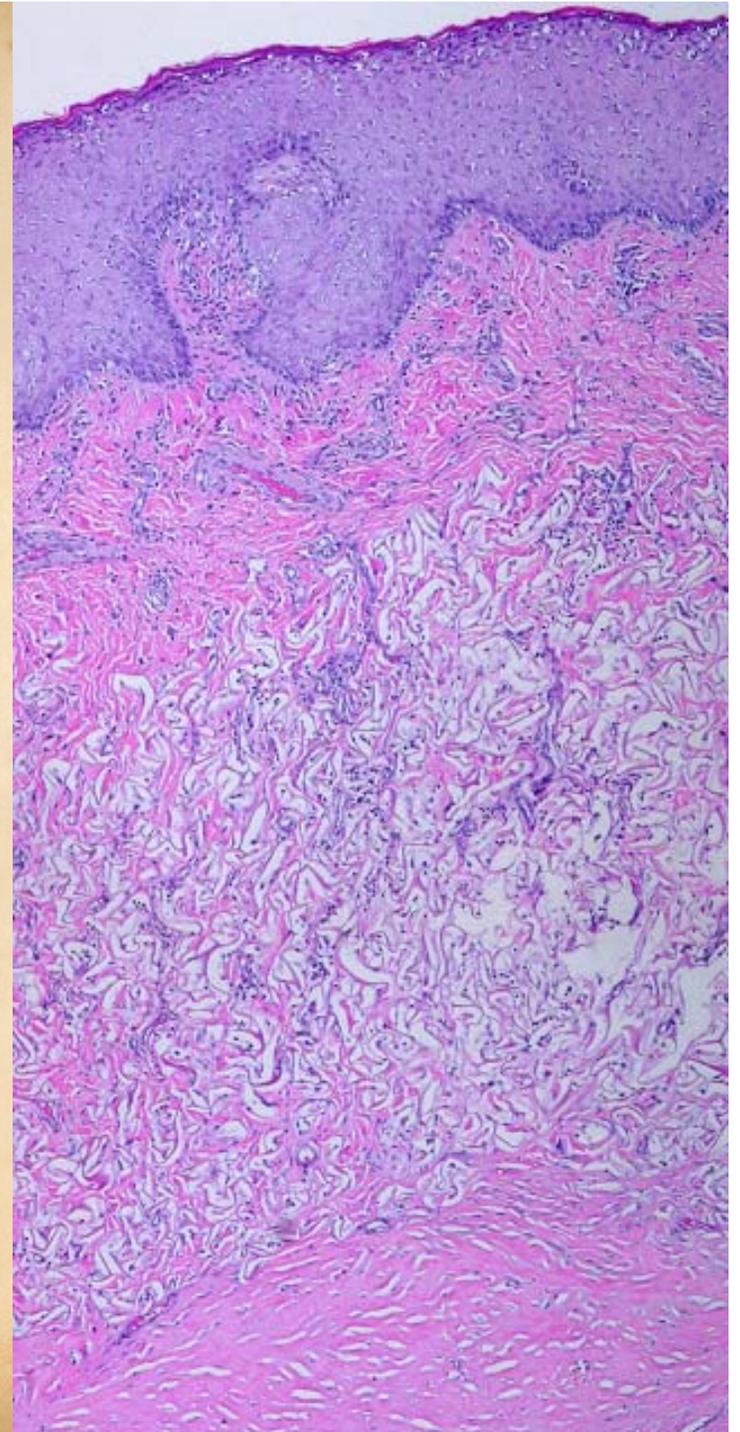
Domain maturation



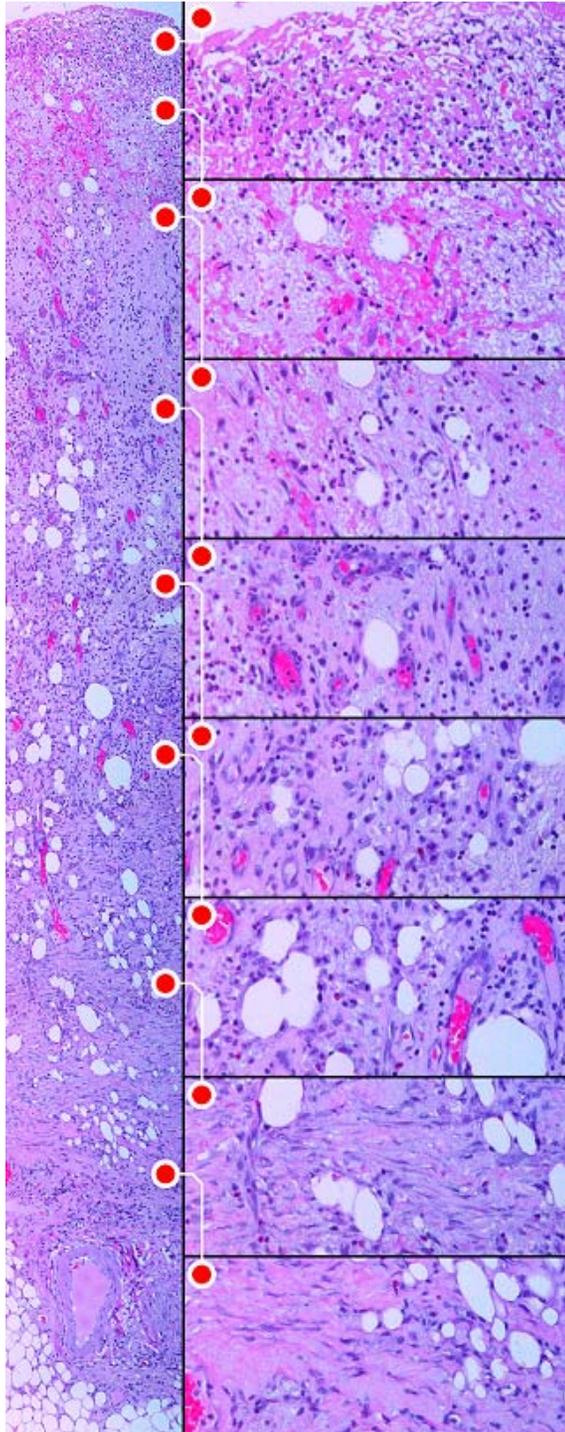
Late maturation



**Epidermal
events, early**



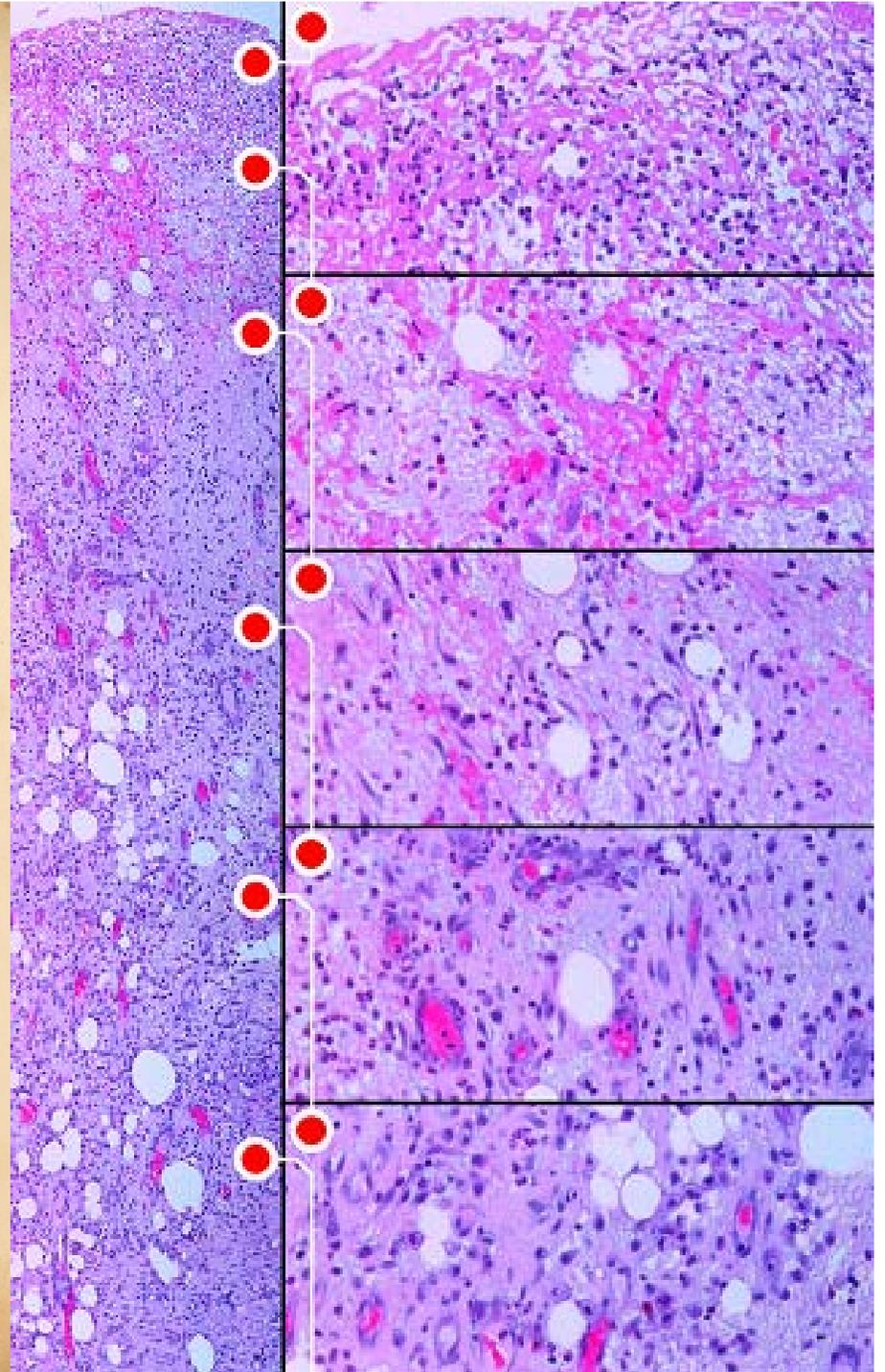
**Epidermal
events, late**

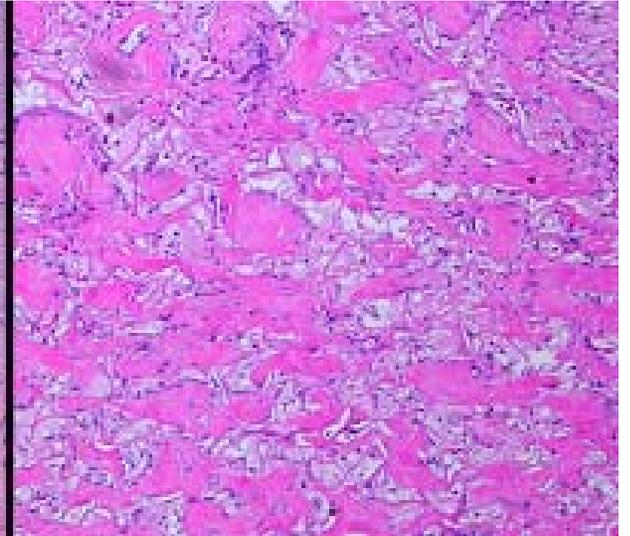
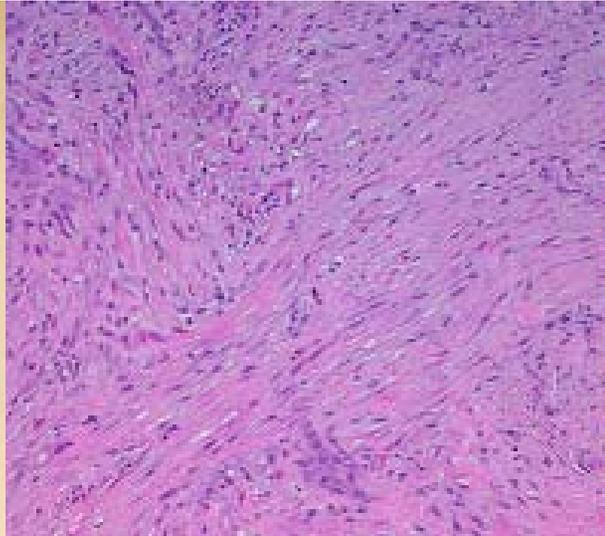


**the
normal
wound**

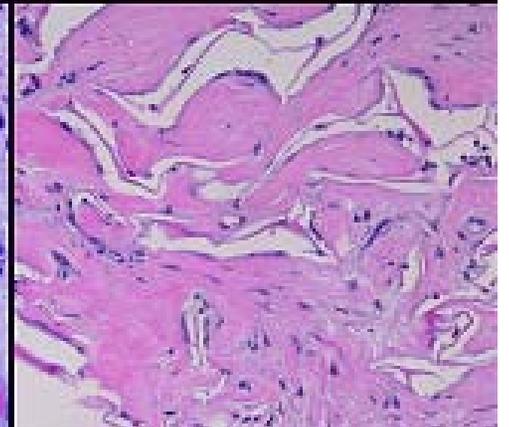
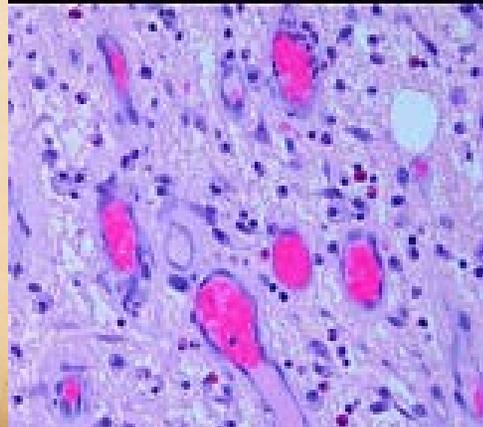
**inflammatory
wound repair**

**the
wound
module**

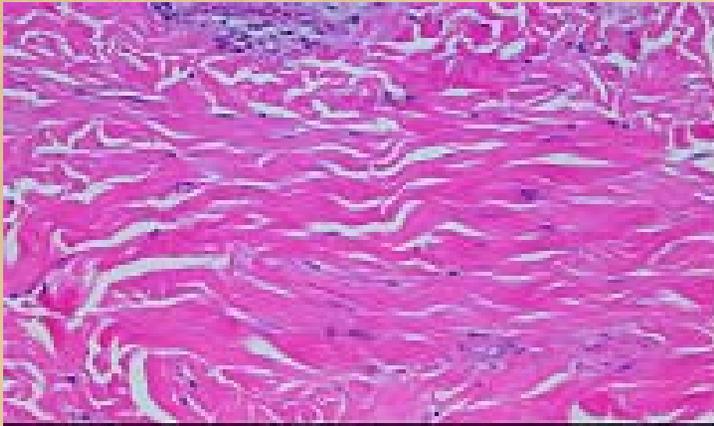




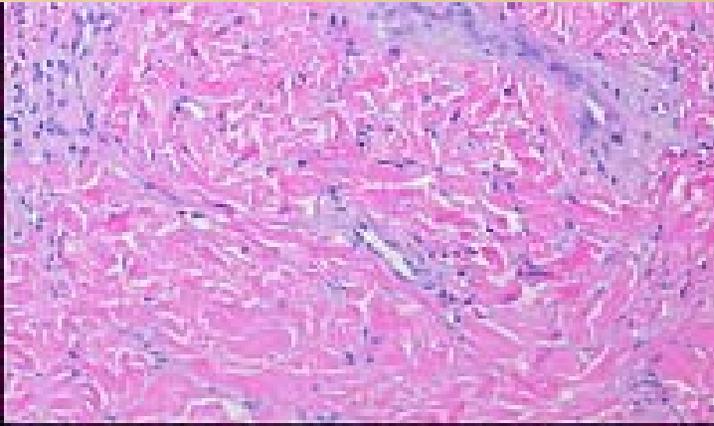
wound
healing
versus
integra
histogenesis



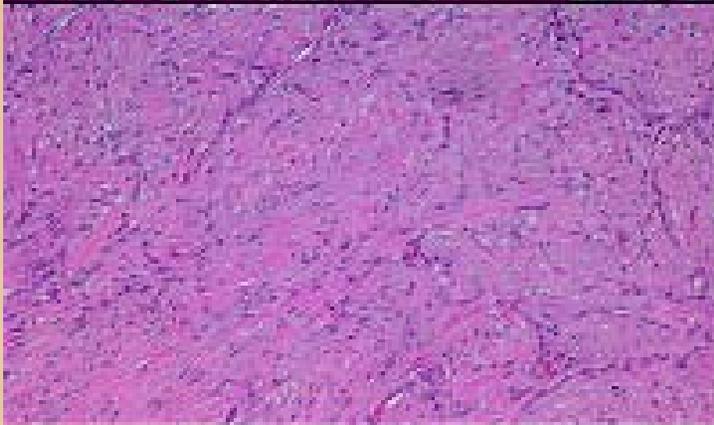
**normal
dermis**



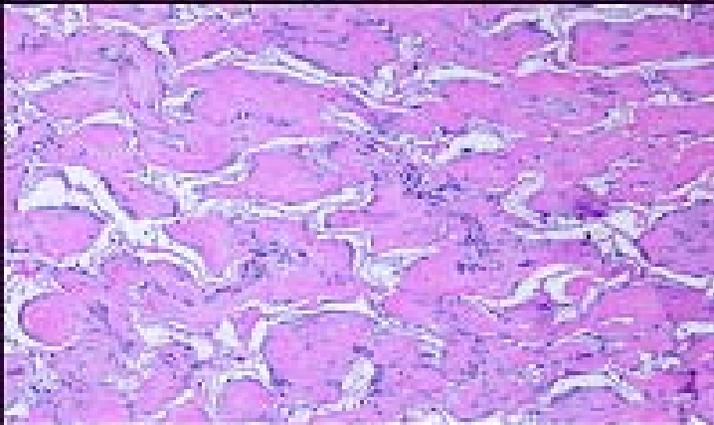
**normal
dermis**



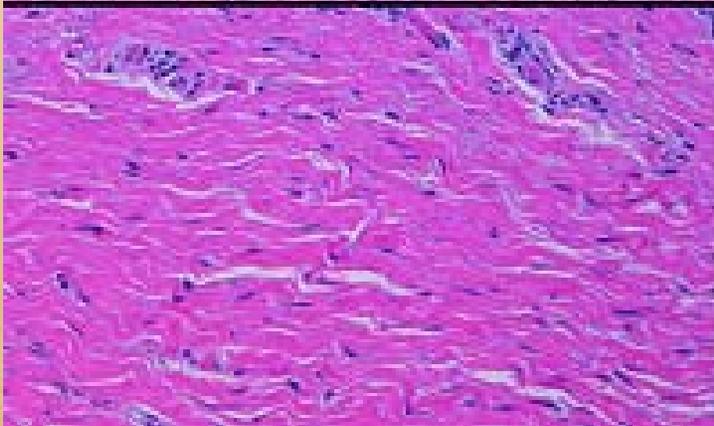
**early
wound
scar**



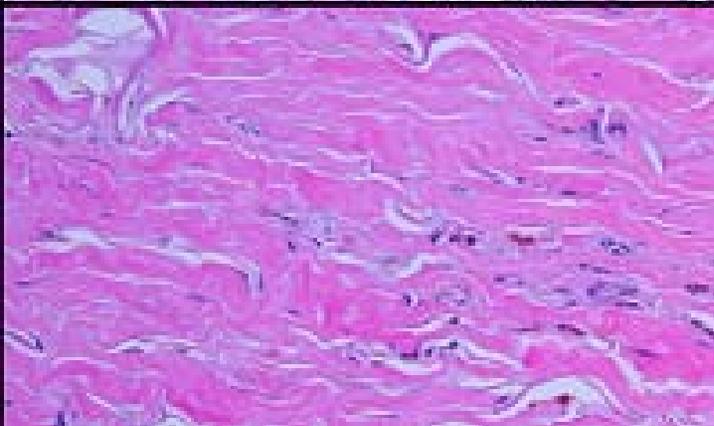
**early
integra**

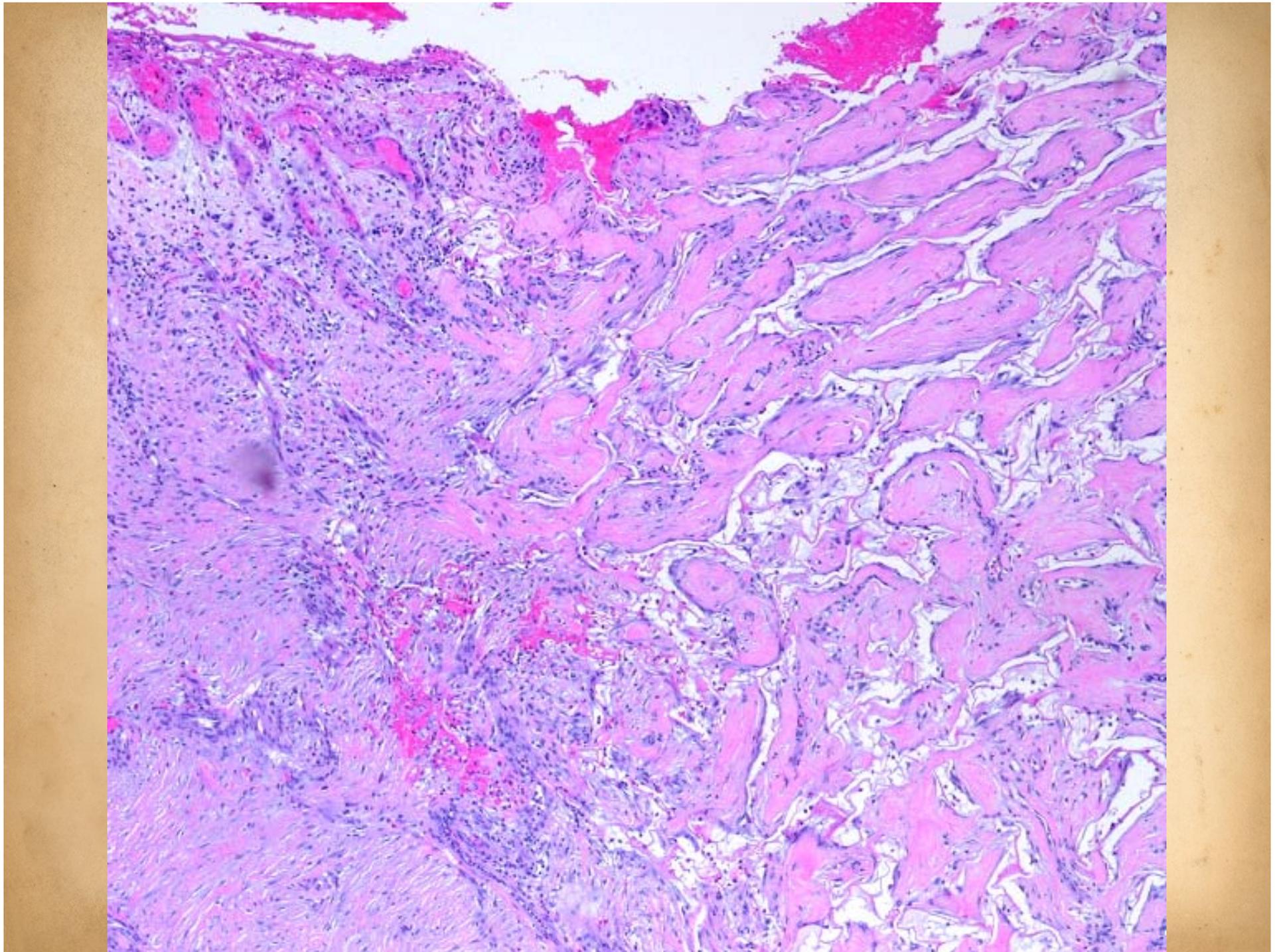


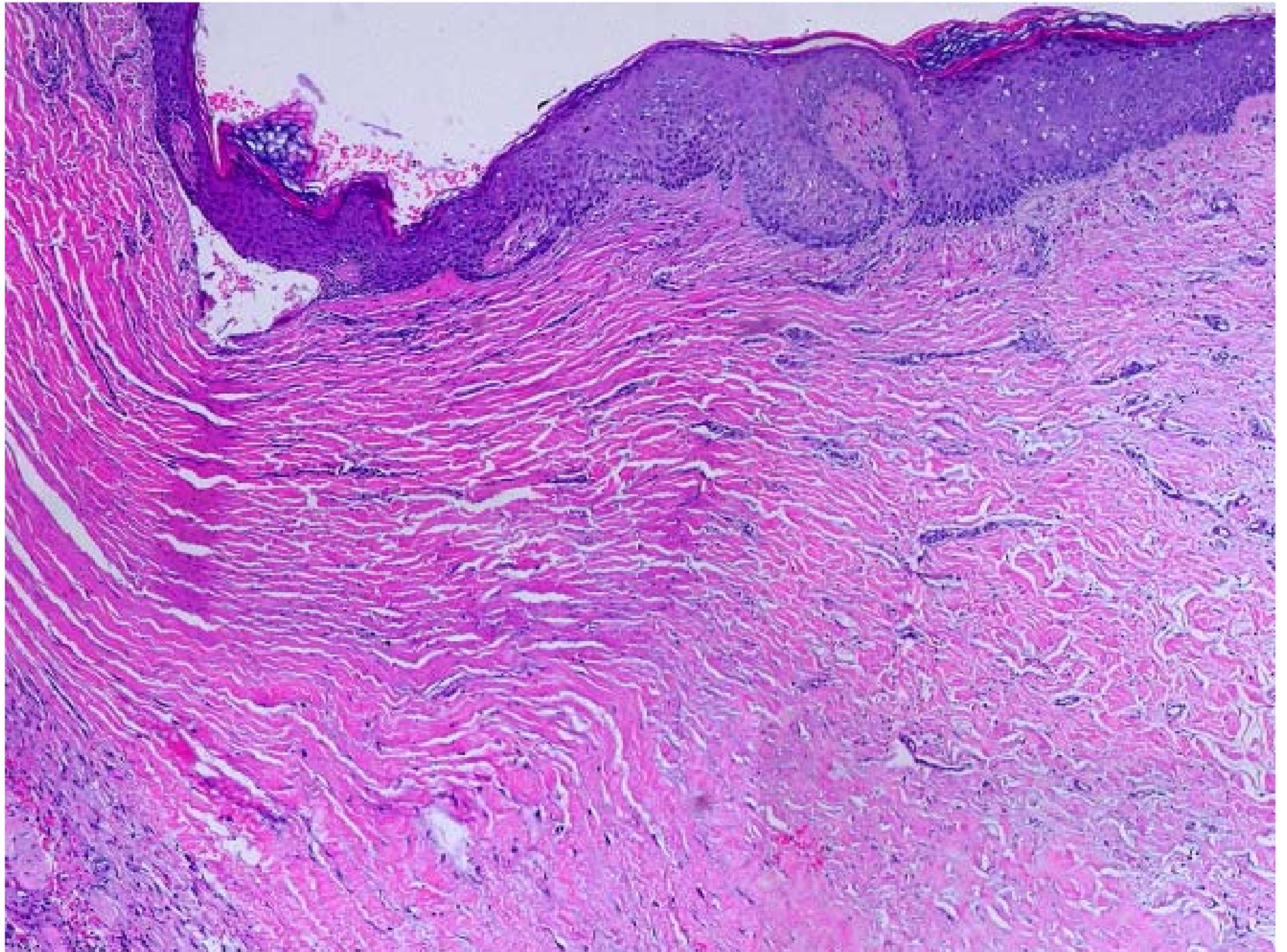
**late
wound
scar**



**late
integra**









LE MORTE DE
Flapalot

A FOURTH INDEPENDENT PARADIGM OF SURGERY

In-Situ Tissue Engineering

Integra is a distinct new paradigm of surgical wound closure, in-situ tissue engineering. Unlike repairs, grafts, flaps, it does not depend on normal wound repair. On the contrary, it suppresses normal repair, initiating embryonic histogenesis. It succeeds where conventional modalities fail.

Integra: not an Alternative, the Indicated Option

In the cases presented, Integra was the preferred option, not just because flaps and grafts would not have worked, but also because it was the most suited modality – superior results with less risk.

The Knight of Pathological Wounds

There are many chronic wounds that conventional surgery simply cannot solve. Flaps remain the heroes of reconstructive plastic surgery. But for closing problem pathological wounds, Integra is the modern Excalibur.

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

Marc E. Gottlieb, MD, FACS Phoenix, AZ

THE MICROSCOPIC ANATOMY
AND
BIOPHYSICS OF
INTEGRA HISTOGENESIS