2022 MID-ATLANTIC CONFERENCE

10th ANNUAL CURRENT CONCEPTS IN

VASCULAR THERAPIES

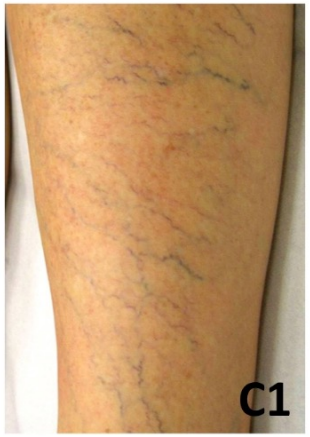
Spider Veins to Venous Ulcers: What is Going on with My Patient?

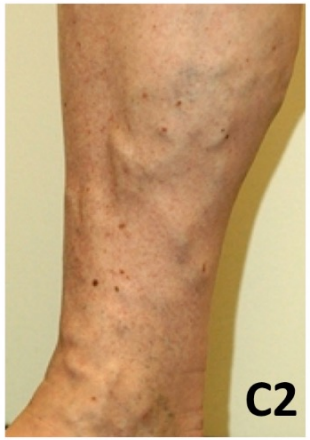
April 29, 2022

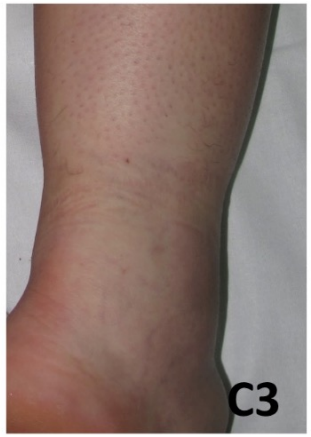
Todd W Gensler MD, FACS

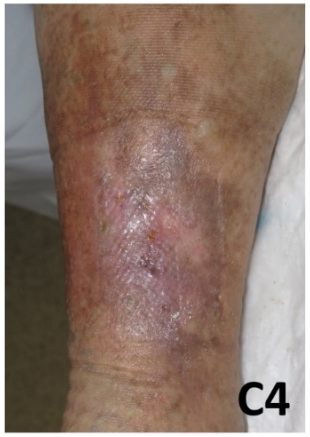
What lies above and what lies beneath

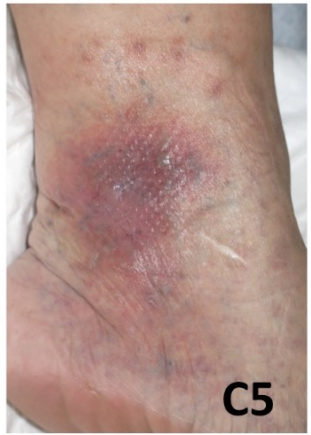
ABOVE

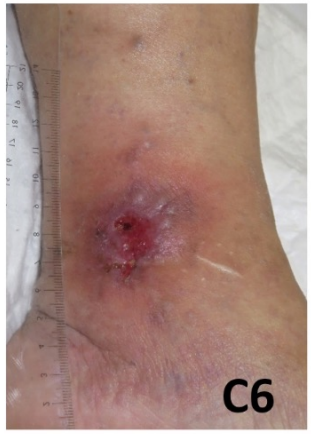






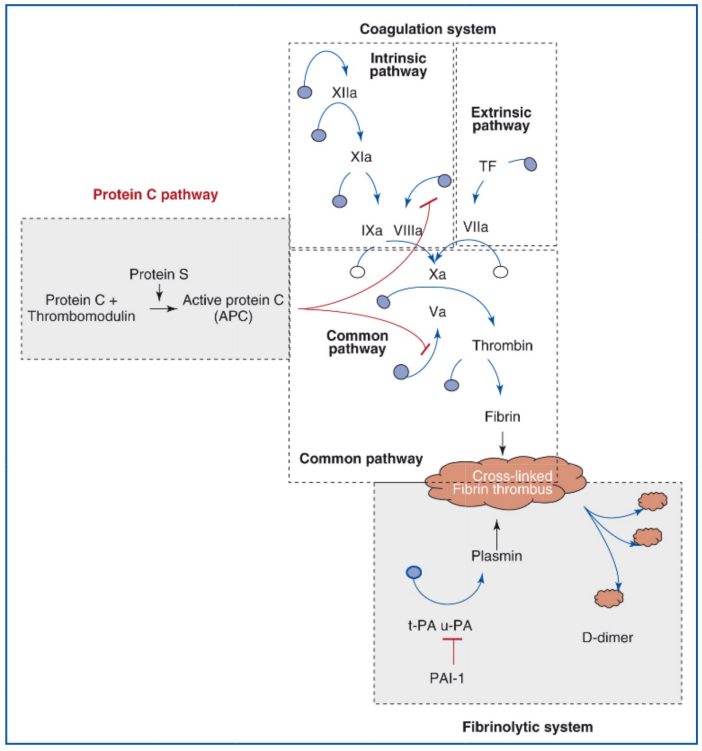






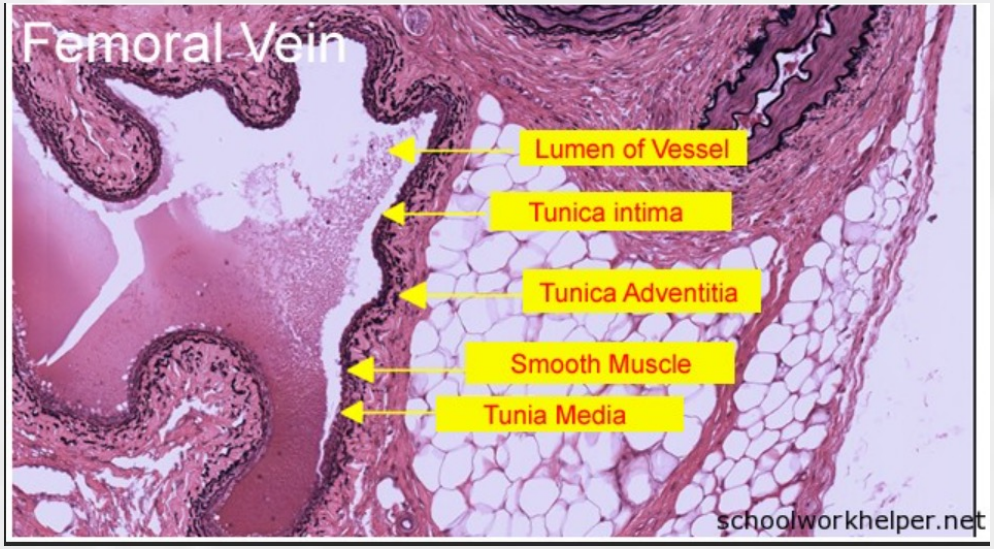
ENDOTHELIUM

- Under normal conditions, endothelial cells maintain a vasodilatory and local fibrinolytic state in which coagulation, platelet adhesion, and activation are suppressed
- A NON-THROMBOGENIC STATE IS MAINTAINED BY
  - (1) endothelial production of thrombomodulin and subsequent activation of protein C
  - (2) endothelial expression of heparan sulfate and dermatin sulfate, which accelerate antithrombin (AT) and heparin cofactor II activity
  - (3) constitutive expression of tissue factor pathway inhibitor (TFPI)
  - (4) local production of tissue plasminogen activator (tPA) and urokinase-type plasminogen activator (uPA)



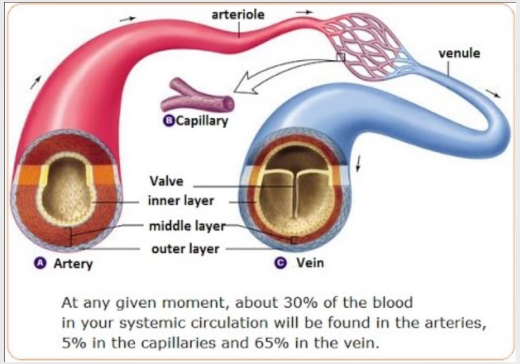
ENDOTHELIUM

- Produces Nitric Oxide and Prostacyclin
  - Inhibits adhesion and activation of leukocytes
  - Produces vasodilatation
  - Inhibits production of tissue factor(TF)
- vonWillebrand Factor (vWF)
  - **VEINS>>** arteries



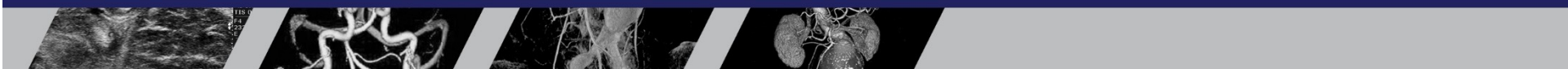
VENOUS BIOMECHANICS

- LARGE VOLUME CAPACITANCE AND TONAL REGULATION
  - Can rapidly redistribute blood volume
  - 60-80% of circulating blood in venules and systemic veins
- VENOUS PRESSURES
  - 100mm Hg at foot standing (5’10”, 165 lbs)
  - Rapidly decreases with recumbency and ambulation



VENOUS BIOMECHANICS

- VEINS CHANGE SHAPE TO ACCOMMODATE
  - Blood volume change
  - Pressure change
- VASCULAR RESISTANCE
  - Lower with circular shape than elliptical shape
  - Larger volume→circular shape→decreased resistance

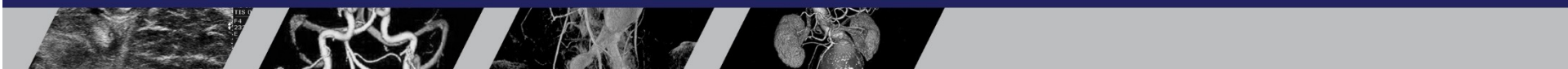


VENOUS BIOMECHANICS

- VEINS
  - Lack extensive elastic lamella but remain markedly distensible in low pressure range
  - ↓ratio of wall thickness/radius=↑elastic modulus=↑rupture pressure than arteries

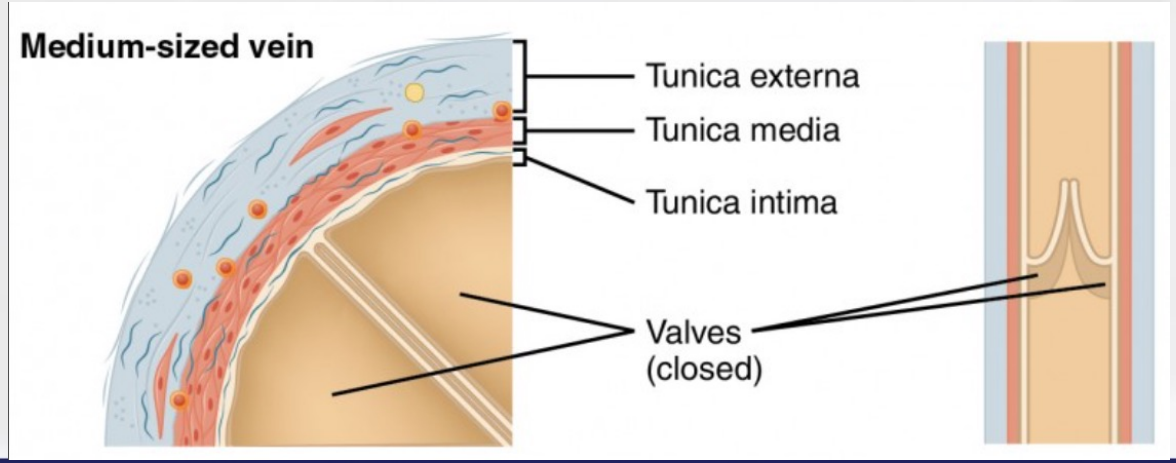
VEINS 

BETTER



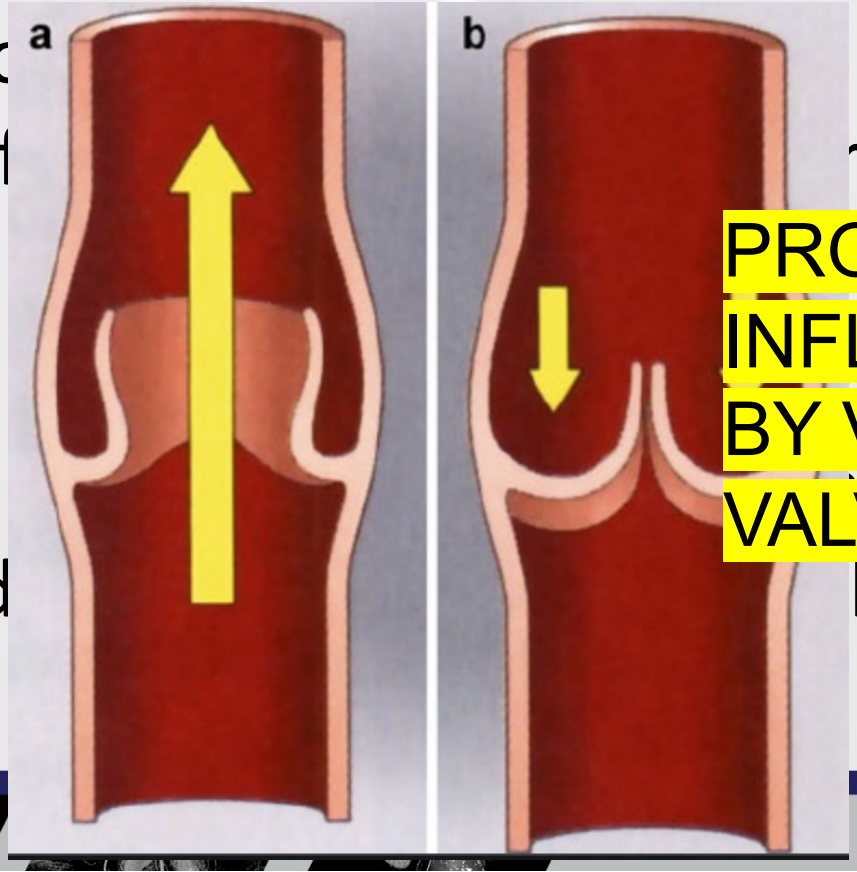
VENOUS VALVES

- Endothelial-lined folds of tunica intima
  - Allow unidirectional flow
  - Contribute to pressure reduction
  - Maintain blood flow



DETERMINANTS OF PRESSURE IN VEINS OF LEGS

- Hydrostatic co… weight of the column of… rium to the foot
- Hydrodynami… generated by … muscles of the leg and … llary network.



PROFOUNDLY INFLUENCED BY VENOUS VALVES

VENOUS VALVE FUNCTION

- Operated by pressure as opposed to flow
  - Very little reflux results in complete closure
- Valves open and close approx 20x/min
- Leaflets do not contact wall of the vein
- 2 types of flow
  - Axial through the valve
  - Vortical in valve sinus
    - Prevents stasis
    - All surfaces of valve exposed to shear stress

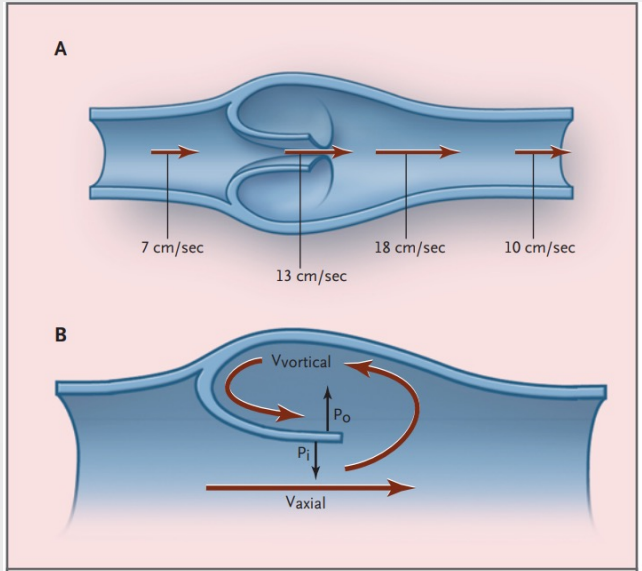
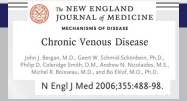


Figure 3. Velocity of Blood Flow through a Venous Valve (Panel A) and Forces Acting on a Venous Valve Leaflet (Panel B).

In Panel A, the reduced cross-sectional area between the valve leaflets produces a proximally directed jet of increased axial velocity. In Panel B, axial flow between the leaflets generates a pressure (P_o) that tends to keep the leaflet in the open position, and vortical flow in the valve pocket generates a pressure (P_i) that tends to close the leaflet. These pressures depend on the respective flow velocities ($V_{vortical}$ and V_{axial}); pressure is inversely related to velocity. (Adapted from Lurie et al.[49] with the permission of the publisher.)



VENOUS PRESSURE VARIANCE

- STANDING
  - HYDROSTATIC PRESSURE 80-90mm Hg
- WALKING
  - Transient increase in deep veins
  - If venous valves competent, superficial and deep veins empty with muscle contraction and pressure drops to 30mm

  -- If venous valves incompetent, deep venous pressure transmitted to superficial veins and skin

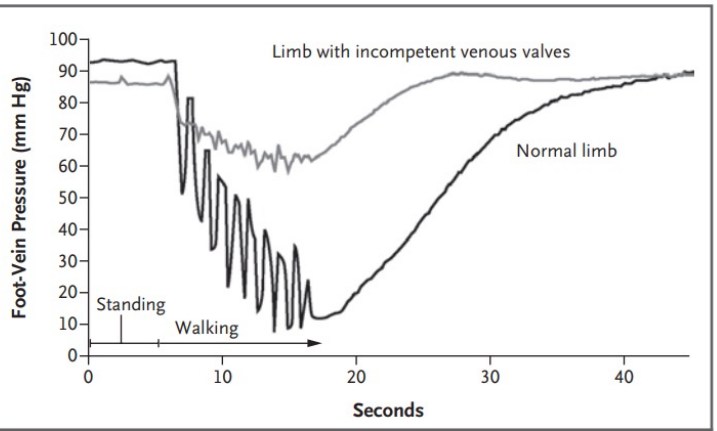


Figure 2. Action of the Musculovenous Pump in Lowering Venous Pressure in the Leg.

After prolonged standing, venous pressure in the foot is approximately 90 mm Hg in both a patient with incompetent venous valves and a person with a normal leg. During walking, the musculovenous pump rapidly lowers the venous pressure in the normal leg but is ineffective in the leg with valvular incompetence. (Reproduced from Coleridge Smith[26] with the permission of the publisher.)

The NEW ENGLAND JOURNAL of MEDICINE

MECHANISMS OF DISEASE

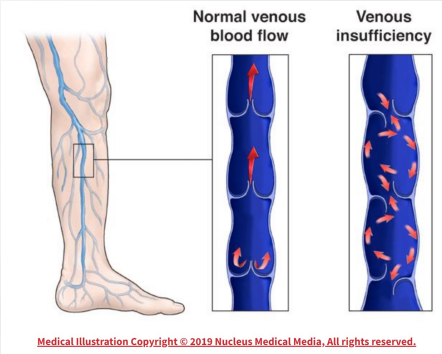
Chronic Venous Disease

John J. Bergan, M.D., Geert W. Schmid-Schönbein, Ph.D., Philip D. Coleridge Smith, D.M., Andrew N. Nicolaides, M.S., Michel R. Boisseau, M.D., and Bo Eklof, M.D., Ph.D.

N Engl J Med 2006;355:488-98

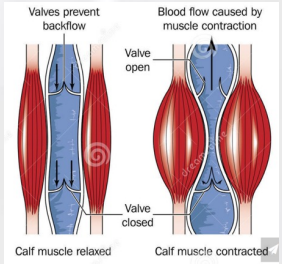
CHRONIC VENOUS INSUFFICIENCY (CVI)

VENOUS REFLUX

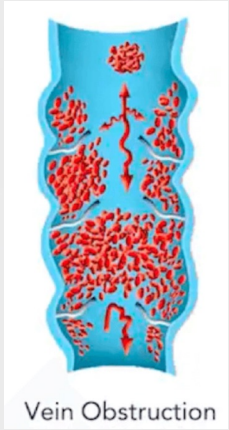


OBESITY/IMMOBILITY

(FAILURE OF CALF PUMP)

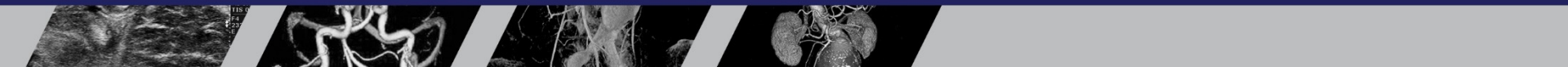


OBSTRUCTION



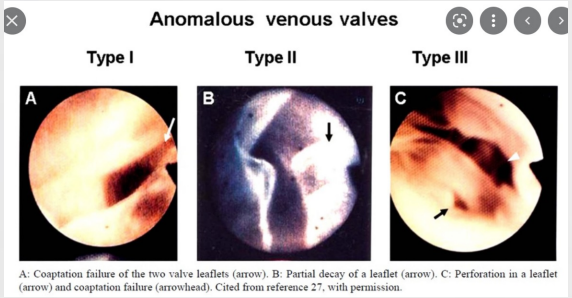
↓↓↓↓↓↓↓↓↓

VENOUS HYPERTENSION



CHRONIC VENOUS INSUFFICIENCY (CVI)

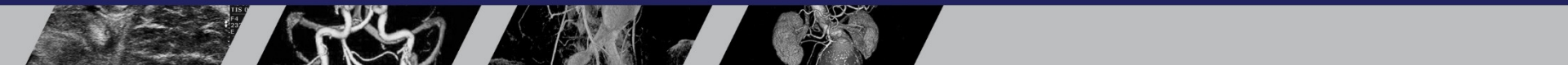
- PRIMARY VALVULAR INCOMPETENCE--70 to 80%
- SECONDARY VALVULAR INCOMPETENCE—18-25%
  - TRAUMA
  - DVT
- CONGENITAL ANOMALY—1-3%



A: Coaptation failure of the two valve leaflets (arrow). B: Partial decay of a leaflet (arrow). C: Perforation in a leaflet (arrow) and coaptation failure (arrowhead). Cited from reference 27, with permission.

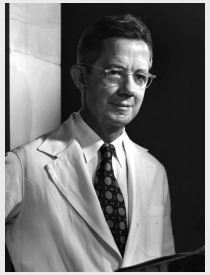
Labropoulos N. Hemodynamic changes according to the CEAP classification. Phlebolymphology 2003;40:130-6.

Kistner RL, Eklof B, Masuda EM. Diagnosis of chronic venous disease of the lower extremities: the “CEAP” classification. Mayo Clin Proc 1996;71:338-45.



HISTORICAL THEORIES

- STASIS/HYPOXIA
  - Homans—stagnant blood in VV led to anoxia and cell death
  - DeTakais—lower O2 content in blood from ankle than antecubital fossa
  - Blalock—DISCOUNTED→found HIGHER O2 content in blood from LE w/ VV and w/ venous ulcer



- ARTERIOVENOUS SHUNTING
  - Piulacks and VidalBarraquer (1953)—>found no direct evidence

HISTORY

- Landis (1930)—pressure elevation in veins translates to capillaries
- Whimster (1956)—showed increase in intradermal capillary bed in some patients with venous stasis disease
- Browse/Burnand (1982)—
  - increased size of capillary bed leads to increased permeability of capillary bed with escape of a large molecule-fibrinogen
  - Interendothelial pores stretch in response to increased pressure
  - Fibrinogen then polymerizes into an insoluble form which produces a barrier to the diffusion of oxygen and other nutrients to the epidermis for its repair

THE CAUSE OF VENOUS ULCERATION

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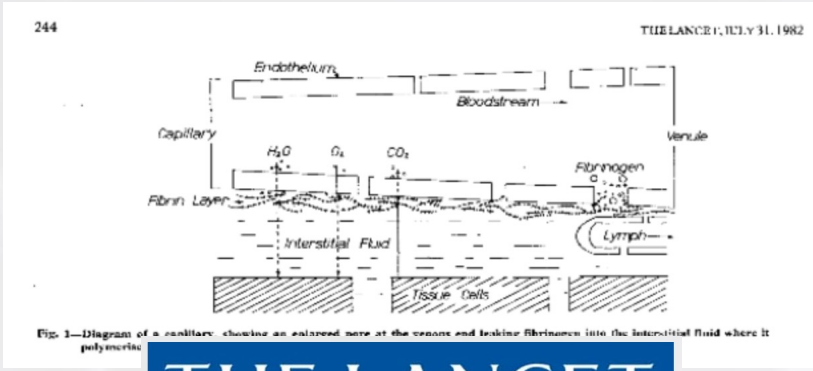


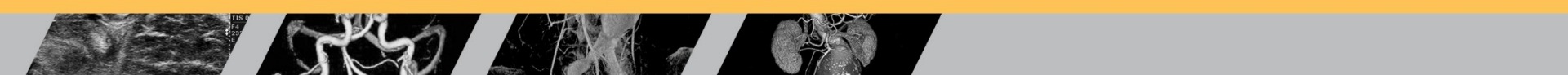
Fig. 1—Diagram of a capillary, showing an enlarged pore at the venous end leaking fibrinogen into the interstitial fluid where it polymerizes

THE LANCET

1982:2(8292):243-245

VARICOSE VEINS

- GENETIC PREDISPOSITION
  - IF both parents→90%
  - One parent→62% if female, 25% if male
  - Neither parent→20%
- ALTERED VASOREACTIVITY
  - Decreased contractility in response to α- and non-α-adrenergic receptors
  - Defining whether this is secondary to **initial wall defect** or a **secondary hemodynamic defect** remains under DEBATE



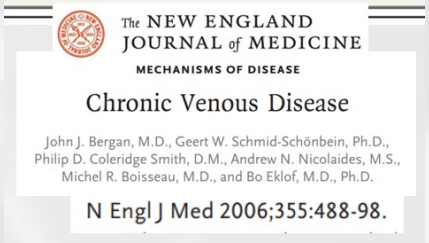
STRUCTURAL CHANGES IN VEIN WALL

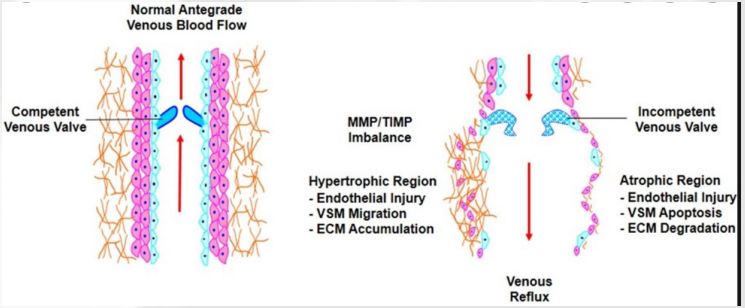
DISTURBED COLLAGEN SYNTHESIS
↑ TYPE 1 (rigidity), ↓ TYPE 3 (distensibility)

DISRUPTION OF SMOOTH MUSCLE CELLS/ELASTIN FIBERS

ALTERNATING AREAS OF HYPERTROPHY AND ATROPHY
DEGRADATION of ECM→atrophy
PROTEOLYTIC ENYMES—MMPs and serine proteases
Produced by vascular and inflammatory cells

MMP (matrix metalloproteinases) inhibition by TIMP (tissue inhibitor of metalloproteinases)→hypertrophy
Ratios of TIMP/MMP greater in VV than in controls
↑Transforming growth factor/Fibroblast growth factor
TGF→stimulates elastin/collagen/TIMP
FGF→mitogen for SMC



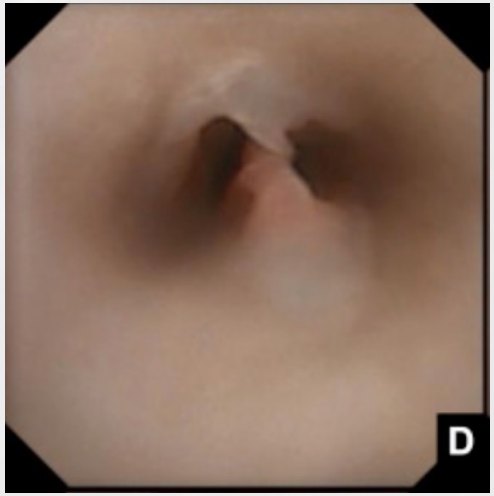


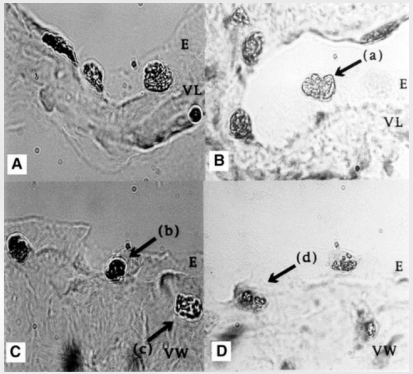
CHANGES IN VALVES ASSOC'D W VENOUS HTN

- ANGIOSCOPIC EVALUATION
  - Tearing van Cleef JF, Hugentobler JP, Desvaux P, Griton P, Cloarec M. Étude endos copique des reflux valvulaires saphéniens. J Mal Vasc 1992;17:Suppl B:113-6.
  - Stretching
  - Splitting
  - Valve leaflet adhesion
- DECREASED NUMBER OF VALVES IN GSV IN PATIENTS WITH CVI

  Sales CM, Rosenthal D, Petrillo KA, et al. The valvular apparatus in venous insufficiency: a problem of quantity? Ann Vasc Surg 1998;12:153-5
- INFILTRATION OF LEAFLETS WITH MONOCYTES/MACROPHAGES

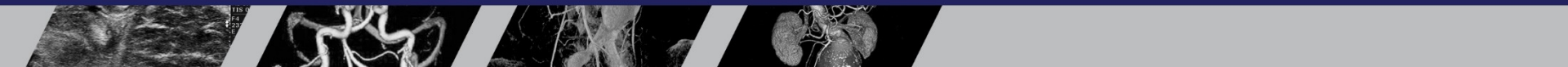
Ono T, Bergan JJ, Schmid-Schönbein GW, Takase S. Monocyte infiltration into venous valves. J Vasc Surg 1998;27:158-66





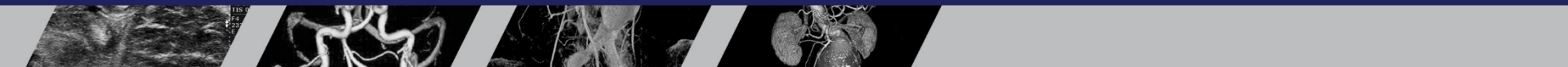
SKIN CHANGES

- AMBULATORY VENOUS PRESSURE
  - IF <30→NO ULCERATION
  - IF >90→100% ULCERATION
  - Nicolaides AN, Hussein MK, Szendro G, Christopoulos D, Vasdekis S, Clarke H. The relation of venous ulceration with ambulatory venous pressure measurements. J Vasc Surg 1993;17:414-9
- CURRENT THEORY
  - NO LONGER FELT TO BE SECONDARY TO FIBRIN CUFFS IMPEDING OXYGEN DIFFUSION
  - NOW FELT SECONDARY TO CHRONIC INFLAMMATION



EFFECT OF SHEAR STRESS

- Pulsatile, laminar shear stress (PROTECTIVE)
  - Reduces inflammation
  - Reduces free radical generation
- Leukocyte response to shear stress
  - Retraction of pseudopods
  - Shedding of CD18 adhesion molecules
- Low shear stress (turbulent flow, flow reversal)
  - Promotes thrombotic and inflammatory phenotype



EFFECTS OF SHEAR STRESS

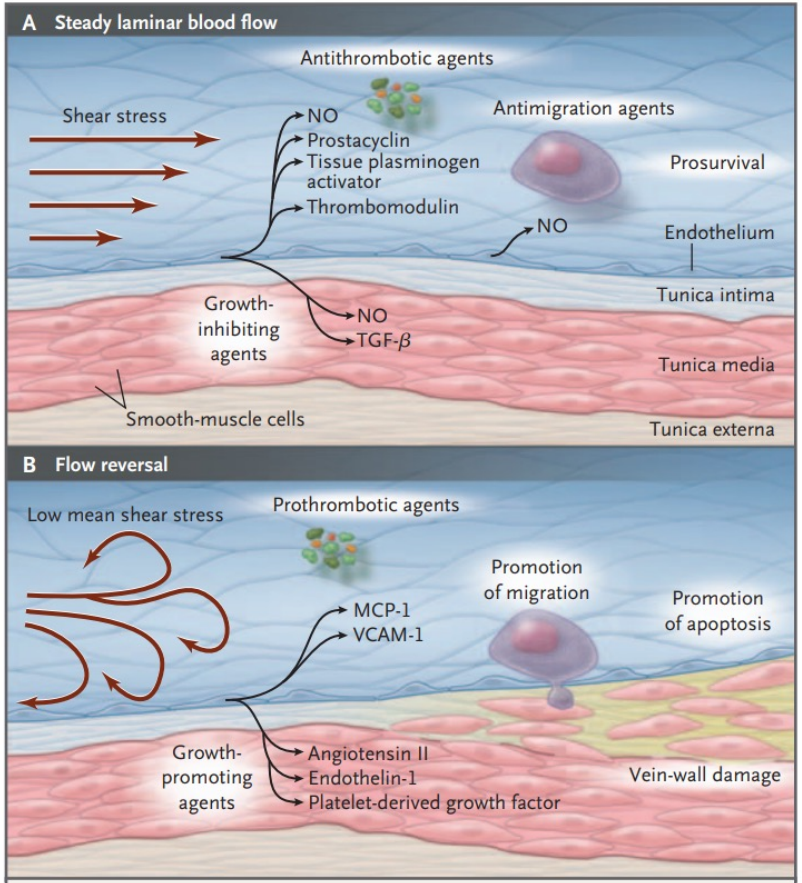
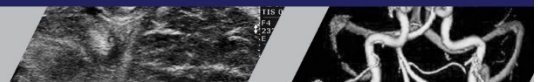


Figure 4. Contrasting Effects of Steady, Laminar Shear Stress (Panel A) and Turbulent or Reversing Shear Stress (Panel B) on Vessel Walls.

NO denotes nitric oxide, MCP-1 monocyte chemoattractant protein 1, and VCAM-1 vascular-cell adhesion molecule. (Reproduced from Traub and Berk[50] with the permission of the publisher.)



CHRONIC INFLAMMATION

- VENOUS BLOOD RETURN FROM DEPENDENT FEET
  - DEPLETED OF LEUKOCYTES ESPECIALLY IN CVI PTS
  - SUGGESTS THAT LEUKOCYTES ACCUMULATE IN LIMBS WITH ELEVATED VENOUS PRESSURE

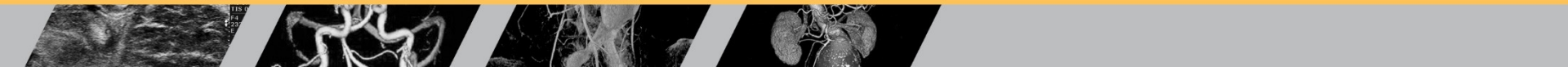
LEUKOCYTE TRAPPING HYPOTHESIS

VENULES

- VENOUS CONGESTION
  - PLASMINOGEN ACTIVATOR RELEASED WHICH ACTIVATES LEUKOCYTES

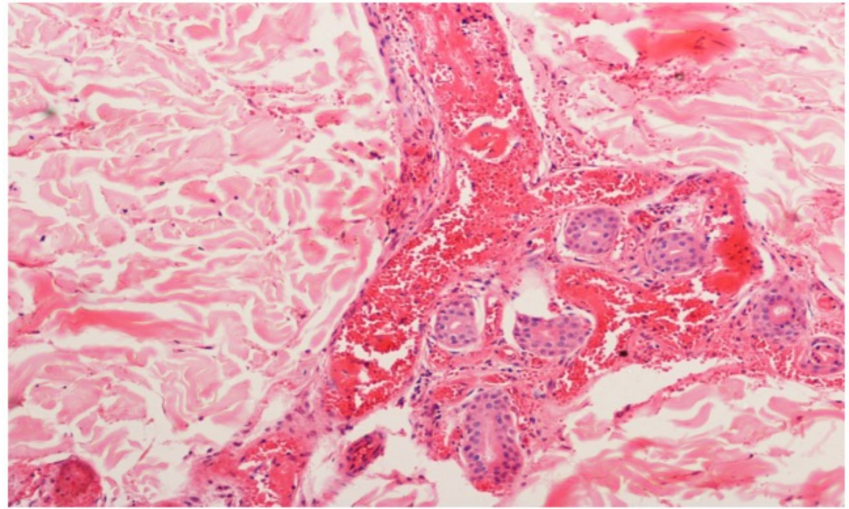
MECHANISMS OF INFLAMMATION

- Inactivated LEUKOCYTES ROLL
  - Leukocyte—L selectin + endothelial--E selectin
- ACTIVATED LEUKOCYTES ADHERE
  - Leukocytes shed L selectin into plasma and express integrin—CD 11b which binds to intercellular adhesion molecule (ICAM)
  - This is the first step in leukocyte migration



Link b/t INFLAMMATION & SKIN CHANGES

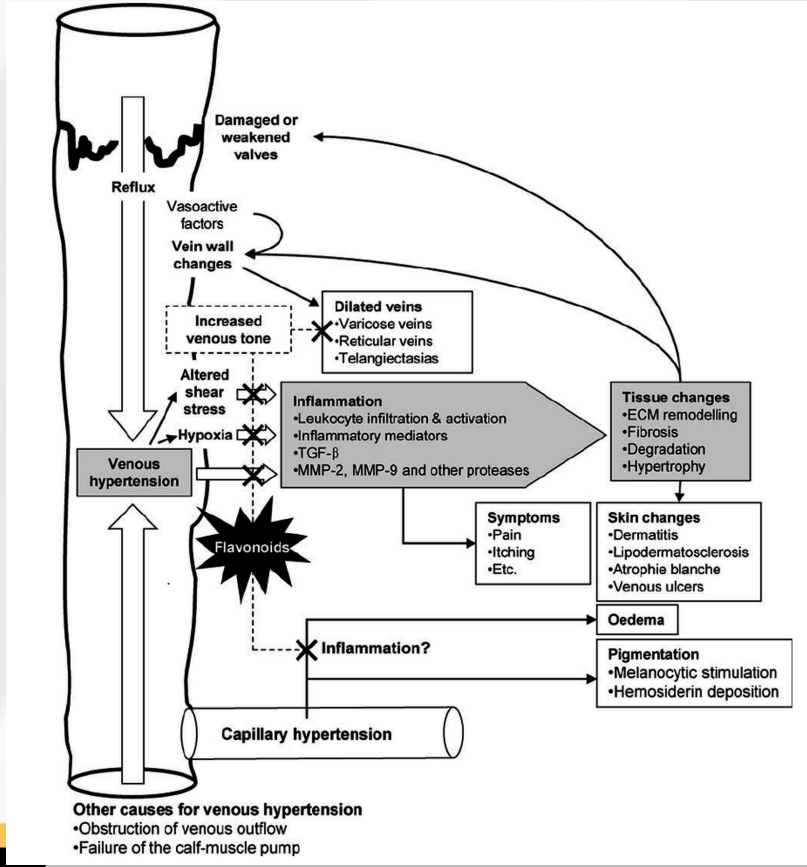
- ↑VEGF—increased capillary permeability
- ↑ TGF-β—leads to dermal fibrosis
- RBC extravasation→ ↑ ferritin and ferric iron
  - Oxidative stress
  - ↑MMP



Skin biopsy showing extravasation RBC in the dermis

SUMMARY

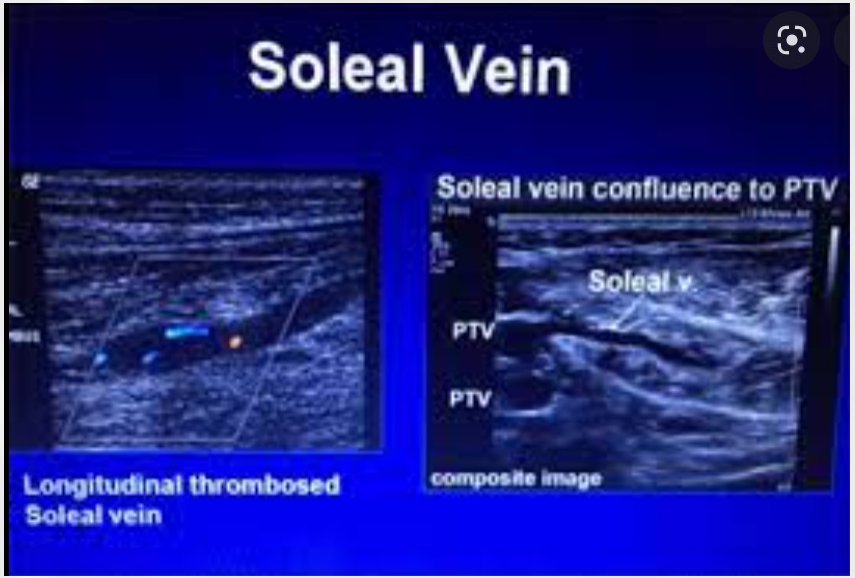
- VENOUS HYPERTENSION
- CHANGES IN VEIN WALL
  - Collagen, SMC, Elastin,ECM
- LOW SHEAR STRESS (flow rev)
- INFLAMMATORY PHENOTYPE



THANK YOU

RESTING STATE OF FIBRINOLYTIC SYSTEM

- LOWEST IN THE AREA OF THE VALVE
- DEEP VEINS IN LOWER EXTREMITY HAVE THE LOWEST FIBRINOLYTIC ACTIVITY IN THE SOLEAL SINUSES/POPLITEAL AND FEMORAL REGIONS
- THIS HYPOTHESIS AS TO WHY DVT ORIGINATES IN THE LOWER LIMB



Overall, it appears that inflammatory processes involving leukocyte–endothelial interactions and triggered largely in response to abnormal venous flow are important in causing the adverse changes in venous valves and vein walls.

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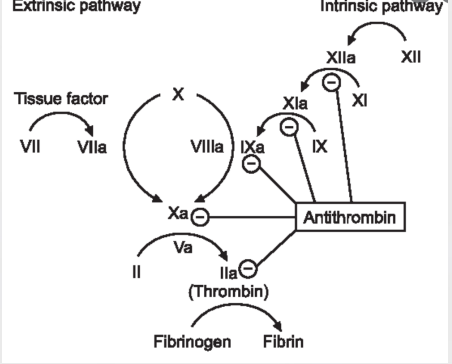

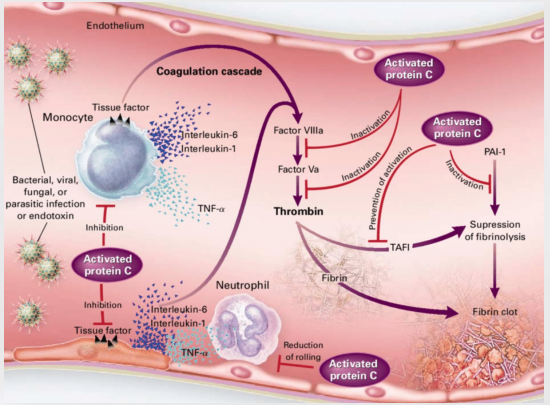

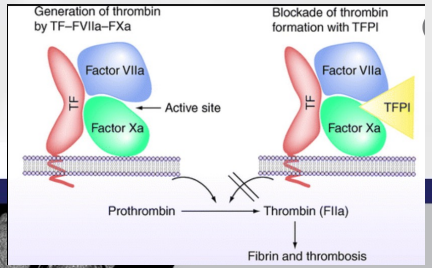

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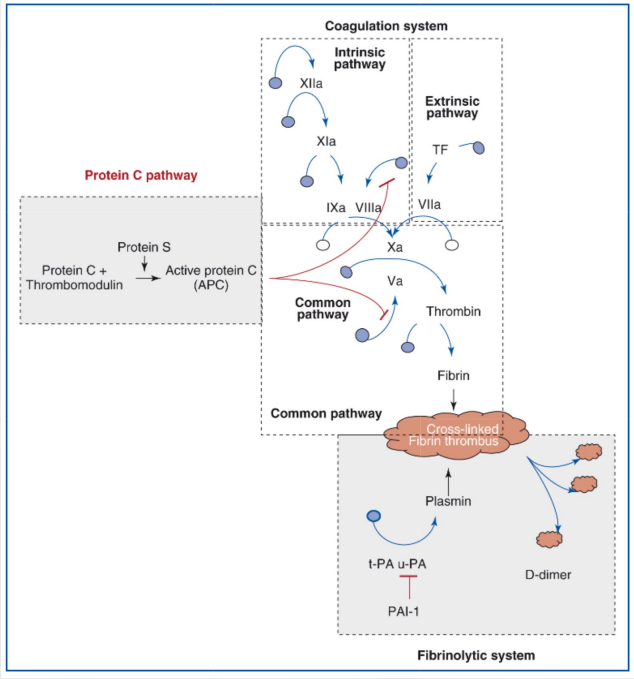

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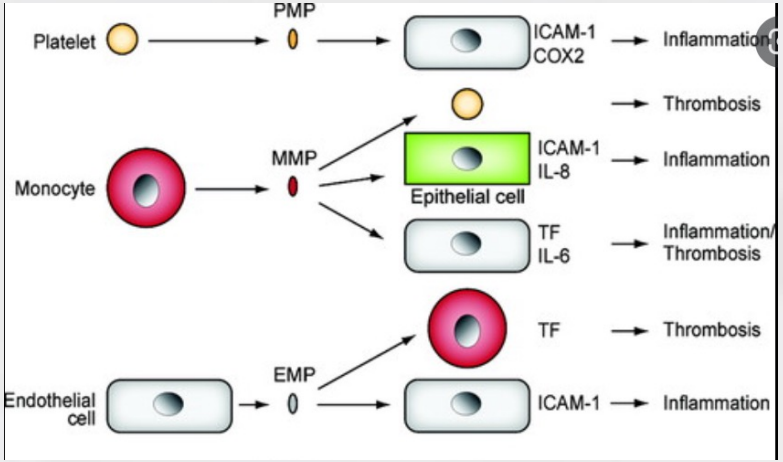

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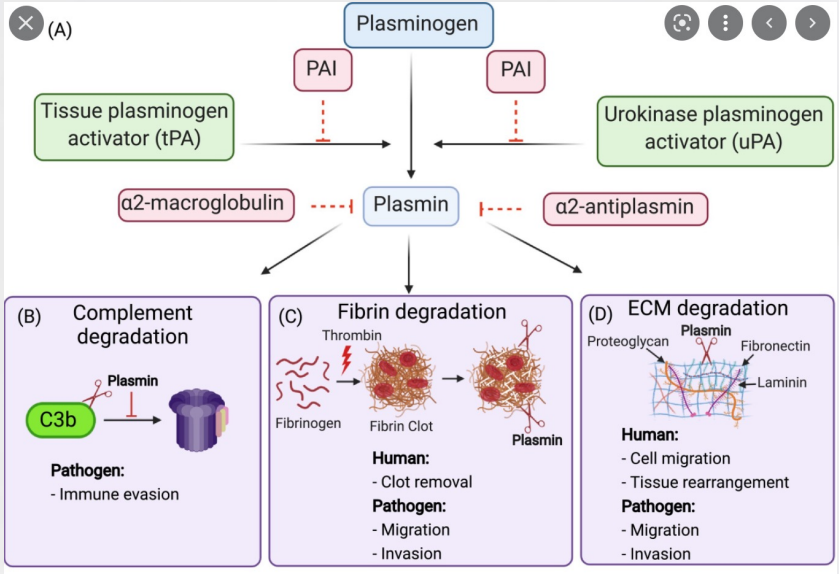

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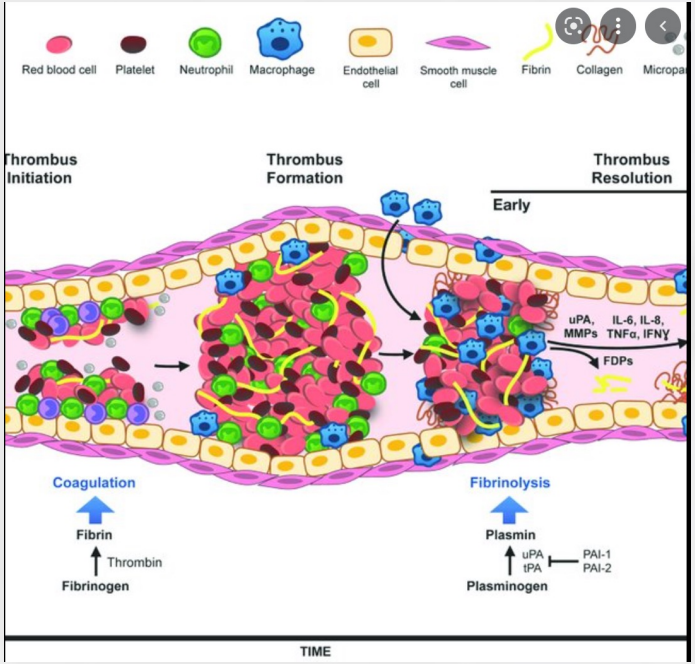

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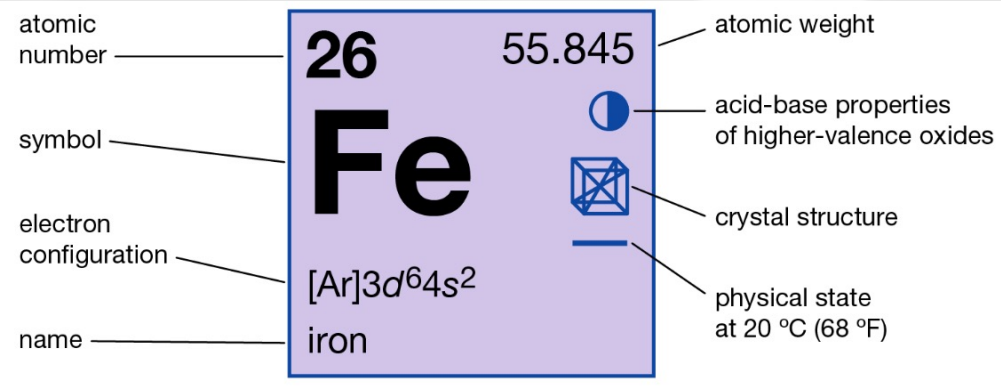
        - » Fifth level

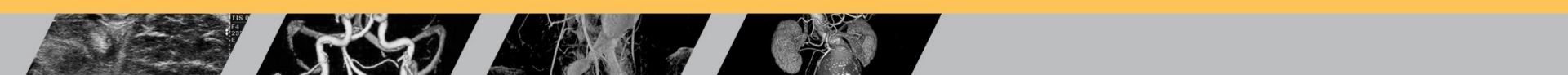
Link b/t INFLAMMATION & SKIN CHANGES

- IRON METABOLISM
  - RISK OF ULCER DEVELOPMENT IN PTS WITH CLASS 4-6 CVI WAS 7X GREATER IN THOSE WITH C282Y genotype—a mutation related to iron processing



VARICOSE VEINS

- GENETIC PREDISPOSITION
  - IF both parents→90%
  - One parent→62% if female, 25% if male
  - Neither parent→20%
- MATRIX DYSREGULATION
  - Altered expressions of Collagen I and III
  - Net effect of matrix deposition
  - Upregulation of MMP's and fibrinolytic activity
- ALTERED VASOREACTIVITY
  - Decreased contractility in response to α- and non-α-adrenergic receptors
  - Defining whether this is secondary to **initial wall defect** or a **secondary hemodynamic defect** remains under DEBATE

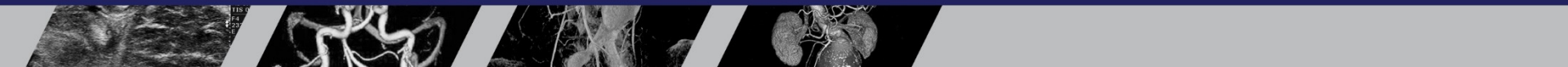


VENOUS ULCERATION

- SUPERFICIAL REFLUX—45%.
- DEEP REFLUX—12%
- BOTH—43%

European Journal of Vascular & Endovascular Surgery
esvs Journal

Tassiopoulos AK, Golts E, Oh DS, Labropoulos N. Current concepts in chronic venous ulceration. Eur J Vasc Endovasc Surg 2000;20:227-32



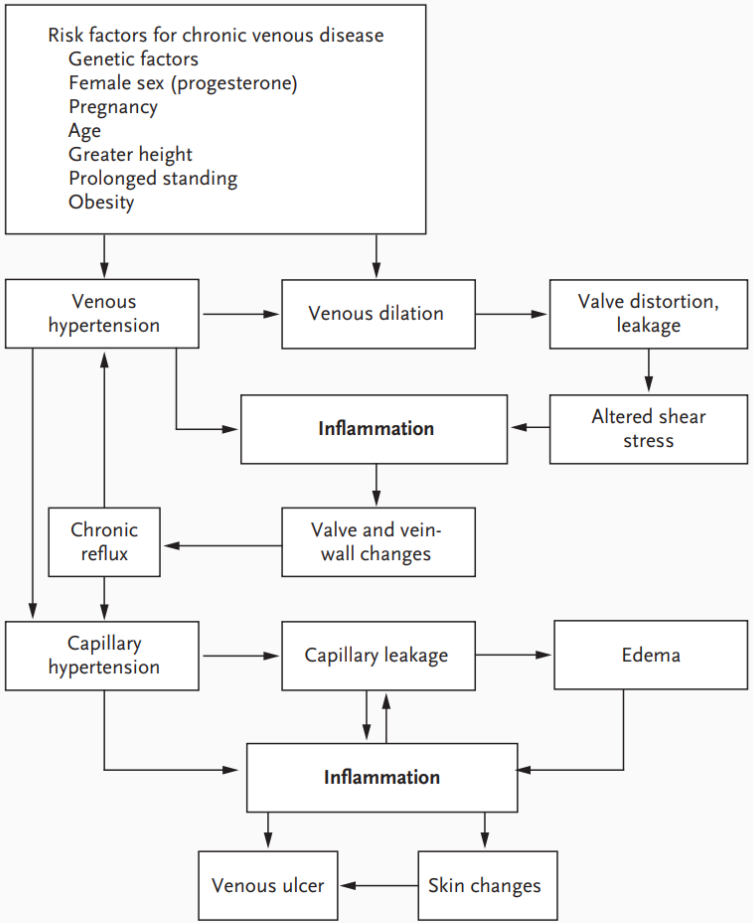


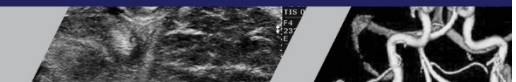
Figure 5. Venous Hypertension as the Hypothetical Cause of the Clinical Manifestations of Chronic Venous Disease, Emphasizing the Importance of Inflammation.

The NEW ENGLAND JOURNAL of MEDICINE
MECHANISMS OF DISEASE

Chronic Venous Disease

John J. Bergan, M.D., Geert W. Schmid-Schönbein, Ph.D., Philip D. Coleridge Smith, D.M., Andrew N. Nicolaides, M.S., Michel R. Boisseau, M.D., and Bo Eklof, M.D., Ph.D.

N Engl J Med 2006;355:488-98.



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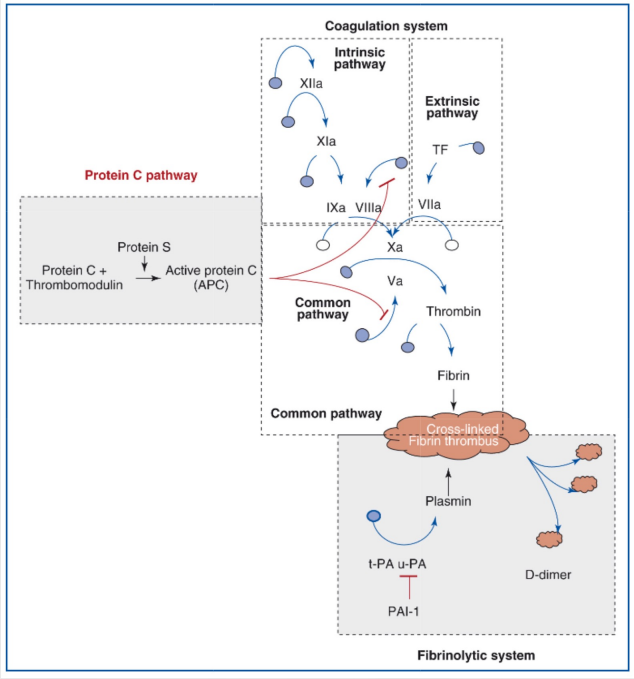

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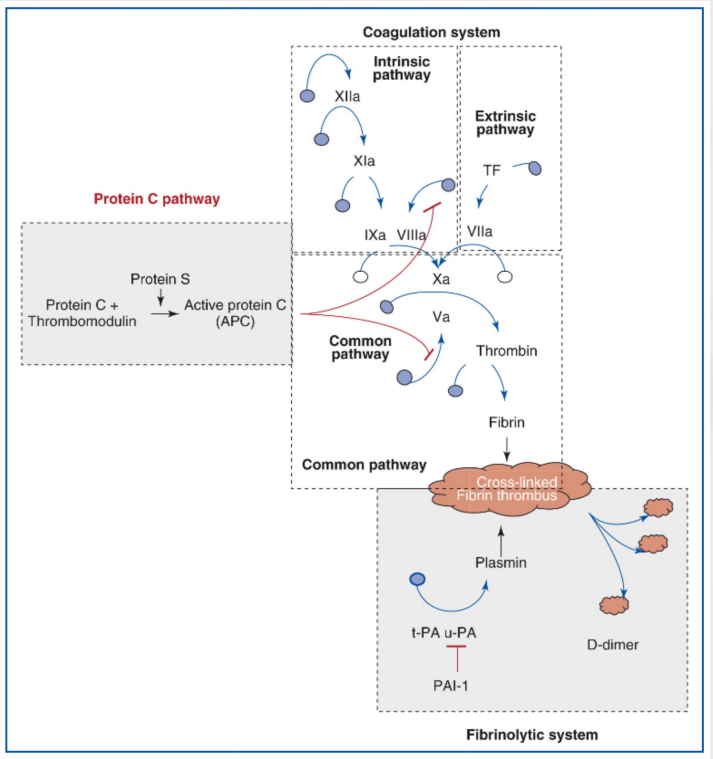

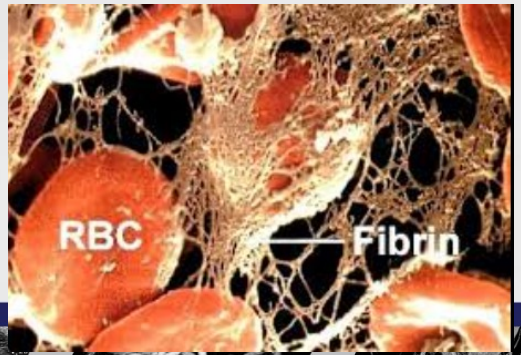

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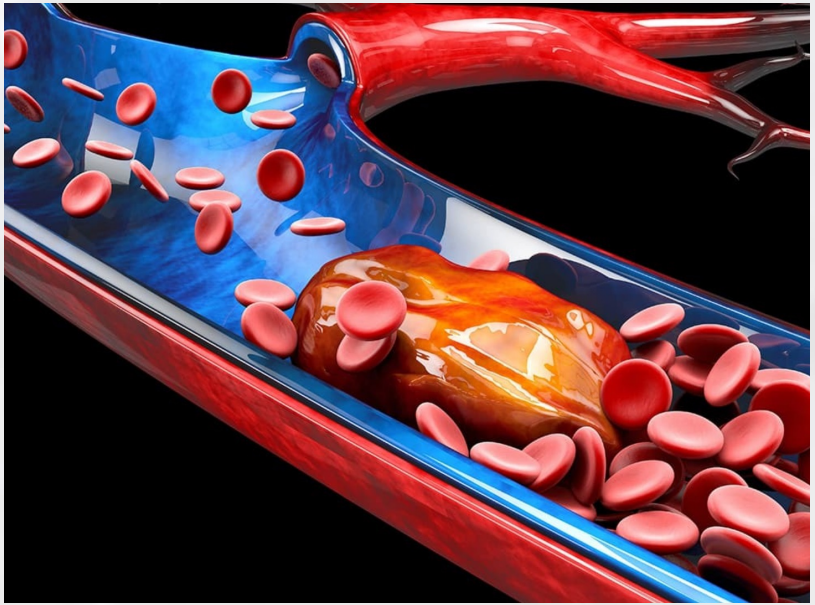

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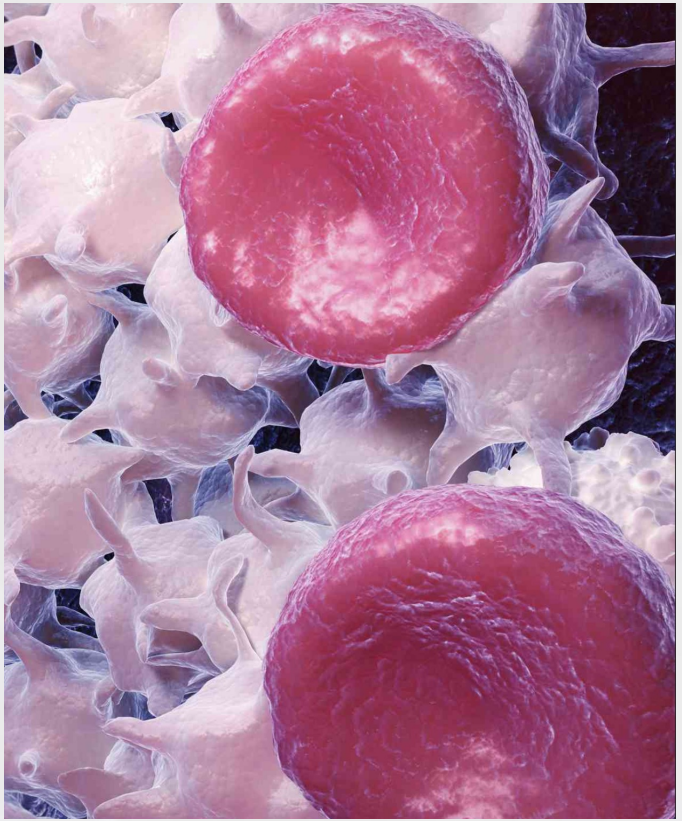

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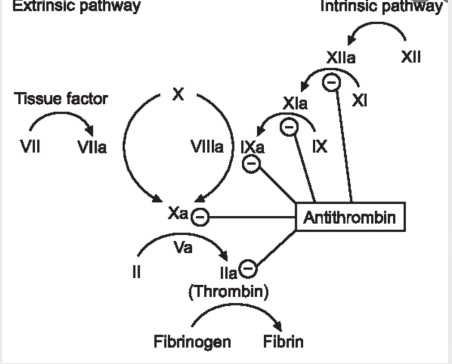

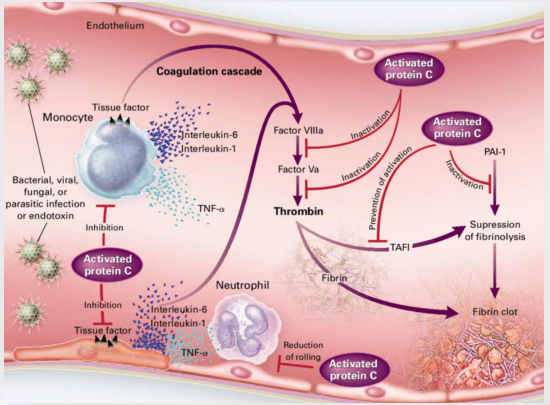

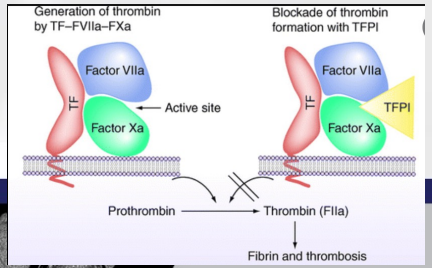

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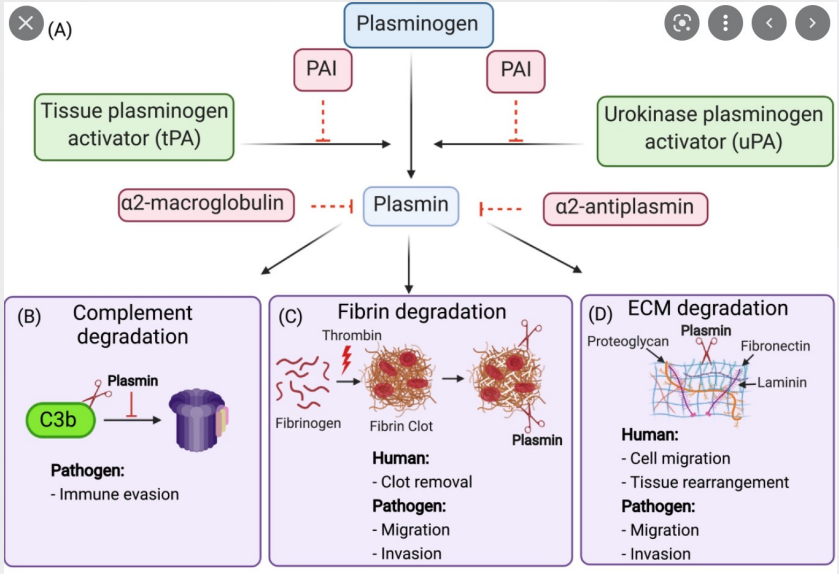

RESTING STATE OF FIBRINOLYTIC SYSTEM

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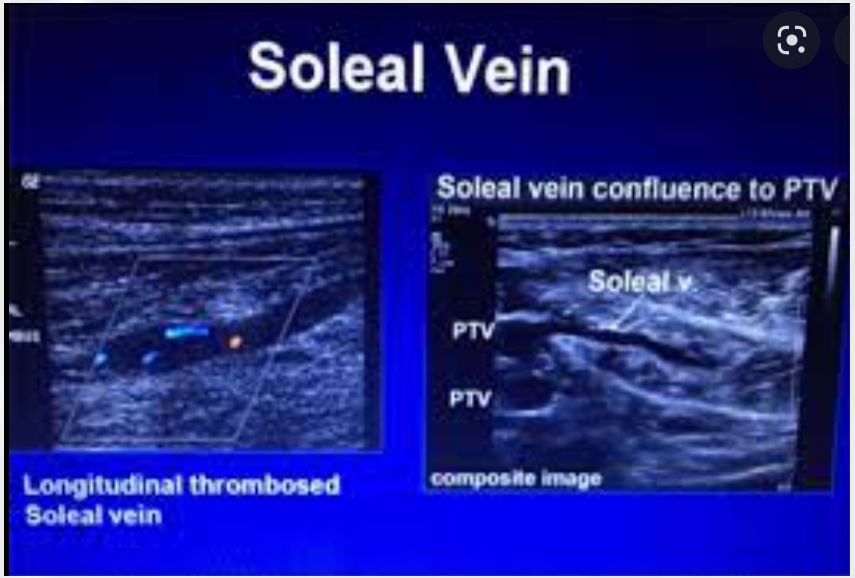
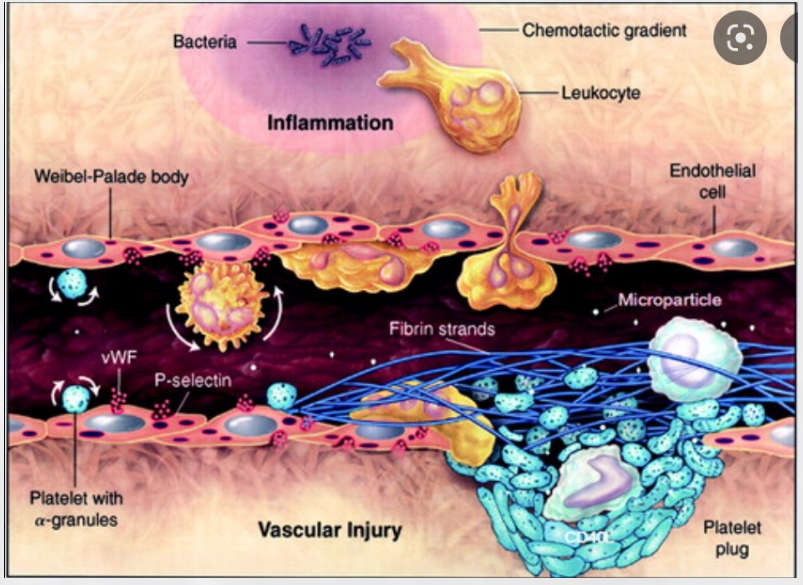


INFLAMMATION & THROMBOSIS

- INCREASES
  - TISSUE FACTOR
  - MEMBRANCE PHOSPHOLIPIDS
  - FIBRINOGEN
  - PLATELET REACTIVITY
- DECREASES
  - THROMBOMODULIN
  - INHIBITS FIBRINOLYSIS



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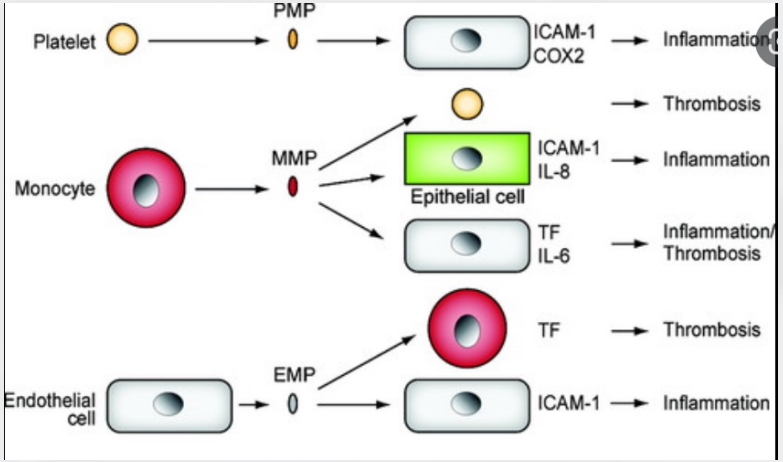

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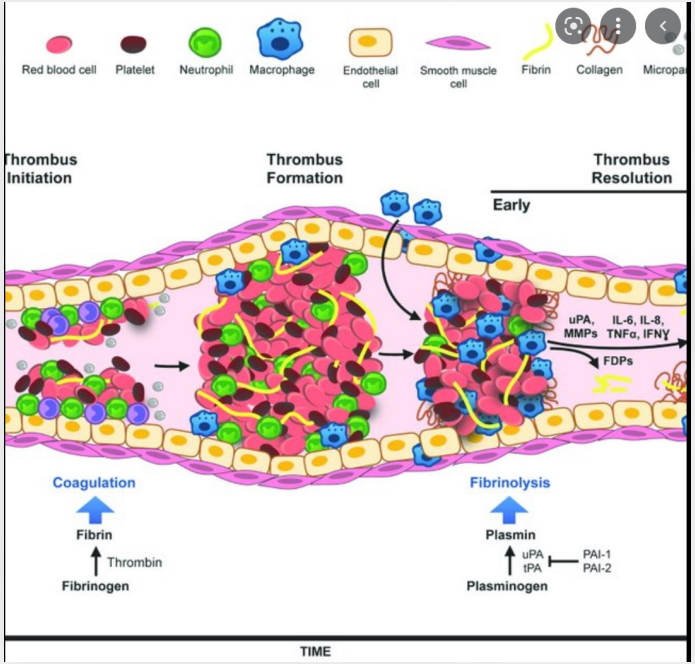

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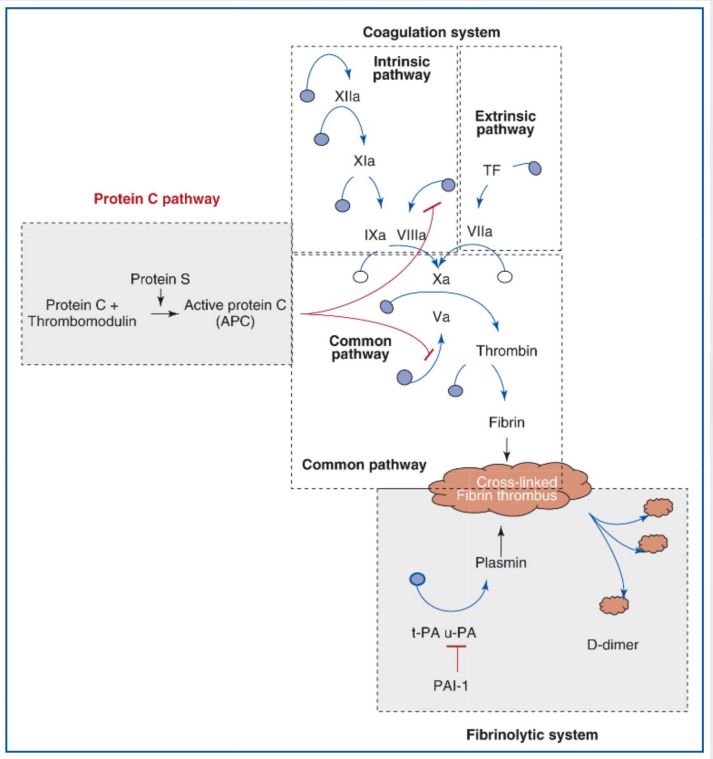

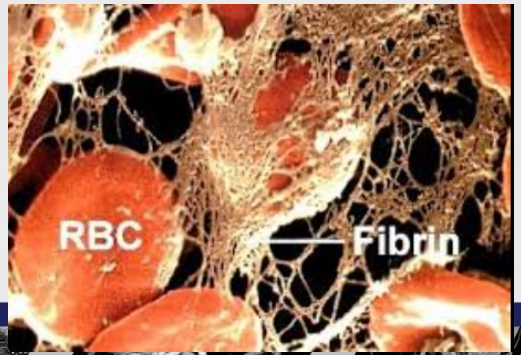

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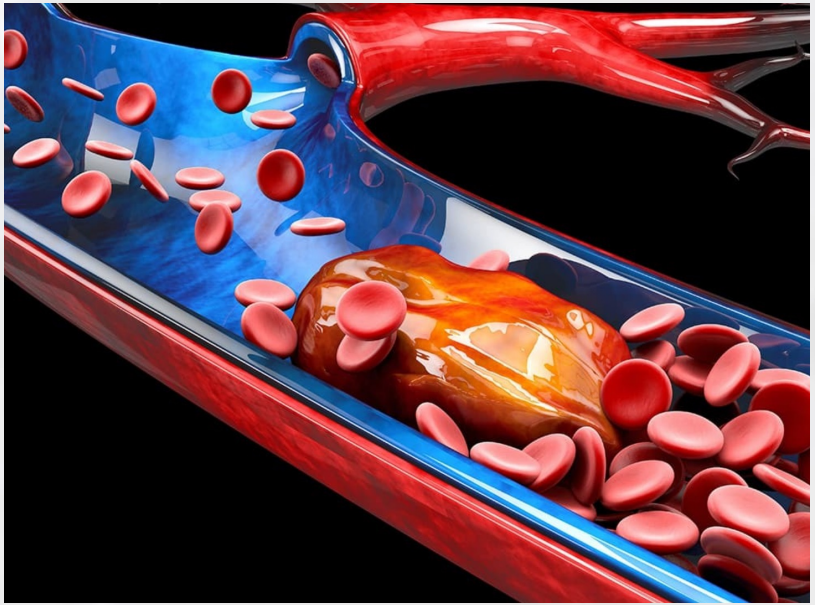

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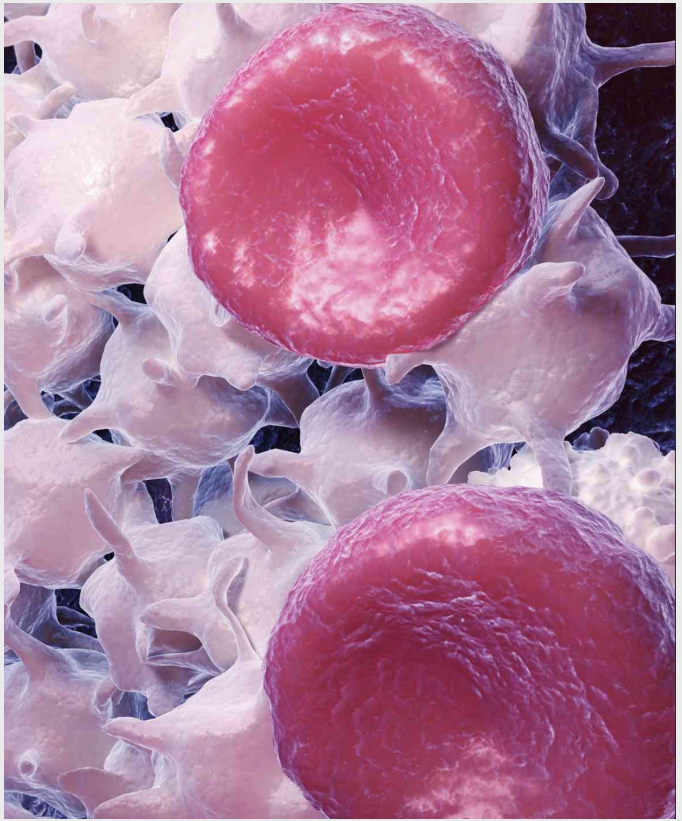
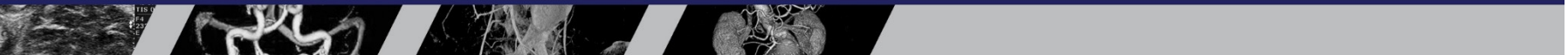


THE CAUSE OF VENOUS ULCERATION

N. L. BROWSE K. G. BURNAND

Department of Surgery, St Thomas' Hospital, London SE1



Hypothesis

THE CAUSE OF VENOUS ULCERATION

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THE association between ulceration at the ankle and venous disorders of the lower limb has been known for over 2000 years.[1] The major role of deep-vein damage has been recognised[2] since Gay and Spender in 1868[3,4] reported that many "venous ulcers" developed in the absence of varicose veins. Although the effect of a venous abnormality can now be defined by measuring the fall in foot-vein pressure that can be achieved by exercise,[5] the mechanism by which the lack of venous hypotension during exercise leads to skin ulceration remains uncertain.

EXISTING THEORIES

The two principal theories of the cause of venous ulcers—venous stasis and arteriovenous shunting—have both been criticised following experimental studies designed to test their validity. We now review this work and summarise the experimental work which has led us to formulate and attempt to verify a new theory.

Venous Stasis

Homans[6] suggested that stagnant blood lying within tortuous and dilated veins close to the skin might cause tissue anoxia and cell death. This concept was supported by De Takats et al.,[7] who found that the oxygen content of blood taken from varicose veins was lower than that in blood taken from the antecubital vein of the same patient. These findings were criticised by Blalock,[8] who suggested that these differences were solely the result of the dependent posture of the limb at the time of sampling. He showed that patients with unilateral varicose veins had a higher oxygen content in the femoral venous blood of the diseased leg. He also found a higher oxygen content in the venous blood of limbs with venous ulcers, thus demolishing the concept that stasis causes anoxia and ulceration. His findings have subsequently been confirmed with more sophisticated sampling techniques and better equipment for blood-gas analysis.[9-11] Despite this work the concept of anoxia caused by stasis producing "gravitational ulcers"[12] is still taught today.[13]

Arteriovenous Shunting

In 1953 Piulachs and Vidal Barraquer[14] confirmed that the venous blood in limbs with varicose veins, the post-thrombotic syndrome, or ulceration all had a higher venous oxygen content and a faster circulation time than normal. This led them to support the tentative ideas of Pratt[15] and Brewer[16] that these haemodynamic features were caused by arteriovenous communications opening up beneath the skin, resulting in the death of the overlying tissues by anaemic anoxia. This concept received support from a number of indirect observations,[16,17] but direct evidence for the existence of these fistulae is poor and open to criticism.[18] Techniques using radioactively labelled macroaggregates[19] or microspheres[20] have not demonstrated shunting in patients with venous insufficiency or ulceration. Consequently this theory must also be viewed with suspicion.

A NEW THEORY

In 1930 Landis showed that elevation of the venous pressure produces an equivalent rise in the intraluminal pressure of the capillary bed.[21] Isolated limb perfusion studies have shown that changes of venous pressure affect capillary filtration and absorption five to ten times more than an equivalent change in arterial pressure.[22] In 1956 Whimster reported an enlargement of the local dermal capillary bed in some patients with chronic venous insufficiency.[23] We have investigated a large number of limbs to see if there is a relation between the efficiency of the calf pump and the size of the capillary bed within the ulcer bearing skin.[24] We found a strong correlation, with maximum enlargement of the capillary bed in patients with liposclerosis and deep-vein damage. A causal association was confirmed when experimental elevation of the venous pressure in the hind limb of the dog was found to induce an identical enlargement of the capillary bed.[25] Studies of the permeability of this enlarged capillary bed showed that the large molecule, fibrinogen, escaped from the capillaries significantly faster than normal, whereas the rates of albumin and sodium loss were not affected. The interendothelial pores stretch when the intraluminal capillary pressure is raised.[26,27] Experimental ligation of the renal vein produces an identical rise in the fibrinogen concentration of renal lymph,[28] confirming that large quantities of fibrinogen accumulate within the interstitial fluid when the venous pressure is raised. A similar rise in the fibrinogen content of lymph of the dog's hind limb was found to follow femoral-vein ligation.[29]

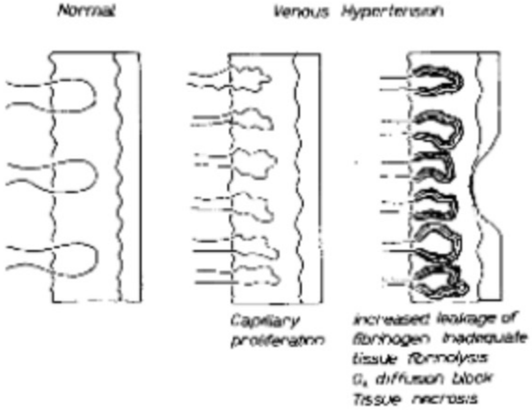

Fig. 2—Development of liposclerosis and ulceration.

Increase in the number of capillary loops is followed by fibrinogen leakage with development of a pericapillary fibrin cuff.

Skin biopsy specimens from the ulcer-bearing area of patients with post-phlebitic damage and liposclerosis showed pericapillary fibrin deposition in all cases, but those from patients with mild uncomplicated venous disease did not.[30] The fibrinolytic system normally breaks down fibrin to soluble fibrin-degradation products, preventing excessive fibrin accumulation, but in patients with lipodermatosclerosis and post-phlebitic limbs we found that both blood and tissue fibrinolytic activity were significantly depressed. In a controlled double-blind crossover trial of fibrinolytic enhancement, the anabolic steroid stanozolol ('Stromba') produced rapid resolution of liposclerotic skin in patients with severe lipodermatosclerosis.[12] Water-bath studies with fibrin sheets showed that fibrin dramatically reduced the transport of oxygen while remaining fully permeable to carbon dioxide.[30] Studies with radioactively labelled water, oxygen, and carbon monoxide have shown that the bed of a venous ulcer has a high blood flow with diminished cellular metabolism indicative of a diffusion block.[31]

HYPOTHESIS

We suggest that a high ambulatory venous pressure within the calf-muscle pump is transmitted through communicating veins to the superficial veins within the skin and subcutaneous tissues of the calf. This distends the local capillary bed and widens the endothelial pores, thus allowing

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23. Bowman RH. Inhibition of citrate metabolism by sodium fluorocitrate in the perfused rat heart and the effect on phosphofructokinase activity and glucose utilization. *Biochem J* 1966; **98:** [illegible].
24. Ruderman NB, Toews CJ, Shafrir E. Role of free fatty acids in glucose homeostasis. *Arch Intern Med* 1969; **123:** 299–313.
25. Bondy PK, Rosenberg LE. Metabolic control and disease. 8th ed. Philadelphia: W. B. Saunders, 1980: 445.
26. Reaven GM, Olefsky J, Farquhar JW. Does hyperglycaemia or hyperinsulinaemia characterise the patient with chemical diabetes? *Lancet* 1972; i: 1247–49.

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fibrinolytic activity within both the blood and the tissue fluid. The fibrin deposited around the capillary forms a barrier (fig. 2) to the passage of oxygen and other nutrients which sustain the cells of the epidermis. This leads directly to cell death and ulceration.

At an early stage this process may be reversed by reducing the venous pressure by surgery or elastic stockings and enhancing the fibrinolytic activity of the cells with drugs. If unchecked, however, the deposition of fibrin within the skin results in irreversible fibrosis and permanent tissue damage which makes the ulceration resistant to all our present forms of treatment.

REFERENCES

1. Adams FF. The genuine works of Hippocrates. London: Sydenham Press, 1849.
2. Burnand KG, O'Donnell TF, Lea Thomas M, Browse NL. Relationship between postphlebitic changes in the deep veins and results of surgical treatment of venous ulcers. *Lancet* 1976; i: 936–38.
3. Gay J. On varicose disease of the lower extremities. The Lettsomian lectures of 1867. London: Churchill, 1868.
4. Spender JK. A manual of the pathology and treatment of ulcers and subcutaneous diseases of the lower limbs. London: Churchill, 1868.
5. Ludbrook J. The analysis of the venous system. Berne: Hans Huber, 1972.
6. Homans J. The aetiology and treatment of varicose ulcers of the leg. *Surg Gynaecol Obstet* 1917; 24: 300–11.
7. De Takats G, Quint H, Tillotson R, Crittendon PJ. The impairment of the circulation in the varicose extremity. *Arch Surg* 1929; 18: 671–86.
8. Blalock A. Oxygen content of blood in patients with varicose veins. *Arch Surg* 1929; 18: 898–905.
9. Holling HE, Beecher HK, Linton RR. Study of the tendency to oedema formation associated with incompetence of the valves of the communicating veins of the leg. Oxygen content of the blood contained in varicose veins. *J Clin Invest* 1938; 17: 555–61.
10. [illegible] R. Remarks concerning venous thrombosis and its sequelae. *Surgery* 1952; 31: 6–27.
11. Blumoff R, Johnson G. Are arteriovenous shunts present in varicose veins? Paper presented to the Society of Academic Surgeons, 1976.
12. Dickson Wright A. The treatment of indolent ulcer of the leg. *Lancet* 1931; i: 457–60.
13. Schanzer H, Peirce EC. A rational approach to surgery of the chronic venous stasis syndrome. *Ann Surg* 1982; 195: 25–29.
14. Piulachs P, Vidal Barraquer F. Pathogenic study of varicose veins. *Angiology* 1953; 4: 59–100.
15. Pratt GH. Arterial varices. A syndrome. *Am J Surg* 1949; 77: 456–60.
16. Brewer AC. Arteriovenous shunts. *Br Med J* 1950; ii: 270.
17. Haimovici H, Steinmann C, Caplan LH. Role of arteriovenous anastomosis in vascular disease of the lower extremity. *Ann Surg* 1966; 164: 990–1002.
18. Gius JA. Arteriovenous anastomoses and varicose veins. *Arch Surg* 1960; 81: 299–308.
19. Lindemayr W, Loefferer O, Mostbeck A, Partsch H. Arteriovenous shunts in primary varicosis: A critical essay. *Vasc Surg* 1972; 6: 9–13.
20. Haber [illegible], Locher JT, Waibel PP, Pretsch [illegible]. Zur Bedeutung arteriovenoeser anastomosen bei der primaeren Varicosis und der chronisch-venoesen Insuffizienz. *Vasa* 1974; 3: 196–98.
21. Landis EM. Microinjection studies of capillary blood pressure in human skin. *Heart* 1930; 15: 101–53.
22. Pappenheimer JR, Soto Rivera A. Effective osmotic pressure of plasma proteins and other quantities associated with capillary circulation in the hind limb of cats and dogs. *Am J Physiol* 1948; 152: 471–91.
23. Whimster I. Cited by Dodd H, Cockett FB. The pathology and surgery of the veins of the lower limb. Edinburgh: Churchill Livingstone, 1956.
24. Burnand KG, Whimster IW, Clemenson G, Lea Thomas M, Browse NL. The relationship between the number of capillaries in the skin of the venous ulcer bearing area of the lower leg and the fall in foot vein pressure during exercise. *Br J Surg* 1981; 68: 297–300.
25. Burnand KG, Clemenson G, Gaunt J, Browse NL. The effect of sustained venous hypertension in the skin capillaries of the canine hind limb. *Br J Surg* 1982; 69: 41–44.
26. Shirley HH, Wolfram CG, Wasserman K, Mayerson HS. Capillary permeability to macromolecules: stretched pore phenomenon. *J Physiol* 1957; 190: 189–94.
27. Pietra GG, Szidon JP, Leventhal MM, Fishman AP. Haemoglobin as a tracer in haemodynamic pulmonary oedema. *Science* 1969; 166: 1643–46.
28. Beard RC. MS thesis, Cambridge University, 1982.
29. Leach RD, Browse NL. Lymph fibrinogen in long and short term venous hypertension in the hind limb of the dog. *Br J Surg* 1981; 68: 354.
30. Burnand KG, Whimster I, Naidoo A, Browse NL. Pericapillary fibrin deposition in the ulcer bearing skin of the lower limb. The cause of lipodermatosclerosis and venous ulceration. *Br Med J* (in press).
31. Browse NL, Jarrett PEM, Morland M, Burnand KG. Treatment of lipodermatosclerosis of the leg by fibrinolytic enhancement: a preliminary report. *Br Med J* 1977; ii: 434–35.
32. Burnand KG, Clemenson G, Morland M, Jarrett PEM, Browse NL. Venous lipodermatosclerosis: treatment by fibrinolytic enhancement and elastic compression. *Br Med J* 1980; 280: 7–11.
33. Hughes NFG, Rhodes CG, Spinks T, Jones T, Jamieson CW. Position emission tomography in venous ulceration. *Br J Surg* (in press).

THE CAUSE OF VENOUS ULCERATION

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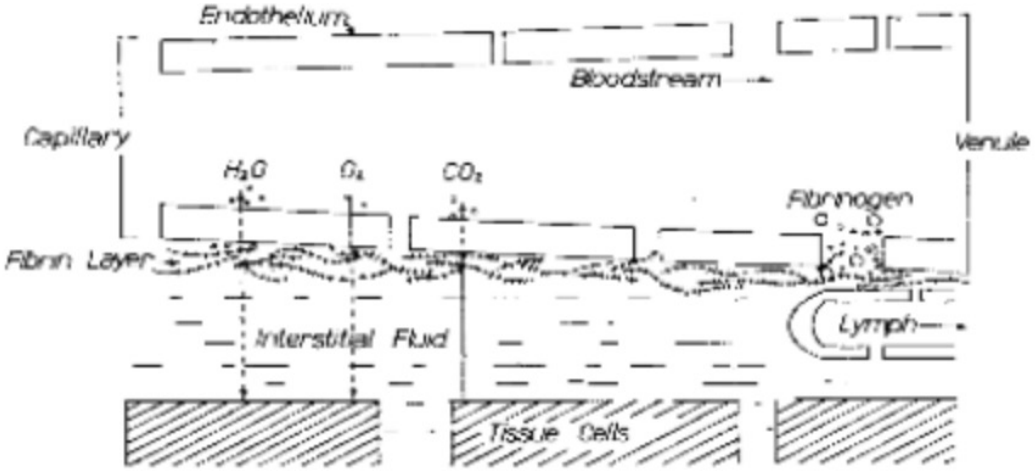

Fig. 1—Diagram of a capillary, showing an enlarged pore at the venous end leaking fibrinogen into the interstitial fluid where it polymerises to form an insoluble layer of fibrin.

The Cause of Venous Hypertension

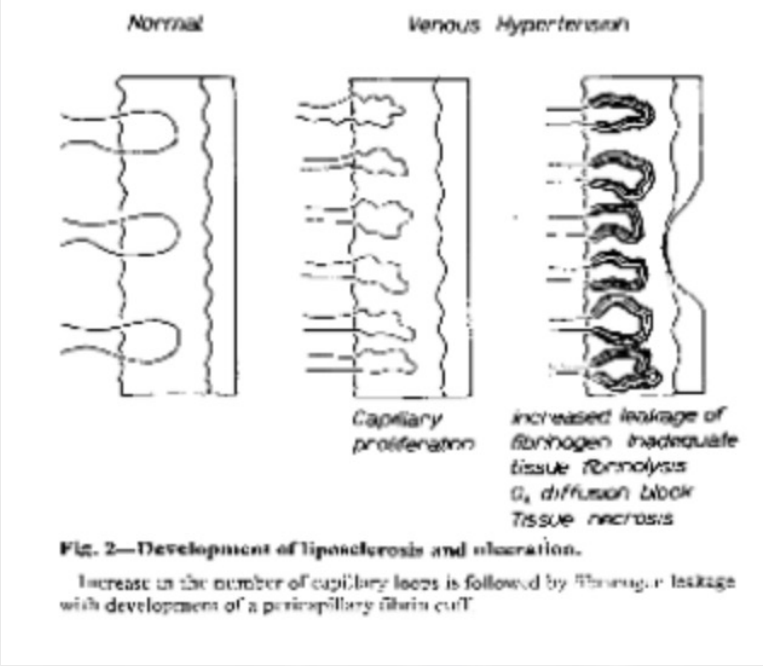

Fig. 2—Development of liposclerosis and ulceration.

Increase in the number of capillary loops is followed by fibrinogen leakage with development of a perivascular fibrin cuff

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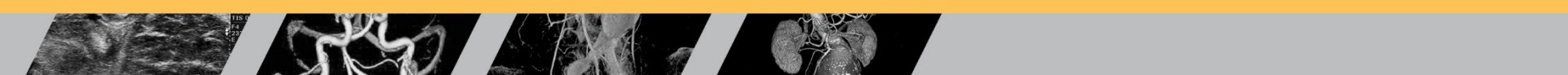
EFFECT OF ELEVATED VENOUS PRESSURE—RAT MODEL

- VALVES STRETCHED IMMEDIATELY
- REFLUX AT 2 DAYS WHICH INCREASED W/ TIME
- Granulocytes, monocytes, machrophages, lymphocytes @ 3 weeks
- Reduction in leaflet height, width, some disappeared

Takase S, Pascarella L, Bergan JJ, Schmid-Schönbein GW. Hypertension induced venous valve remodeling. J Vasc Surg 2004;39:1329-34.

JVS Journal of Vascular Surgery



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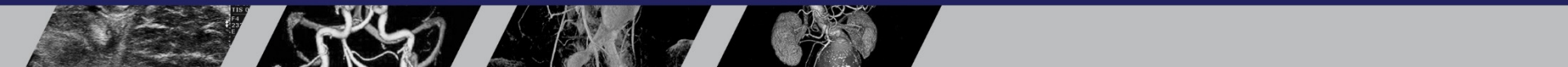

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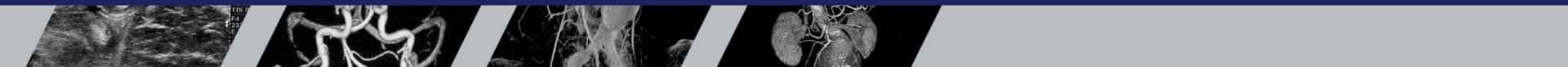

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