Pathology of Cardiovascular Interventions

APPROVED

- Body and Disease 2011

This lecture is generally in chronological order; we will start with the old school treatments and move to current therapy.

Coronary Artery Atherosclerosis

- **Intervention Goals:**
  - **Acute Coronary Syndromes: Treat plaque rupture and thrombosis**
  - **Significant Disease: Prevent development of complications**

This happens when we aren't successful with prophylaxis

In this case, we identify cardiovascular issues and we try to stem off significant problems before they occur

ACS: Thrombolysis

Acute coronary syndrome usually refers to plaque rupture and thrombus (but it can also refer to other things like coronary dissection or spasm)

historically, this was the first approach

- **Goals:**
  - **Restoration of blood flow**
  - **Rescue ischemic myocardium**
    - **Wavefront phenomenon**
    - **Target: < 6 hours from onset**
      - **Likely some benefit within 12 hours if significant collaterals**

the collaterals may buy us some time if they form

- **Agents:**

make sure they aren't hemorrhaging somewhere else or have bleeding issues

  - **tPA, Streptokinase, Urokinase**
  - **No definite efficacy advantage of one over the others.**

Now we do catheter for thrombolysis and direct injection of the lytic agent right at the area where we want the effect to be. Catheters are used a lot in AV fistulas (used for dialysis) which are prone to clotting. They also now have a thrombectomy catheter to physically remove the thrombus. Basically catheters are getting really good, think of Inspector Gadget.

Thrombolysis: Complications

- Hemorrhage – ROS, PMHx, PE
- Reocclusion
  - No treatment of underlying cause (rupture)
  - Up to 10% reocclusion with 5% infarct extension
- Reperfusion injury
  - Flow restoration causes injury of viable myocytes.
    - Oxygen free radical generation
    - "No Reflow" phenomenon
- Stunned Myocardium
  - Prolonged functional impairment

don't forget the rectal exam to look for hemorrhoids before giving thrombolytic drugs

The cells from the inflammatory response flow into area of infarct. When they get into the microcirculation they plug it up and you don't get reprofusion on a microscopic level even though the large clot is gone.

prolonged dysfunction of the heart can persist even after reprofusion and you wont get immediate improvement.

Coronary Interventions

Slide summary: we do a lot of these treatments, they are expensive, and men get more than women. His summary: "It's big business".

- **United States:**
  - **Percutaneous Transluminal Coronary Angioplasty (PTCA) aka percutaneous coronary intervention**
    - **1,204,000 in 2002**
    - **Male:female 2:1**
    - **Cost ~ $25,000 – $35,000**
  - **Coronary Artery Bypass Grafting (CABG)**
    - **515,000 in 2001**
    - **Male:Female ~ 3:1**
    - **Cost - $45,000- $60,000**

Balloon Angioplasty

Patients that don't have coronary syndromes and have significant plaque may get a balloon.

- **Procedure**
  - **Traverse plaque with guidewire**
  - **Balloon inflated to 6-12 ATM**

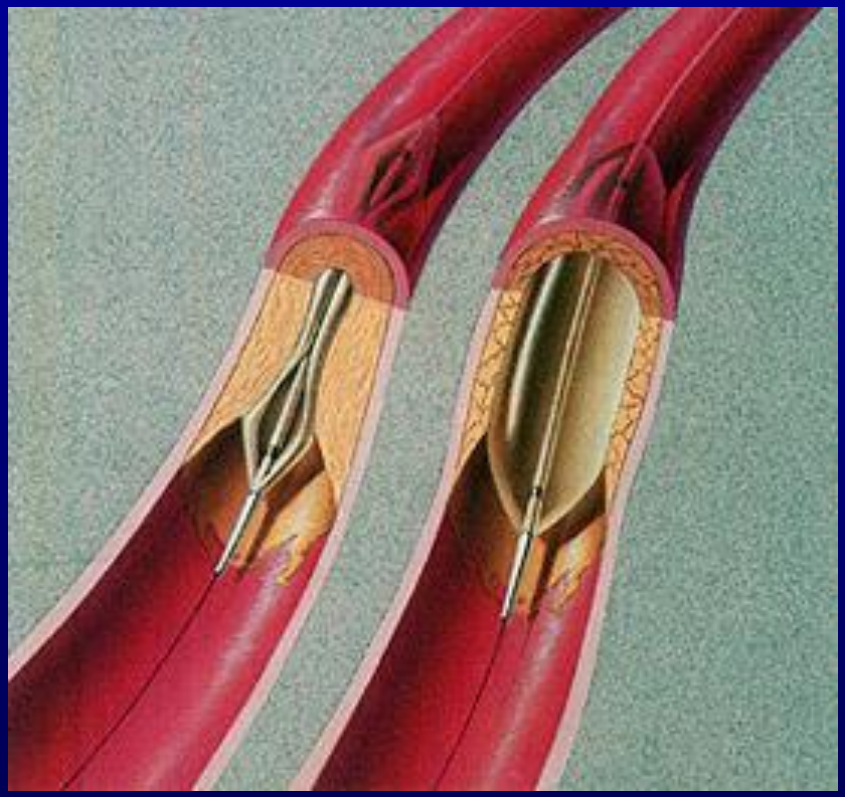
high pressure

- **Outcome**
  - **Initially >90% of lesions reduced by >20% with resulting stenosis < 50% of vessel.**

good outcome

- **Desired Lesion Characteristics**
  - **Length, Location, Number**

these factors may limit your success with a balloon.



Full metal jacket = when you have stents lining over half of the coronary surface.

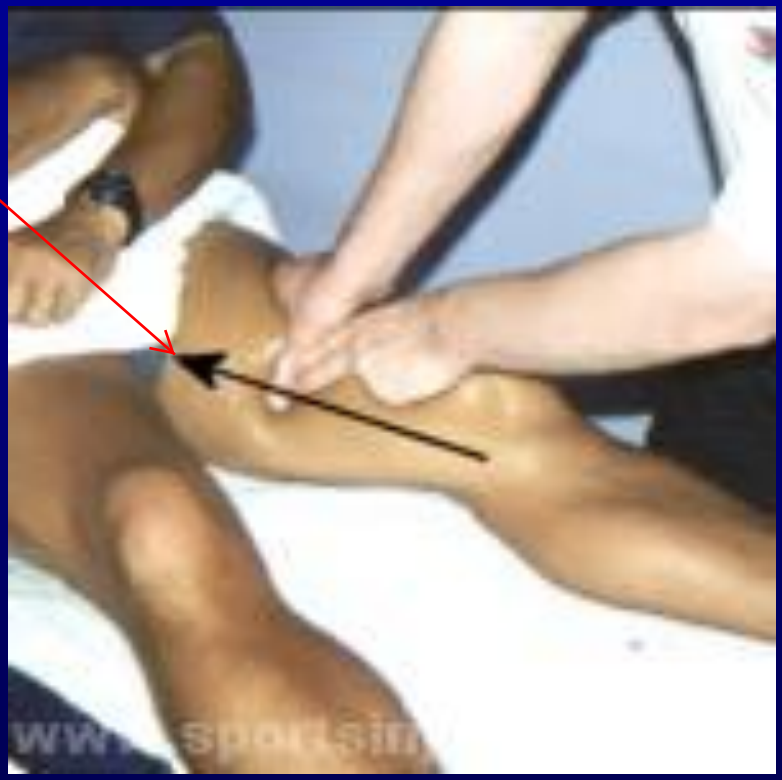
Cardiac Catheterization: Duke Criteria

To determine cath versus angioplasty

- Presence of a groin
- Presence of a groin substitute

can be radial artery, but Duke doesn't do it that much for some reason

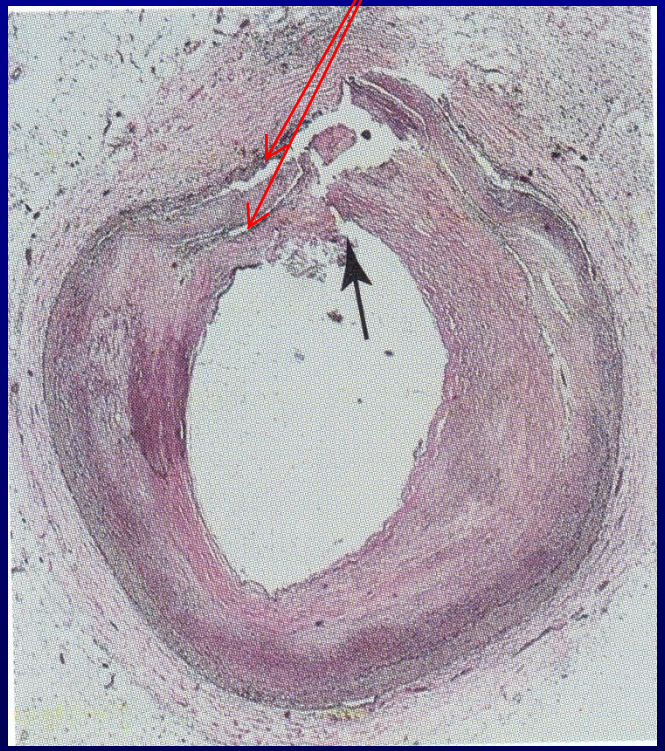
- Patient slower than the cardiologist



Angioplasty: Pathology

What does the balloon actually do?

- **Plaque Splitting**
  - Non-distensible
  - Plaque splits at weak point
  - Split extends to media and often into media
  - Mural hemorrhage
- Medial Dissection
- Endothelial Denudation
- Medial and Adventitial Stretch



Angioplasty: Pathology

we ARE NOT squishing or compressing the plaque, luminal increase comes from things below.

- **Lumen Increase**
  - **Plaque Fracture**
  - **Medial and Adventitial Stretching**
  - **Medial Dissection**
  - **Plaque Stretching**
  - **Plaque Compression and Redistribution**

very small percentage of the actual effect

- **Favorable plaques:**
  - **Eccentric v concentric – long term 48 v 18%**
  - **Large Necrotic Cores**

not equal diameter around the lumen, more likely to have a good tear with balloon whereas concentric don't get a great tear

makes for a better/ easier tear

Angioplasty: Complications

You are basically creating what you are trying to avoid (a ruptured plaque) and you can get thrombosis via acute closure.

- **Acute closure (4-9%)**
  - **Procedure creates "rupture-like" state with thrombogenic surfaces**
  - **Medial flaps alter flow and create stasis**

from medial dissection areas

- **Glycoprotein IIb/IIIa receptor antagonist**
  - **Abciximab (Reopro)**
  - **Eptifibatide (Integrilin)**
  - **Blocks platelet aggregation**

give drugs like this to stop clotting and avoid complications from acute thrombosis

Complications after the acute phase

Angioplasty: Complications

- **Late Restenosis: 40% - primarily within 6 months**
- **Neointimal Proliferation**

we are creating injury and that will create a healing response at the site on the intima, which can cause stenosis.

  - **Exuberant healing response with ingrowth of smooth muscle cells from intima and media**

Sort of mimic atherosclerotic plaques

  - Smooth muscle cells secrete extracellular matrix
    - Collagen in increasing density
    - Glycosaminoglycans
  - Leukocyte adhesion molecules – Integrins, selectins
    - Mac-1 level – chemoattractant correlates with risk of restenosis
  - Inflammation – increases injury, cytokine release

Angioplasty: Complications

- **Late Restenosis: 40% - primarily within 6 months**
- **Negative Remodeling**
  - **Healing of medial and adventitial stretch injury leads to late fibrosis and contraction with collagen scar maturation**
  - **Reduces overall vessel size**

last slide was more focused on initmal healing, this is medial and adventitial

as the outer layers remodel, they can shrink the vessel

Endoluminal Stents

Stents can fix some of the issues created by the angioplasty

- **Scaffold function**
  - **Compresses acute post-angioplasty intimal/medial flaps**
  - **Buttresses against late negative remodeling**

Significant reduction in primary endpoints and restenosis versus PTCA alone

Stents aren't perfect either...

Endoluminal Stents

- Neointimalization
  - NOT prevented by stenting
  - Leads to in-stent restenosis

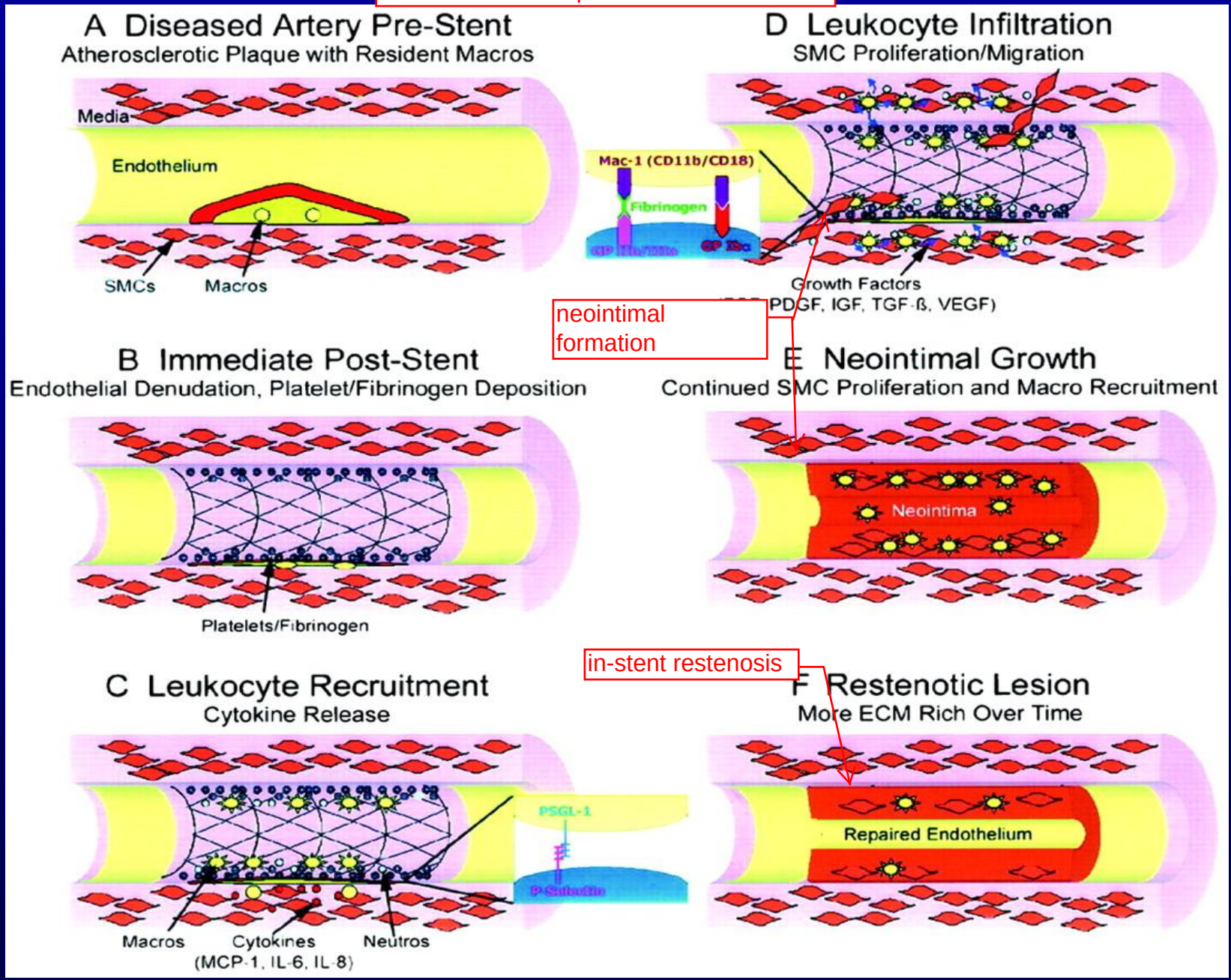
when the intimal healing just grows through the chicken wire of the stent

- Injury

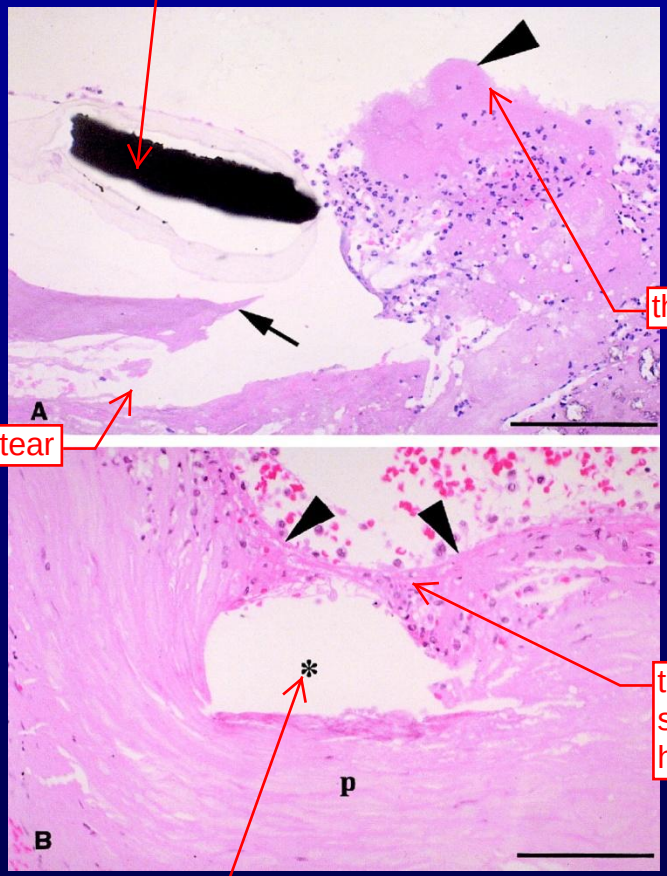
The stent can cause injury on it's own

  - Implantation of stent wires into arterial wall
  - Inflammation stimulated by stent
- Pathology
  - Initially thrombus and inflammation with subsequent covering by thickened intima with smooth muscle cells and matrix

Just shows the steps of in-stent restenosis



Stent Response



stent

thrombus formation

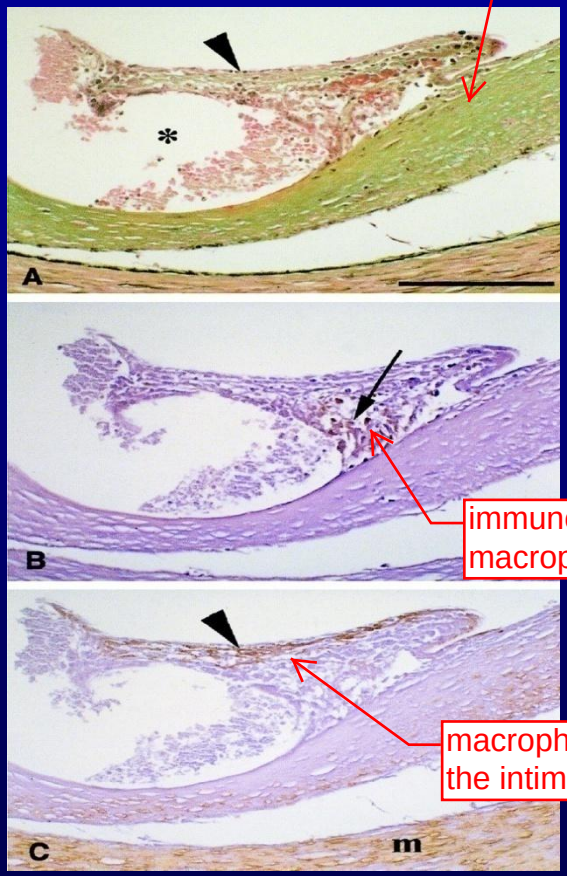
tear

thrombus surrounding stent hole

asterix implies the spot where a stent was pulled out

Acute

movat's stain: matrix is green, fibrosis is yellow, elastin is black, blood is red.



immunostain for macrophages

macrophages up in the intima

Early Neointima

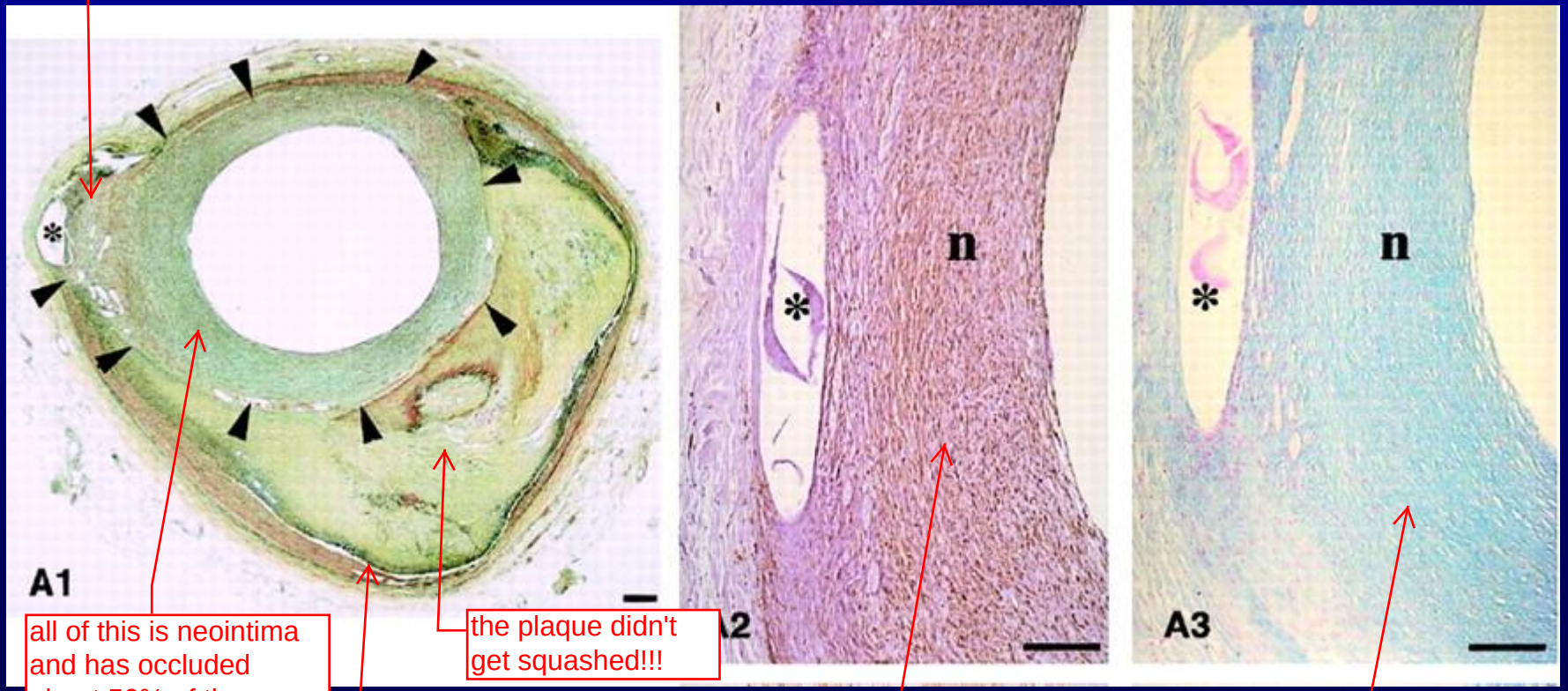
Virmani

rupture site. this is where the increase in the size of the lumen came from

He started going fast at this point, so there were things on his slide that he didn't mention from here on out.

Stent Response

Arrows show where the stent actually was



all of this is neointima and has occluded about 50% of the lumen (**main point of this slide: neointimal proliferation can cause significant stenosis**)

the plaque didn't get squashed!!!

Internal elastic lamina

Smooth muscle

Matrix

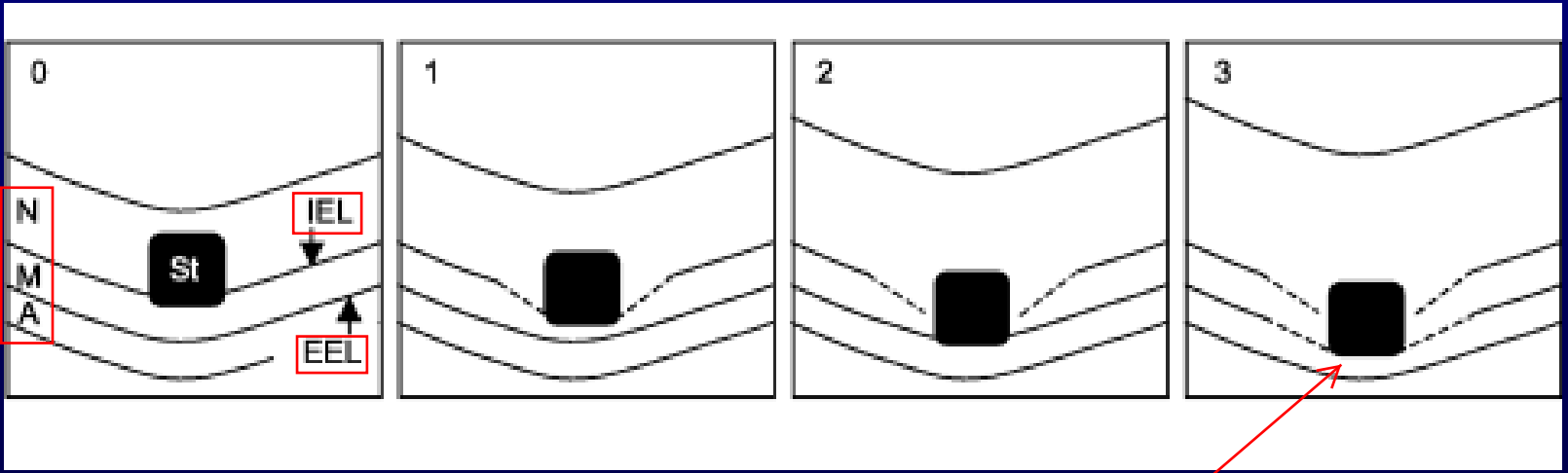
im
ury and lack of
sion

Virmani

Endoluminal Stents

- **Arterial Injury**
  - **Schwartz Score: 0 – 3 based on compression and injury to IEL and media and EEL**

tells us how far into the wall the stent is driven and this will determine the propensity to form neointima



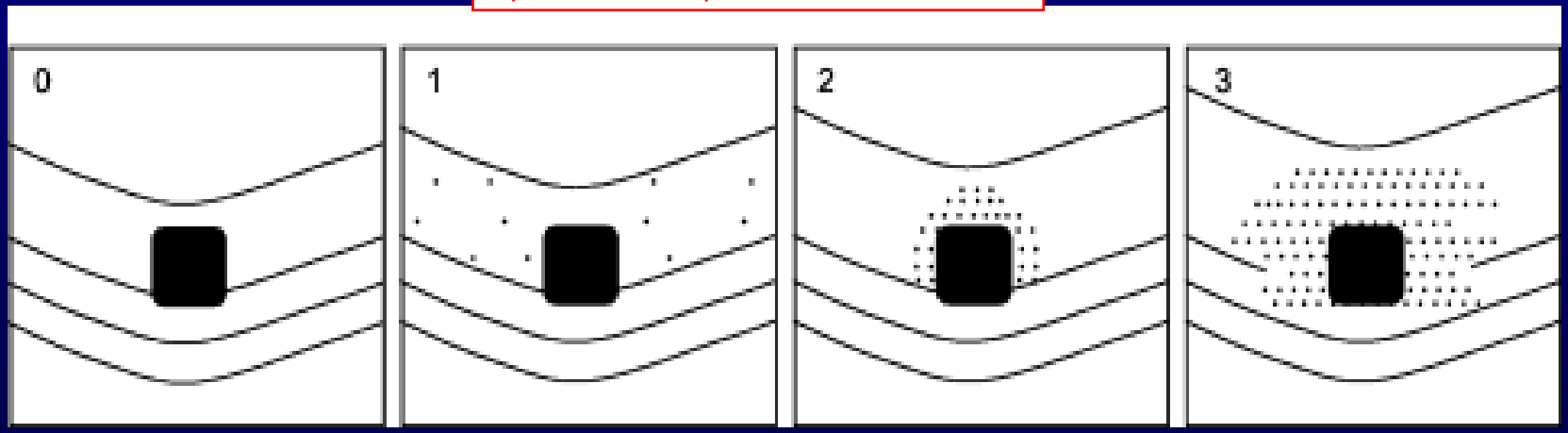
The stent can go all the way through the artery wall => this procedure can be very aggressive.

Lowe, et al

Endoluminal Stents

- **Inflammation:**
  - **Amount and duration reflects extent of injury**
  - **Kornowski Score: 0-3 based on density and extent of stent induced inflammation**

Shows varying amounts of inflammation dependent on depth of stent



Lowe, et al

Endoluminal Stents

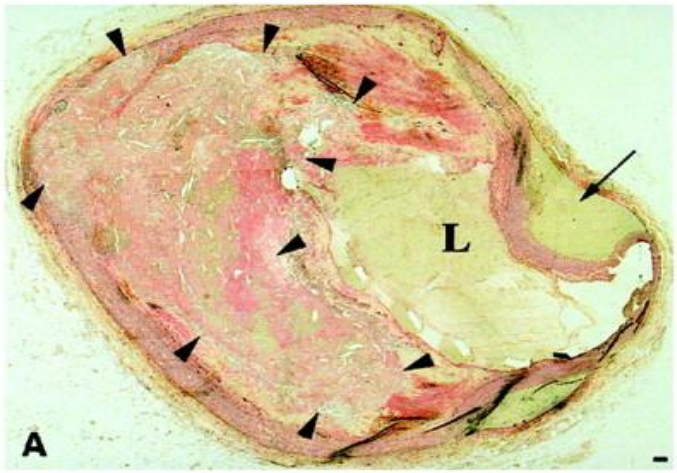
The type of plaque also determines how far in we have to press the stent which in turn determines the amount of inflammation

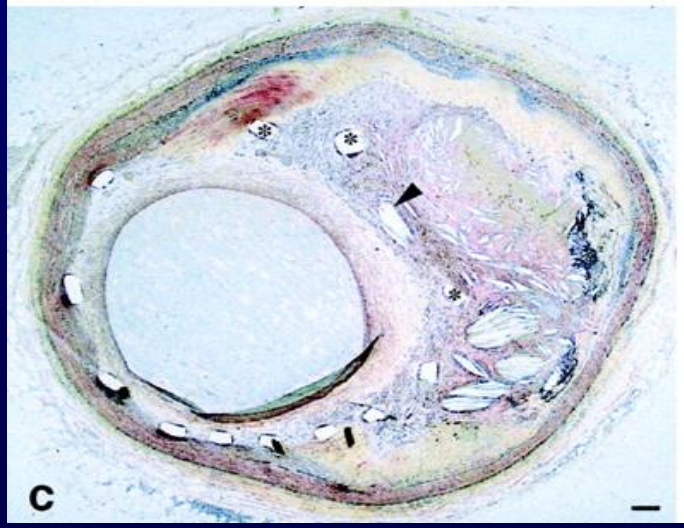
- **Long Term Results/Restenosis**
  - **Correlate with stent injury and inflammation**
  - **Stent strut location affects reactive inflammation**
    - **Fibrous Plaque** ← not at much inflammation, don't press in as far
    - **Medial Injury** ← obviously causes lots of inflammation
    - **Lipid core penetration** ← can drive stent right into fat and cause lots of inflammation

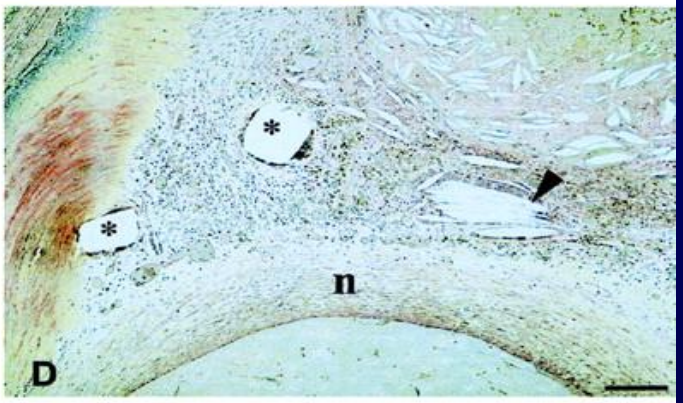
Lipid Core Penetration

Can see stent struts in the fat portion of the plaque. Also notice that the plaque WAS NOT SQUISHED, just pushed over.

higher mag



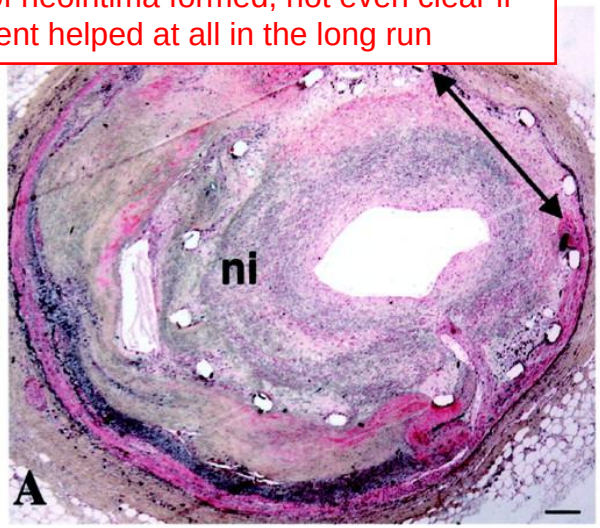


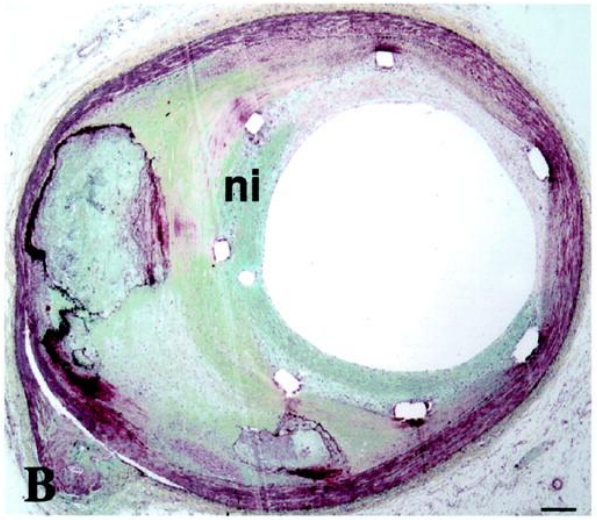


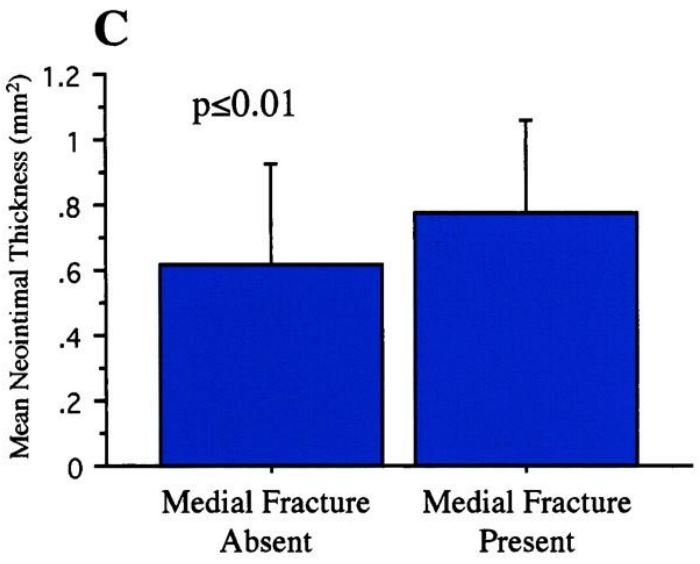
More movat's stains

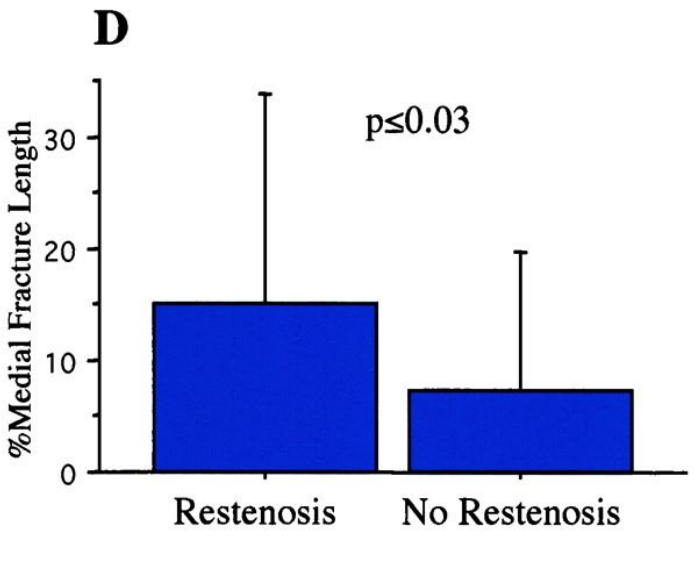
Medial Fracture

Lots of neointima formed, not even clear if the stent helped at all in the long run





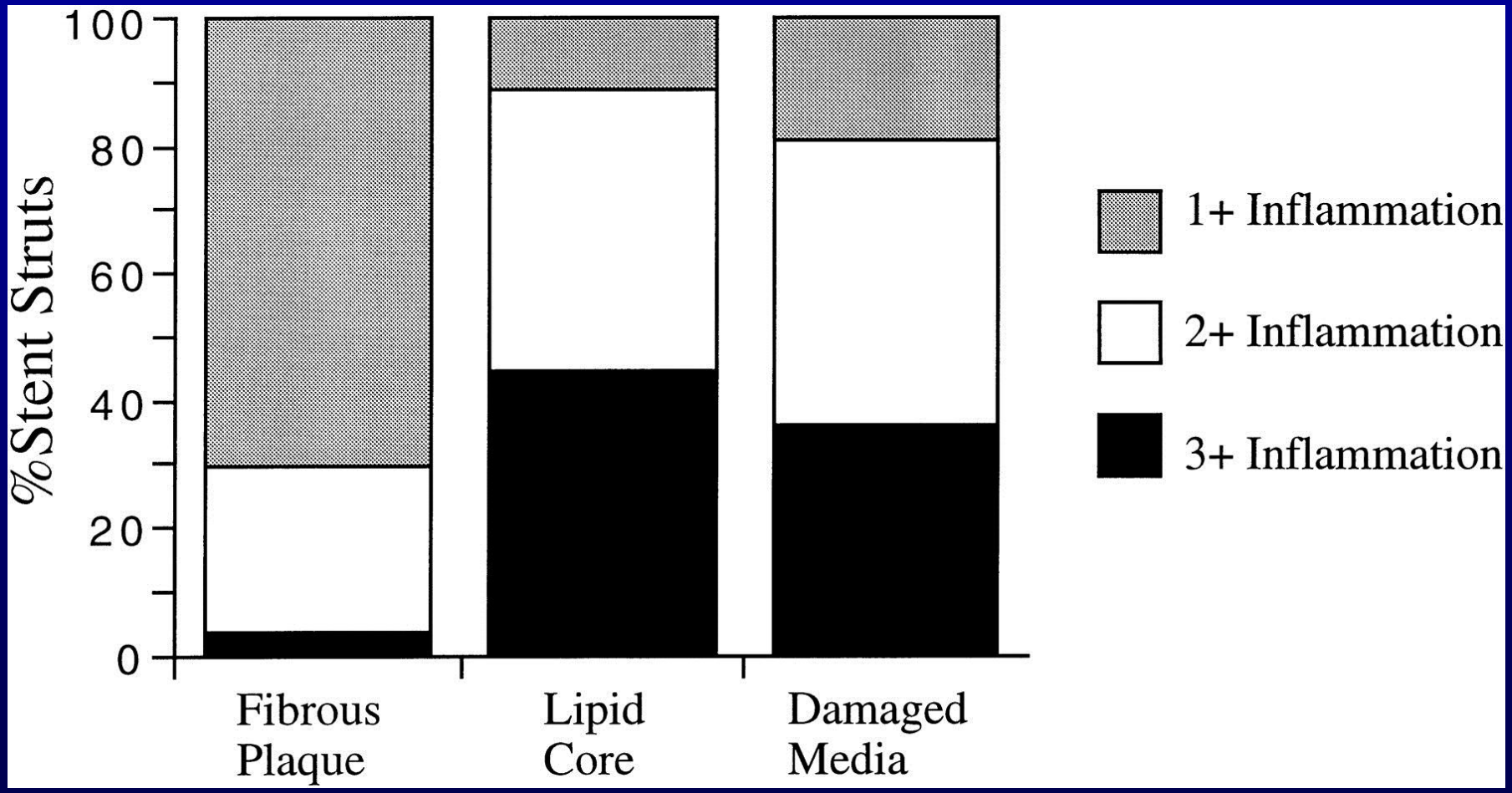




Graphs not mentioned

Farb et al

Endoluminal Stents



More inflammation comes from damaged media and lipid core penetration. More inflammation => worse outcome.

Farb et al

These are coated stents desiged to prevent neointima formation. Do nothing for clot formation.

Drug Eluting Stents

- **Stent releases drug to prevent restenosis**
  - Prevent thrombus formation?
    - More commonly via systemic therapy
  - Prevent tissue proliferation
    - Sirolimus – protein kinase binder
    - Paclitaxel – Microtubule stabilization, blocks mitosis
    - Efficacy?
      - Conor/Costar II stent pulled from development for poorer results vs sirolimus
        - » Cited drug delivery issue vs efficacy
      - Est $200 million market share loss in 2008

these are actually chemotherapy drugs which stop tissue proliferation

This can get complicated because they have time-release coatings so you don't just get all the drug at once and you get a continuous release.

drug wasn't released properly and lost them a lot of money.

Overall market?

> $5 BILLION

Big market for these stents.

Drug Eluting Stents

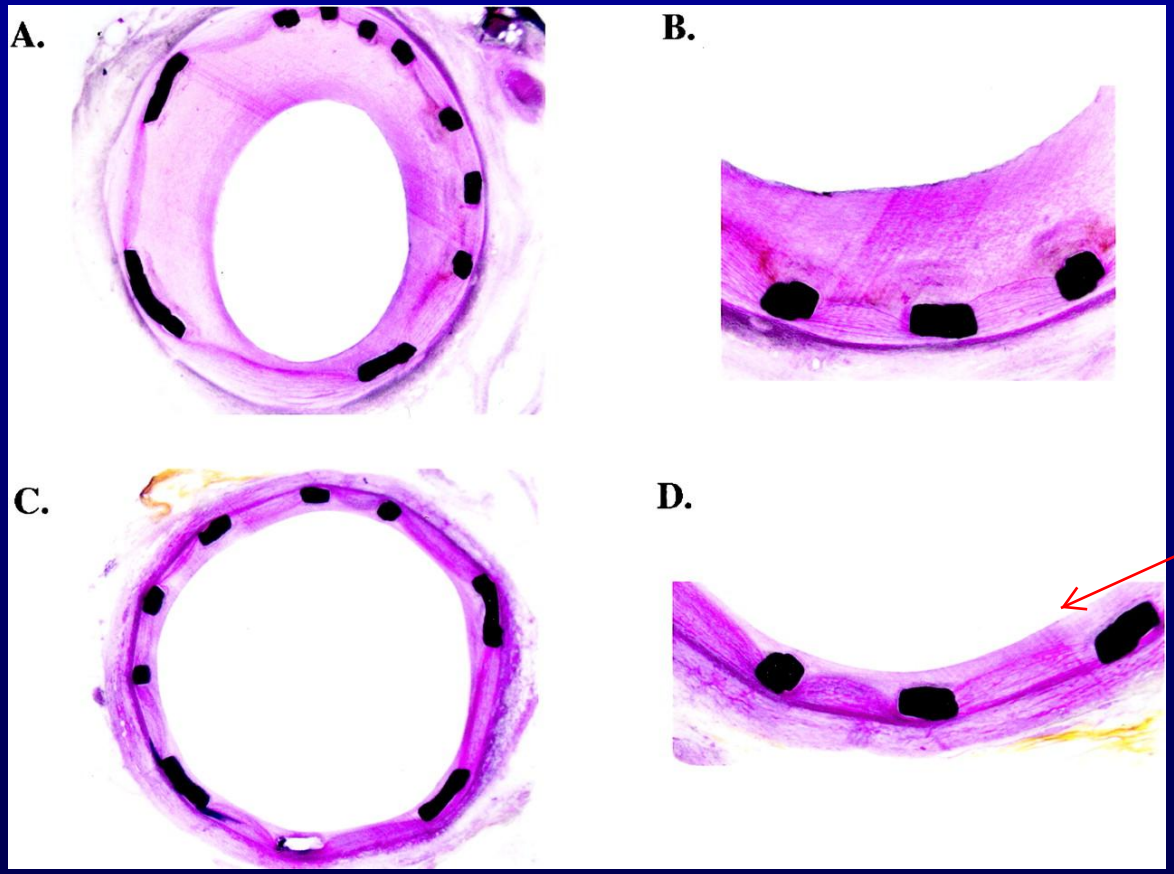
Take away: they work

Bare

No drug

Sirolimus

With drug



less neointima. YAY

The time scale is around 6 months in these photos.

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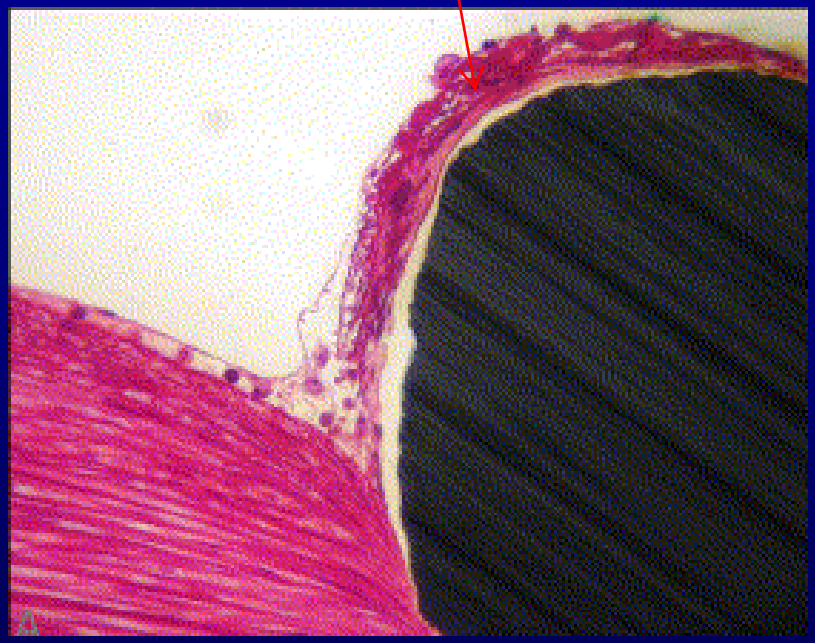
Drug Eluting Stents

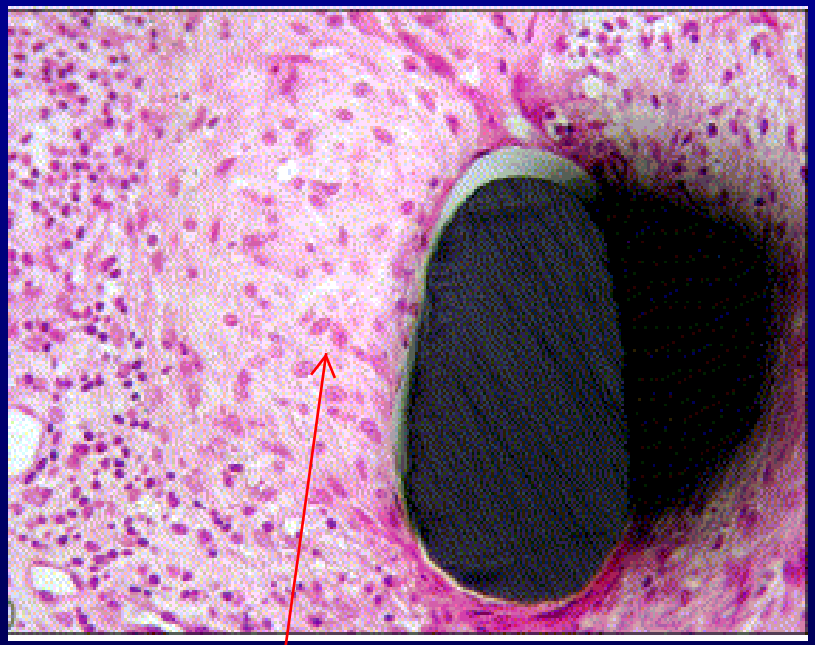
Still not sure what happens in the long term once the drugs wear off from the stent. Are we just delaying the inevitable neointimal formation?

- **Efficacy**
  - **Effective at limiting short and medium term restenosis**
  - **Long term results unclear**
    - **Prolonged acute phase with inflammation and thrombus**
    - **Possible hypersensitivity response**

Drug Eluting Stents

Neointimal formation after the drug has worn off





hypersensitivity granuloma = bad news

Prolonged “acute” state

Medial granuloma

Drug Eluting Stents

- **Risk of Late Thrombosis**
  - Preservation of "acute" state of surface
  - Need for prolonged antiplatelet therapy?
    - **Very late thrombosis**: >12 months
    - Slight risk of very late thrombosis compared to bare metal stents
    - ~0.2%/year excess risk of thrombosis unless dual antiplatelet therapy continued beyond 3-6 months
    - **Risk higher in "off-label" use (non FDA-approved by clinical trials) Ex. Bifurcations, acute MI**
      - **50-60% of stents are used off label**

study from Duke that there is a risk for thrombosis a year after the stent in certain populations

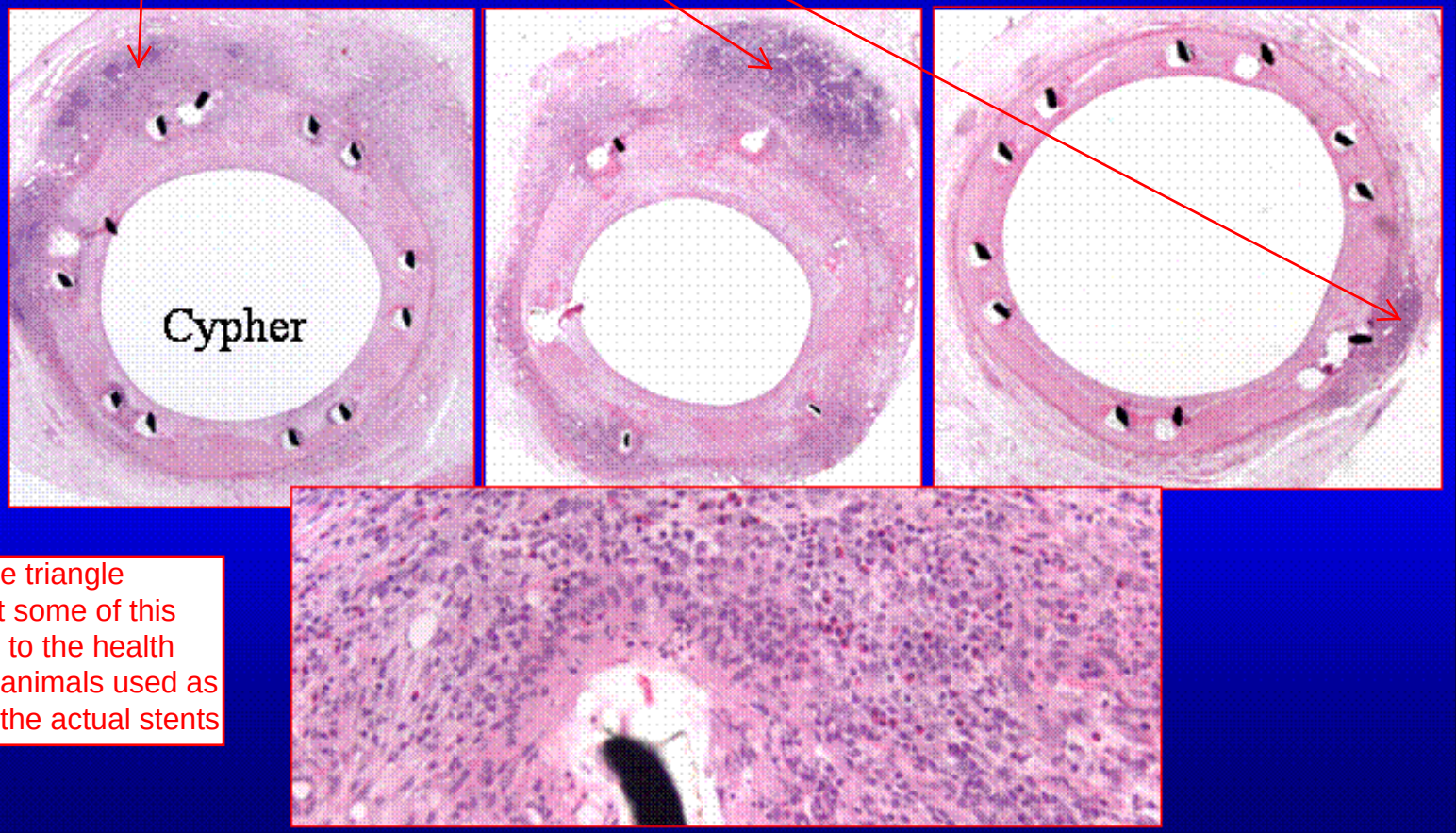
stents not approved for these things

inflamation

Sirolimus

Another example of the hypersensitivity granuloma formation

Granulomatous reaction seen in CYPHER Stents Implanted for 28 and 90 days in Pig Coronary Arteries



His lab in the triangle showed that some of this may be due to the health state of the animals used as opposed to the actual stents

Virmani

"buy 2 vessel diseases for the price of one" (left main = LAD + circumflex)

Coronary Bypass

- **Revascularize "at risk" myocardium**
  - **Left main, three vessel disease**
- **Improve left ventricular function**
  - **"Hibernating" myocardium**
  - **Ischemic valve dysfunction**
- **2-3% perioperative mortality and higher short term risk than PTCA but improved long term**

some of your heart may be living at low O2 and will be reactivated after bypass

like the mitral valve

for patients with 2 or 3 vessel disease

Coronary Bypass: Grafts

best graft because the artery is ready for the pressure and has its own vasovasora => longer life expectancy

- **Internal Mammary Artery (Thoracic Artery)**
  - **90% 5 year patency, 80% 10 year patency – Why?**
  - **Atherosclerosis is rare**
  - **Generally Left IMA to LAD distribution**
- **Reversed Vein Grafts - Saphenous vein**
  - **80-85% 5 year patency; 50-60% 10 year patency**
- **Other vessels:**
  - **Radial artery (free graft)**
  - **gastroepiploic**

Most issues are because we are using veins as arteries

Vein Graft Stenosis

- **Thrombosis** – acute, 15%
  - Factors include runoff obstruction, technical issues
  - Uncommon cause of perioperative mortality
- **Fibrointimal Hyperplasia**
  - Response to injury – stretch, shear - hypertension
  - Onset is relatively early
- **Atherosclerosis**
  - Tendency towards plaques with large lipid cores, thin caps and hemorrhage.
  - Less frequent fibrocalcific plaques
    - Rupture and embolization increased

basically the same thing that happens with stents can happen to veins that we graft => restenosis

Vein Graft Stenosis

- **Treatment:**
  - **Percutaneous intervention – PTCA, stent**
  - **Redo CABG**
    - **Higher risk of morbidity and mortality.**

If people don't change their lifestyle, they will probably need another one

The Future

- Stent modifications
  - **Bioabsorbable stents** – release drugs through healing phase and **"dissolve" to prevent stimulation of late restenosis or very late thrombosis**

Stent gets you though acute and healing phase. These are hitting the market now.

these 2 are farther off

- Trend towards **less invasive surgery**
  - Off pump, MIDCAB, robotic CABG
- Angiogenesis
  - Stem cells – endothelial progenitor cells
- Gene therapy
  - Prevention and treatment

Skipped

Damaged Hearts

- Ischemic Cardiomyopathy
  - Stem cell and myoblast therapy
  - Ventricular assist devices (VAD's)
  - Transplantation
- Other Cardiomyopathies
  - Similar options – VAD, Transplant
- Considerations:
  - Systemic?
  - Recurrence?
  - Age? Comorbidities?

saw this with Dr. Rogers

Saw this with Dr. Rogers

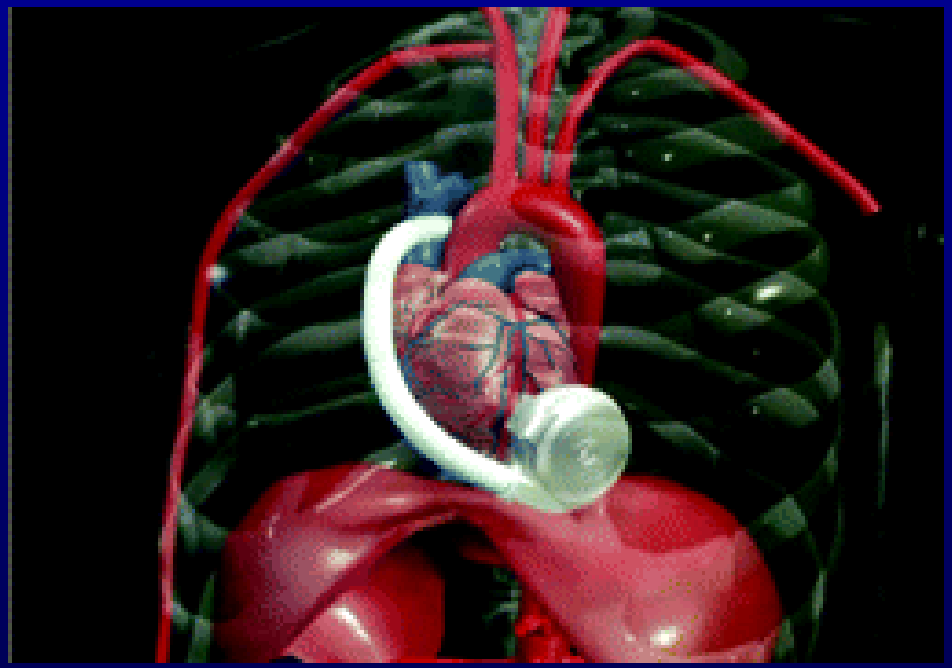
Ventricular Assist Devices

Thoratek

The latest wave. Emplanted in the heart, no outflow cannula. The battery is still external.

Ventricular Assist Devices

For some people this is the end of their treatment, for others this is used until a transplant becomes available.



HeartWare

Questions?