History

- 1550 BCE
  - Ebers Papyrus

- 2nd Century CE
  - First repair
  - Antylius
  - Ligation and evacuation

- 1817
  - Cooper repairs ruptured iliac aneurysm
  - Cooper also reported first aortoenteric fistula
  - Attention to multiple aneurysms
More Recently

- **Late 1800s**
  - Halstead repairs subclavian aneurysm by proximal ligation in the chest

- **1906**
  - Matas introduced the technique of endoaneurysmorrhaphy

- **1912**
  - Carrell and Guthrie win Nobel prize for anastomotic techniques
Bringing us to...

1951

- Dubost
  - First successful replacement of an AAA using the retroperitoneal approach with a freeze-dried thoracic aortic homograft

1953

- DeBakey and Cooley
  - Five of six patients operated on for replacement of AAAs survive
- Bahnson
  - First repair of a ruptured aortic aneurysm
- Vorhees
  - Prosthetic cloth graft for aortic replacement

1957

- DeBakey
  - Knitted Dacron
What is an Aneurysm?

- True aneurysm
  - All layers of vessel wall
  - 2x normal vessel diameter
- Ectasia
- Arteriomegaly
- Pseudoaneurysm
<table>
<thead>
<tr>
<th>Category</th>
<th>Types</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital</td>
<td>Idiopathic</td>
</tr>
<tr>
<td></td>
<td>Tuberous sclerosis</td>
</tr>
<tr>
<td></td>
<td>Turner’s syndrome</td>
</tr>
<tr>
<td>Connective tissue disorder</td>
<td>Marfan’s syndrome</td>
</tr>
<tr>
<td></td>
<td>Ehlers-Danlos</td>
</tr>
<tr>
<td>Degenerative</td>
<td>Fibromuscular dysplasia</td>
</tr>
<tr>
<td>Infectious</td>
<td>Bacterial</td>
</tr>
<tr>
<td></td>
<td>Syphilitic</td>
</tr>
<tr>
<td>Inflammatory</td>
<td>Arteritis</td>
</tr>
</tbody>
</table>
Classification

* Post-dissection
  * Idiopathic
  * Cystic medial necrosis
  * Trauma

* Post-stenotic
  * Thoracic outlet
  * Trauma

* Pseudoaneurysm
  * Anastomotic disruption

* Miscellaneous
  * Pregnancy-associated
  * Inflammatory AAA
Who Gets Aneurysms

- Older population
  - Men over 55
  - Women over 70

- Smokers
  - Seven fold over non-smokers
  - More associated with duration than amount
    - Increases by 4% for each year of smoking
  - A 2002 study found an independent association between smoking and high-grade tissue inflammation in AAAs

- Male more than women
  - 5:1

- White more than African American
  - 3.5:1
Epidemiology

- 10th most common cause of death
- Potential increasing frequency in western countries
National Trend in Diagnoses of AAA

Per 1000 Capita

Year

Diagnoses (Elective + Ruptured)
## Risk Factors for AAA

### TABLE 1. Risks Factors Associated With Aortic Aneurysm in Population Screening Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>AAA detected/ screened (%)</th>
<th>Age</th>
<th>Smoking</th>
<th>FH</th>
<th>Age</th>
<th>CHD</th>
<th>Cholesterol</th>
<th>Hypertension</th>
<th>Female</th>
<th>Black Race</th>
<th>Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADAM</td>
<td>1031/73,451 (1.4)</td>
<td>50–70</td>
<td>5.57</td>
<td>1.95</td>
<td>1.65</td>
<td>1.62</td>
<td>1.54</td>
<td>1.16</td>
<td>0.22</td>
<td>0.49</td>
<td>0.54</td>
</tr>
<tr>
<td>Amsterdam11,12</td>
<td>112/5283 (2.1)</td>
<td>≥55</td>
<td>6.5</td>
<td>NA</td>
<td>2.70</td>
<td>1.70</td>
<td>1.80</td>
<td>1.80</td>
<td>0.15</td>
<td>NA</td>
<td>0.71</td>
</tr>
<tr>
<td>Torroso</td>
<td>337/6366 (5.3)</td>
<td>≥25</td>
<td>7.37</td>
<td>NA</td>
<td>3.31</td>
<td>NA</td>
<td>1.19</td>
<td>1.61</td>
<td>0.22</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Genoa</td>
<td>70/1601 (4.4)</td>
<td>65–75</td>
<td>3.70</td>
<td>NA</td>
<td>NA</td>
<td>3.48</td>
<td>1.12</td>
<td>1.50</td>
<td>0.06</td>
<td>NA</td>
<td>1.02</td>
</tr>
<tr>
<td>Pittsburgh2</td>
<td>451/4741 (9.5)</td>
<td>≥65</td>
<td>1.68</td>
<td>NA</td>
<td>1.31</td>
<td>1.85</td>
<td>NA</td>
<td>1.22</td>
<td>0.40</td>
<td>0.81</td>
<td>1.06</td>
</tr>
<tr>
<td>WA</td>
<td>875/11650 (7.5)</td>
<td>65–83</td>
<td>2.90</td>
<td>2.40</td>
<td>2.40</td>
<td>2.20</td>
<td>1.50</td>
<td>1.63</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Birmingham16</td>
<td>219/2567 (8.4)</td>
<td>65–75</td>
<td>2.97</td>
<td>NA</td>
<td>NA</td>
<td>2.13</td>
<td>NA</td>
<td>1.24</td>
<td>NA</td>
<td>NA</td>
<td>0.83</td>
</tr>
<tr>
<td>Chichester17</td>
<td>218/5362 (4.0)</td>
<td>65–80</td>
<td>1.56</td>
<td>NA</td>
<td>1.05</td>
<td>1.66</td>
<td>NA</td>
<td>0.16</td>
<td>NA</td>
<td>0.80</td>
<td></td>
</tr>
<tr>
<td>Weighted mean</td>
<td>3313/111101 (4.0)</td>
<td>≥50</td>
<td>2.77</td>
<td>1.99</td>
<td>1.13</td>
<td>1.84</td>
<td>1.37</td>
<td>1.35</td>
<td>0.27</td>
<td>0.67</td>
<td>0.67</td>
</tr>
</tbody>
</table>

Screening studies with ≥1000 patients were included, except for Oslo18 Edinburgh19 and Viborg20 studies, which were excluded because only a small proportion of the control population had risk factors assessed or reported. ADAM indicates Aneurysm, Detection and Management study; WA, Western Australia; FH, family history; CHD, coronary heart disease, defined as history of myocardial infarction and/or angina.

*Weighted means for % aneurysm and for odds ratio are combined overall effect assuming fixed effects.*
Epidemiology

- Genetics
  - Familiar clustering in 15-25% of patients undergoing AAA repair
  - Inheritance patterns
    - Autosomal dominant
    - Autosomal recessive
    - X chromosome linked
  - First degree relative
    - 11-fold increase in relative risk
    - Odds ratio of 1.9 to 2.4
  - 20% of brothers with AAA
  - Female siblings are at particularly high risk

- Familiar types
  - Develop earlier in life
  - Male:Female ratio difference
    - 2:1
  - Higher rupture risk
### TABLE 2. Examples of Gene Products Altered in Human AAA Formation or Expansion

<table>
<thead>
<tr>
<th></th>
<th>Proteolysis</th>
<th>Inflammation</th>
<th>Lipids</th>
<th>Extracellular Matrix</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tissue</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>↑ MMP-1, -2 &amp; -9</td>
<td>↑ Adhesion molecules</td>
<td>↑ Apo E</td>
<td>↓ Collagen VIα1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>↑ Cathepsin H &amp; L</td>
<td>↑ Cytokines</td>
<td></td>
<td>↓ Glycoprotein IIIA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>↓ Cystatin C</td>
<td>↑ Chlamydia antigens</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Circulating markers</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>for AAA presence</td>
<td>↑ PAI-1</td>
<td>↑ Chlamydia antibodies</td>
<td></td>
<td>↑ Tenascin-X</td>
</tr>
<tr>
<td></td>
<td>↑ MMP-9</td>
<td>↑ Homocysteine</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>↑ LDL</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>↑ Lp (a)</td>
<td></td>
</tr>
<tr>
<td><strong>Circulating markers</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>for AAA expansion</td>
<td>↑ MMP-9</td>
<td>↑ Chlamydia antibodies</td>
<td></td>
<td>↑ PAP</td>
</tr>
<tr>
<td></td>
<td>↑ tPA</td>
<td>↑ Osteoprotegerin</td>
<td></td>
<td>↑ SEPs</td>
</tr>
<tr>
<td></td>
<td>↓ Cystatin C</td>
<td></td>
<td></td>
<td>↑ PIINP</td>
</tr>
</tbody>
</table>

MMP indicates Matrix Metalloproteinase; Apo E, apolipoprotein E; PAI-1, plasminogen activator inhibitor type 1; HDL, high density lipoprotein; LDL, low density lipoprotein; Lp(a), Lipoprotein a; tPA, tissue plasminogen activator; PAP, P-plasmin-antiplasmin complexes; SEPs, serum-elastin-peptides; PIINP, procollagen-III terminal propeptide. Data with respect to mRNA (*), protein (†) or both (‡).
Why do Aneurysms Occur?

- Vote
  - Atherosclerosis
  - Matrix metabolism
  - Inflammation
  - Genetics
  - Other
Atherosclerosis and AAA

- Association with atherosclerosis
  - More than 90% of aneurysms are associated with atherosclerosis
  - 75% of patients with aneurysmal disease do not have occlusive vascular disease involving the aortoiliacofemoral segments
  - Induction of aneurysms in animals fed an atherogenic diet has not been predictable
  - Atherosclerosis is likely a coincidental finding or a facilitating process rather than causative
Inflammation and AAA

- Inflammation and matrix-degrading enzymes likely the primary factors in AAA development
- Lipids appear to play a minor role in AAA progression
  - Lipoprotein (a) has been found to be an independent risk factor for atherosclerosis
    - Elevated in patients with AAAs independently of the patients' cardiovascular risk factors or the extent of atherosclerosis
  - Statins reduce the production of MMPs in the wall of AAAs
Connective Tissue

- Connective tissue
  - Normal aortic wall
    - Lamellar units that consist of elastin, collagen (mainly types I and III), and vascular smooth muscle cells
    - Elastin
      - Medial
      - Load-bearing component
      - Provide elastic recoil
    - Collagen
      - Tensile strength
      - Structural integrity
      - Bears load at high pressures or when elastin fails
  - Adventitia
    - Responsible for the resistance of the aorta in the absence of medial elastin
Connective Tissue and AAA

* Proteolytic enzymes have also been shown to play a role in aneurysm formation
  * There is increased expression and activity of MMPs in the wall of AAAs
  * MMPs and other proteinases derived from macrophages and aortic smooth muscle cells are secreted into the extracellular matrix and are integral to aneurysm formation
  * MMP activation favors elastin and collagen degradation

* Interstitial collagen degradation accompanies increased expression of collagenases MMP-1 and MMP-13 in AAAs in humans.

* Elastases MMP-2, MMP-9, and MMP-12 also have an increased expression in aneurysmal aortic tissue
  * MMP-12 is highly expressed along the proximal leading edge of AAAs in humans and may be important in aneurysm formation
  * MMP-2 is found in high concentrations in small aneurysmal aortas, suggesting a role during early aneurysm formation
  * MMP-9 is found in abundance in medial smooth muscle cells, and increased levels have been found in the aortic wall and serum in up to half of patients with aortic aneurysms, but not in those with aortic occlusive disease
    * MMP-9 has also been found to have a threefold higher activity in aneurysms 5 to 7 cm in diameter compared with aneurysms smaller than 5 cm, consistent with the increased expansion rates observed for larger AAAs
  * The important role that MMP-9 plays in aneurysm formation is reinforced by the observation that MMP-9 knockout mice do not form experimental aneurysms. Wild-type bone marrow transplantation, however, restores the aneurysm phenotype
  * Interestingly, these increased serum levels return to normal after aneurysm repair
Connective Tissue and AAAs

- In addition, the expression of tissue inhibitors of MMPs (TIMPs) has been found to be decreased in the wall of aneurysms.
- Promoting overexpression of MMPs and consequently elastin and collagen degradation.
- $\alpha_1$-antitrypsin, has been shown to be deficient in aortic aneurysms.
- This may explain the association of AAA ruptures with chronic obstructive pulmonary disease (emphysema patients with reduced $\alpha_1$-antitrypsin levels).
- Based on this information, it can be concluded that during aortic aneurysm formation, the balance of vessel wall remodeling between MMPs, TIMPS, and other protease inhibitors favors elastin and collagen degradation.
- The prevalence of AAA in men with a history of an inguinal hernia is higher than in men without such history.
  - This remains true when adjusted for smoking history.
- Ventral hernia formation more likely after AAA repair than aortic procedures for occlusive disease.
Inflammation and AAAs

- A prominent histologic feature of aortic aneurysms is the presence of an inflammatory infiltrate
  - Plasma cells in the media
  - T cells in the adventitia
    - These cells may release a cascade of cytokines that result in the activation of multiple proteases
    - Exposed elastin degradation products may serve as a chemotactic agent for infiltrating macrophages

- The potential that aneurysm formation is autoimmune is supported by
  - Extensive lymphocytic and monocytic infiltrate in the media and adventitia
  - Deposition of IgG in the aortic wall

- Macrophage- and lymphocyte-generated cytokines are increased in the wall of AAA

- These inflammatory cytokines induce the expression and activation of MMPs and TIMPs.
An infectious cause of aneurysm formation has also been suggested:
- As many as 55% of aortic aneurysms demonstrate Chlamydia pneumoniae by immunohistochemistry.
- Chlamydia has been shown to induce AAA in rabbits.

Culture of thrombus from AAA:
- 500 out of 796 patients had microbiology.
  - 37% were positive
    - mostly for skin flora (80%)
- 3.2% had infectious aortitis.
- Graft sepsis in only six out of 296 with negative cultures.
- Positive culture was not a risk for secondary graft sepsis.
Role of Vasa Vasora

- Route for infectious agents
  - Obliterative endarteritis of the vaso vasorum seen in syphilitic aneurysms
- Route for inflammatory mediators
- Fewer number in the distal aorta
  - May hinder body’s ability to repair initial damage to artery
Other Potentials

- Reactive oxygen species such as superoxide (O$_2^-$) also have been shown to be increased in human AAAs
- Elastase infusion in animal models has been shown to increase nitric oxide synthase expression and decrease the expression of the antioxidant, superoxide dismutase
- O$_2^-$ levels in human aneurysmal tissue are 2.5-fold higher than adjacent nonaneurysmal aortic tissue and 10-fold higher than control aorta
Where do Aneurysms Occur?

- Infrarenal aorta – Most common
- Thoracic aorta
- Extremity
  - Femoral
    - A patient with a femoral artery aneurysm has an 85% chance of having a concomitant AAA
  - Popliteal
    - A patient with a popliteal artery aneurysm has a 62% chance of having a concomitant AAA
- Association with other aneurysms
  - With a documented AAAs, 14% have either a femoral or a popliteal artery aneurysm
  - There is a significant male predominance
- Visceral
How do Aneurysms Develop?

- Histologic appearance
  - Thinned wall
  - Decreased medial elastin
  - Increased collagen:elastin ratio
  - Elastin fragmentation
  - Elastin completely depleted early in aneurysm formation
    - May be responsible for elongation and tortuosity seen in aneurysms
Pathophysiology

- Experimental studies
  - Enzymatic treatment with elastase leads to arterial dilation and stiffening at physiologic pressures
  - Treatment with collagenase leads to arterial rupture without dilation.
    - Elastin degradation is a key step in the development of aneurysms
    - Collagen degradation is ultimately required for aneurysm rupture

- Histological corollary
  - Fewer lamellar units in the abdominal aorta than the thoracic aorta, and there is even a further abrupt decrease in the number of lamellar units below the renal arteries
  - Relative paucity of elastin and collagen is thought to play a role, among other factors, in the predilection for aneurysm development in the infrarenal aorta
  - Elastin is not synthesized in the adult aorta and has a half-life of 40 to 70 years, accounting for its reduction with age and the occurrence of AAAs in elderly patients.
Why Fix AAAs?

- Rupture
- Distal embolization
- Aortoenteric fistula
- Aortocaval fistula
- Iliac vein compression
  - Deep venous thrombosis
Rupture of AAAs

- **Natural history**
  - Longitudinal studies of cohorts with small aneurysms
  - **Law of LaPlace**
    - \( t = \frac{Pr}{d} \)
    - Tangential stress placed on a cylinder filled with fluid
    - \( P \) is the pressure (dynes/cm\(^2\)) exerted by the fluid, \( r \) is the internal radius (cm) of the cylinder, and \( d \) is the thickness (cm) of the cylinder wall
  - When the aorta expands
    - Radius increases
    - Wall thickness decreases
    - Geometric increase in tangential stress
    - As an aneurysm grows from 2 cm in diameter to 4 cm, tangential pressure increases not twofold but fourfold.
Natural History of AAAs

- The natural history is continuous expansion
- Growth rate varies with size
  - Size < 5 cm
    - 0.32 cm/year
  - Size > 5 cm
    - 0.4-0.5 cm/year
- Risk of rupture
  - 4-5.4 cm diameter
    - 0.5-1 % per year
  - 5.5-6 cm diameter
    - 5-10 % per year
  - 6-7 cm diameter
    - 10-20 % per year
### Risk for Rupture of AAAs

<table>
<thead>
<tr>
<th>RISK FACTOR</th>
<th>LOW RISK</th>
<th>AVERAGE RISK</th>
<th>HIGH RISK</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diameter</td>
<td>&lt;5 cm</td>
<td>5-6 cm</td>
<td>&gt;6 cm</td>
</tr>
<tr>
<td>Expansion</td>
<td>&lt;0.3 cm/yr</td>
<td>0.3-0.6 cm/yr</td>
<td>&gt;0.6 cm/yr</td>
</tr>
<tr>
<td>Smoking, COPD</td>
<td>None, mild</td>
<td>Moderate</td>
<td>Severe/steroids</td>
</tr>
<tr>
<td>Family history</td>
<td>No relatives</td>
<td>One relative</td>
<td>Numerous relatives</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Normal blood pressure</td>
<td>Controlled</td>
<td>Poorly controlled</td>
</tr>
<tr>
<td>Shape</td>
<td>Fusiform</td>
<td>Saccular</td>
<td>Very eccentric</td>
</tr>
<tr>
<td>Gender</td>
<td>Male</td>
<td>Female</td>
<td></td>
</tr>
</tbody>
</table>
Screening for AAAs

UK

- Multicentre Aneurysm Screening Study (MASS)
  - 70,495 men
  - 65 to 74
  - AAA 5.5 cm or larger were referred for surgical repair
  - At 4 years, a 42% reduction in deaths from AAA was found in the screened versus the unscreened group

US

- U.S. Preventive Services Task Force
  - One-time screening for AAA by ultrasonography in men age 65 to 75 years who have ever smoked
  - Short-term impact of AAA screening on quality-of-life measures
Screening for AAAs

- The Society of Vascular Surgery and the Society for Vascular Medicine and Biology
  - All men age 60 to 85 years
  - Women age 60 to 85 years with cardiovascular risk factors
  - Men and women age 50 years and older with a family history of AAA
- Follow-up screening
  - No further testing if aortic diameter is less than 3.0 cm
  - Yearly ultrasonographic screening if aortic diameter is between 3.0 to 4.0 cm
  - Every 6 months if aortic diameter is between 4.0 to 4.5 cm
  - Referral to a vascular specialist if aortic diameter is greater than 4.5 cm
Medical Management of AAAs

- At present, few definitive recommendations can be made regarding the use of medical therapy to reduce AAA growth
- The indications for perioperative beta blockade are primarily cardioprotective
  - Despite initial promising results, recent randomized trials failed to confirm the beneficial effect of β-blockers in slowing growth of aortic aneurysms
- Antihypertensives may be beneficial from a practical perspective, but current level I data supporting this practice are lacking
- Lipid-lowering drugs to patients with AAAs also requires further study
  - The utility of such agents in the presence of CAD, which is found in almost 50% of AAA patients, is well documented
  - Long-term statin use after successful AAA surgery has been associated with reduced mortality
- Smoking cessation is mandatory
MMP inhibitors have been proposed as another therapeutic approach to slow aneurysm expansion

- Tetracycline derivatives (doxycycline) have been shown to be effective inhibitors of MMPs
- Patients undergoing open AAA repair were treated preoperatively with oral doxycycline for 1 week exhibited a fivefold reduction in the amount of MMP-9 expressed within aneurysm wall tissue compared with controls
- Another prospective, randomized placebo-controlled study examining the effects of doxycycline in patients with small asymptomatic AAAs demonstrated a significant difference
  - Doxycycline 7% of patients with AAA expansion >5 mm
  - Placebo 41% of patients with AAA expansion >5 mm
- Potential relationship with prevalence of Chlamydia?