

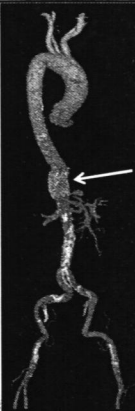
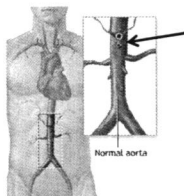
Case 2

- 77 year old man presents with abdominal pain
- Imaging reveals a periaortic soft tissue mass
- Over time this progresses into a penetrating ulcer of the aorta

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Case continued

- Periaortic soft tissue mass with a penetrating ulcer
- Underwent aortic repair



History

- Meat cutter for 30+ years
- Retired, lives with his wife
- No pets or farm animal exposure
- Life long non-smoker
- No out of state travel in the past 17 years
- No family history of TB or autoimmune disease
- No known TB contacts

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Relevant Medical History

- Diagnosed with urothelial carcinoma in situ of the bladder 2 years prior to presentation
- He received 2 courses of **BCG therapy** for his cancer.

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History

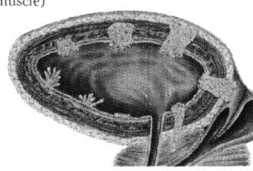
- (1929) Raymond Pearl at John Hopkins Hospital
- Cancer focused autopsy review 1910-1920
 - Cancer free patients nearly 3x more likely to have active TB
 - Patients with active TB had a lower frequency of cancer
 - Experiments started to treat cancer with different forms of "tuberculin" including BCG
- Popularity for BCG as an anti-cancer therapy mounted in the 50's and 60's
- In 1976 clinical trials confirmed improved outcomes in bladder cancer patients and treatment regimen standardized



Pearl, R. Cancer and Tuberculosis. American Journal of Hygiene. 1929; 9:135-97-159.
Meyer J, Pernad R, Gillatt DA. Use of bacille Calmette-Guérin in superficial bladder cancer. Postgraduate Medical Journal 2005; 81:442-453.

Bladder Cancer

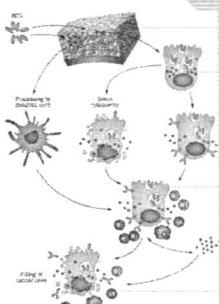
- 4th most common cause of cancer in men, 8th in women
 - Every year ~45,000 new cases and 11,000 deaths
 - 70% are superficial at the time of diagnosis
 - Despite tumor removal and chemotherapy 40% recur
- Criteria of BCG therapy
 - Low grade bladder cancer (non-muscle)



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How does it work?

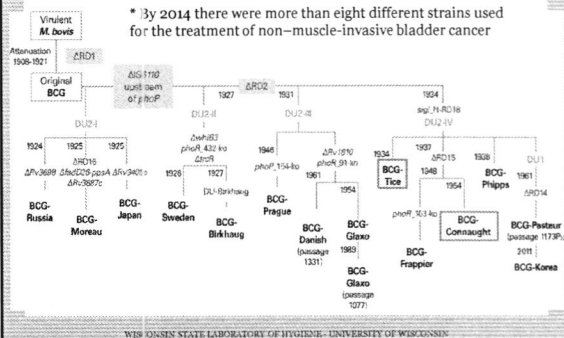
- True mechanism is not known
- Stimulates a local immune reaction
- One theory suggests the bacilli are directly killing the cancer cells.
- Another proposes the bacilli enter cancer cells and induce the immune system to kill the infected cells.
- Only live bacilli can induce the anti-cancer response



Kenderson-Stüb G, Glickman MS, Buchner M. *Nature Reviews Immunology* 11, 553–562 (2011). doi:10.1038/nri3001

Therapy strains

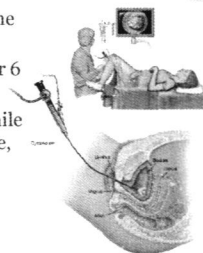
* By 2014 there were more than eight different strains used for the treatment of non-muscle-invasive bladder cancer



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Procedure


- Powdered BCG is mixed with saline
- The solution is instilled in the bladder by catheter every week for 6 weeks
- The fluid is retained for 1 hour while the patient alternates laying prone, supine, and on each side to fully coat the bladder
- Regular cystoscopy follow-up to check for recurrence
- If cancer recurs can do 2nd 6 week course



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Biosafety

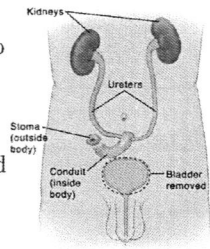
- The Bacteria are alive!
- To prevent infection clinicians should wear eye protection, gloves, gown, and a respirator.
- Patients are advised to bleach their toilets after urinating



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BCG Therapy Failed

- Two 6 weeks BCG treatments were not able to prevent recurrence of his cancer
- Refractory disease required a radical cystectomy with ileal conduit diversion



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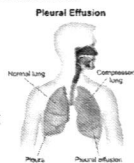
Infection as Therapy

- 53-88% efficacy for Bladder Cancer
- Other cancers showing some improvement:
 - Stomach, colon, prostate, skin (melanoma)
 - Side effects have limited this research
- Therapeutic effect against other mycobacterial diseases
 - Leprosy and Buruli ulcers
- Research in development to genetically alter BCG to express antigens from other pathogens in a new vaccine strategy
 - HIV, HCV, human metapneumovirus, malaria, toxoplasma, Echinococcus, and Schistosomes

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Patients Laboratory Findings

- Biopsy of the aortic mass had 9+ AFB!
- Chest X ray showed mild pleural effusions
- Pleural fluid was also AFB+
- IGRA negative
- PCR identified:
 - *Mycobacterium tuberculosis* complex



Clinicians conclude this is disseminated BCG and no further testing is requested

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Case Conclusion

- Debulking of infection during aortic repair
- Patient treated with rifampin, isoniazid, and ethambutol for 6 months
 - Inherent resistance to pyrazinamide
 - Strains well characterized, AST not needed
- Patient doing well

RIPE

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Our Case is Unusual

- Late presentation, >1 year since treatment
 - Usually within 20 days
- Disseminated infection is very rare
 - 4 cases reported in the US between 2008-2015
- However, side effects are common
 - 8% of patients stop therapy due to side effects

Disseminated and Unusual
Rev Rep Urol. 2015; 7: 257-165.

Side Effects of BCG Therapy

Very Common (>1/10)	Flu-like symptoms, fatigue, malaise, cystitis, dysuria, hematuria
Common (>1/100)	Urinary tract infection, anemia, pneumonitis, abdominal pain, nausea, vomiting, diarrhea, arthralgia's, urinary incontinence, urinary urgency
Uncommon (>1/1000)	Tuberculosis infections, pancytopenia, hepatitis, rashes, urinary retention or obstruction, cough
Rare (>1/10,000)	Epididymitis, hepatic enzyme increase
Very Rare (<1/10,000)	Pharyngitis, orchitis, Lupus, lymphadenopathy, confusion, dizziness, headache, vertigo, hypotension, flatulence, alopecia, back pain, acute renal failure, prostatitis, chest pain, weight loss, sepsis

*Most side effects dissipate within 48 hours

Contraindications

- If there is medical evidence for Tuberculosis infection.
 - PPD should be done before treatment
- Patients currently being treated with anti-TB drugs
- Patients with impaired immunity

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Section 2: Take Home Points

- BCG is used as a treatment for early stage bladder cancer.
- This live attenuated organism can still disseminate and cause disease.
- Further research may identify other anti-cancer and therapy properties of mycobacteria.

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