Emperor of All Maladies Notes

Introduction

- Dr. Siddhartha Mukherjee (Dr. S from now on) is a respected doctor who has recently joined a two year fellowship to work in a cancer ward at a hospital
- He recalls working with a patient, Carla, who had acute leukemia - a treatable, yet highly deadly white-blood cell cancer
- Dr S explains the purpose of the book is to make sense of the history of cancer so that we can better understand it's present and future, with stories of his own woven in

Chapter 1

- Leukemia is "white-blood cell cancer"
- It was discovered in 1845, but baffled doctors as there was no apparent 'cause' (of course the cause was internal, but they couldn't have known that).
- One of the first two was a German doctor, Virchow. He was an early believer in the 'cellular' theory of the body (which we now know is correct). This gave him a keen insight into an explanation for leukemia which other doctors likely wouldn't have considered.
- There's two types of cell growth. Hypertrophy whereby cells literally grow bigger and hyperplasia whereby cells multiply by forming new cells
- Cancer is essentially pathological hyperplasia
- This uninhibited cell growth often spread throughout the body and formed masses of tissues called tumors. This could spread from distant site to distant site creating metastasis.
- Leukemia can be slow and chronic or fast and acute. Acute could be of two forms depending on type (myeloid or lymphoid - two white blood cell types)
- Carla, the patient of Dr. S's from earlier, has acute leukemia (lymphoid) and only hope is to treat it with chemotherapy to just kill all possible bad cells immediately (and inevitably many good ones)
- Sidney Farber decided to study acute childhood leukemia in 1947. Leukemia was a good choice of cancer to study. because it is easily quantifiable by white blood cell count. Other cancers are harder to quantify since the cells may not be free floating in blood. This led to the basis for being able to perform an experiment.

Chapter 2

- Penicillin was so valuable during WWII that it was extracted from the urine of patients
- During the the post-war era there was rapid improvements in medicine - most notably antibiotics and vaccines and hygiene.

- This led to large spendings on medicine and health and the proliferation of hospitals and health services - and with this the desire to cure diseases (hospitals plus this public sentiment essentially established a market for cures)
- Cancer had developed little though. The best chance was removing a tumor and thus the source. This didn't always work though - especially with metastasis. Another option was radiation.
- Part of the reason it didn't come far was also a lack of funding at the time. This would come naturally overtime though as other diseases were defeated and an economy of cures and medicine was created. It was still the second biggest killer in 1926 though...
- Pernicious anemia (a deficiency of red blood cells not due to a lack of iron like usual) was able to be solved through b12. Perhaps a similar strategy could be used on leukemia.
- Another type of anemia, found in impoverished works in Bombay, was found to be solved through Marmite (ultimately found to be folic acid). Folic acid turns out to be crucial for the replication of DNA
- Sidney Farber tried to use folic acid thinking it could help with white blood cells too in leukemia. But it turned out to only make it worse
- Many were angry about this, but he thought it was good data. This meant the answer was to introduce an 'anti-folate' that should logically do the opposite. Ironically this would suggest that the conditions that the impoverished workers in Bombay experienced would help leukemia patients

Chapter 3

- Farber found a potential solution with a new 'antifolate'. It effectively suppressed (but not cured) the cancer. Further, it often didn't last and the effect was largely temporary (order month or years)
- This showed for the first time that cancer could be tackled by a chemical drug (a revolutionary thing at the time)

Chapter 4

- Cancer is clone-al diseases in that there is a direct cell lineage down to the original ancestral cancer if one were to watch the unbounded cell division in reverse.
- However, it is not completely clone-al in that the natural process of evolution happens to it constantly over many fast generations. So each generation gets 'better'.
- The first true medical history of cancer dates back to ancient BC scrolls about an Egyptian physician Imhotep. It was one of the first pieces of evidence of a doctor treating a disease as an objective medical problem. It was also the first documented case of human cancer. Interestingly he provides attempted cures or treatments for the 46 cases he analyzed in this scroll. Although for cancer

he writes ‘there is none’.
- However for most of history cancer was rarely noticed compared to many other more common diseases.
- The first recorded time of cancerous tumors being removed is from Herodotus in 440 b.c.
- Some of the first physical evidence of cancer is from a thousand years ago where bodies were naturally preserved in the harsh Atacama Desert.
- Cancer didn’t appear much in early history because:
    - It’s likeliness increases greatly with age. so when life expectancy was lower, it was less likely to be seen.
    - It is hard to detect early or at all because it happens on a cellular level and often manifests with symptoms that could be other things

Chapter 5

- One of the early Greek doctors Hippocrates based much of his theories off of fluids because that was the predominant technology of the time (fluid engineering).. naturally due to cities needing to build irrigation and waterway and drainage systems. It was only natural and they never could have imagined something such as a cell
- Originally many ancient doctors believed it wasn’t worth removing a tumor. They were right in some sense, since it didn’t cure the cancer. But they were wrong that in some cases it could work or be sufficient. However, when one considers the medical conditions of the time, if often sadly really wasn’t worth it.

Chapter 6

- Early in the year 100-200 the doctor Galen put forth the humoral theory of medicine - that all health was dictated by balancing the 4 fluids in the body (blood, black bile, yellow bile, phlegm). It was often believed black bile was responsible for things like cancer.
- In the 16th century, Vesalius pioneered the field of anatomy - realizing that doctor’s couldn’t make progress without an accurate roadmap of the body.
- In doing so, he found scant evidence for humorism (he fond no black bile).
- A couple/few centuries later the anatomist Baillie studied diseased human anatomy in addition to ‘typical’ human anatomy and also saw no evidence of black bile - largely destroying the theory of humorism.

Chapter 7

- In the 1760’s doctors started trying to cure/treat cancer by removing tumors again. Medicine had advanced and had become more sterile, so it naturally became safer.
- At the time a doctor, Hunter, discovered tumors had stages whereby the were ‘movable’ (excisable) and later stages where they weren’t. Nonetheless, due to

still poor sanitation removing tumors didn't go particularly well.
- Then in the 1850's things improved.
- First in 1846 anesthesia was discovered. A doctor named William Morton as Massachusetts General demonstrated the usage of inhaling ether to knock patients out - during which they would stay asleep despite surgery and feel no pain after. This enabled long and complex surgeries to be performed.
- Then in 1865 Joseph Lister noticed wounds that weren't closed quickly often led to infection and then death. He recalled Pasteur and his invention of Pasteurization that showed by removing exposure to air things wouldn't go bad (the theory being that bacteria going about in the air would get into the sample and multiple and make things go bad). This inspired Lister to try a technique to kill bacteria near a surgery or infection site. He tried doing this using carbolic acid, a sewage cleanser. He had ultimately invented antiseptic medicine and showed how to treat infections and make surgery significantly safer. Lister even went on to perform tumor removal surgeries using antiseptic after. (Thus the name, Listerine).
- This began the first era of modern cancer treatment by surgical removal from 1850-1950
- During that era Theodor Billroth rigorously established the surgical techniques to be used in removing tumors

Chapter 8

- William Halsted revolutionized modern surgery by learning and studying many doctors and combing their techniques. He worked intensely hard but also did a lot of cocaine.
- He tried to treat breast cancer by operating more extensively and removing more tissue. His radical surgeries were based on days that showed the larger the area of the surgery, the less likely resurgence would be
- He only partially realized though that it wasn't just the size of the surgery that mattered. It was when. If done early the surgery actually didn't need to be that big. If it was late A big surgery would only be a temporary fix anyway...
- At the times the famous-ness of surgeons made them overly confident and they often over operated to a fault. They sought to operate sometimes and not cure
- Nonetheless this generation of surgeons did come up with many useful techniques

Chapter 9

- In the late 1890's Wilhelm Roentgen discovers x-rays as a by product of electron movement and uses them to photograph the inside of people because it penetrates flesh but not bone
- Later Marie Curie discovered this property excised naturally in some elements such as uranium. She eventually discovered radium, which gave of such

intention radiation it glowed. Sadly they discovered that it could also invisibly penetrates and damage the flesh from the inside. Radium did this by damaging DNA within a cell - messing up its replication abilities.
- Almost immediately after discovering x-rays, Emil Grubbe tried using them to treat cancer. He found that it could reduce or eliminate local cancers, but only early local ones
- Radiation treatment advanced rapidly and in some cases really could be used to “cure” cancer
- However it had downsides. Very often radiation itself could cause cancer. It was all about balancing probabilities

Chapter 10

- In order to cure cancer one would need to selectively destroy cancer cells. This begs the question of how does one even mark a specific cell for destructions?
- The clothing industry during England’s Industrial Revolution at the start of the 19th century led to the development of modern dyes. The first was aniline mauve (Mauveine) that easily colored code after combining nitrate and benzene and was easy to mass produce.
- Most other dues were discovered soon after in Germany where there was an especially hard need for dyes to them lacking few natural ones. The synthetic chemical industry started to grow rapidly and invent most modern dyes
- Medicine and chemistry started to mesh a bit after that. This began with the Wohler experiment which showed that a synthetic chemical could be turned into a natural chemical. This suggested the two could interact and that natural chemicals weren’t some special thing God had made. the next logical step was using chemistry on/in the body.
- In the late 19th century Paul Ehrlich would first use dye to stain tissue. He was surprised to find it only stained certain parts of the cell.
- He discovered a chemical cure to syphilis this way
- Unfortunately this era stopped short of further medical development due to WWI. Their experience in synthetic chemistry was critical to inventing and deploying mustard gas (which ironically demonstrated cell-differentiating behavior which was only later seem to be useful in developing cancer drugs had anyone been paying attention to actually saving lived at the time)

Chapter 11

- The Bari Incident was a German mustard gas attack on the allies in WWII. It was on a base and an embarrassment - which enabled it to be rigorously studied and with zeal
- One of the compounds were studied by Goodman and Gilman at Yale. They noticed that in addition to burns, the gas somehow targeted white blood cell production and destroyed it specifically (Krmbhaar effect)

- They used it to treat cancers with white blood cell issues and found that while it provided a temporary effect in eliminating the cancerous, it couldn't fix it completely

Chapter 12

- Polio was largely eliminated due to large spending by FDR in his 2nd term. A campaign of every citizen sending in a dime for polio research was a massive success for fund raising and public opinion. These labs then built the basis for eliminating polio
- Sidney Farber wanted to do the same for childhood leukemia to make more advanced in cancer treatment
- The Variety Club (a charitable group of people in show business inspired by an orphaned child left at a theater during the depression) decided to help Farber, inspired by his vision for childhood leukemia
- This led to the "Jimmy" fund. They picked a child with cancer and did a radio show where his favorite baseball team showed up for him and they asked for donations. This kind of thing was revolutionary at the time. It was a huge success and created a new model for funding cancer research that is still in effect today

Chapter 13

- Sidney Farber continue his fundraising through 1952 until he had enough money to build his own cancer ward - and a very nice one. It was one of the first such places to be built with a focus on making the experience enjoyable and happy for patients

Chapter 14

- Mary Lasker and her husband were wealthy socialites that made it in salesmanship and advertising. Due to personal connections they took up philanthropy for cancer - a natural application of their skills.
- They aggressively pushed for funding goals, restricting boards to not have too many doctors to make way for it
- She needed a good doctor to champion it all though and found that it Sidney Farber

Chapter 15

- Eventually Mary Lasker's husband Albert became sick and died of colon cancer
- Afterwards she sought to make cancer development and research faster
- During this time (1950's) Farber may have gotten sick. It's not clear whether it was cancer or not due to him and his family never talking about it.
- This fit with the growing model of scientific research. Prior to the development of the atomic bomb a few years early people thought science research was

more about curiosity and stumbling on something useful - not something that could be taken on as a direct project with a goal like the Manhattan Project did.
- However after the war Vannevar Bush, a director of scientific research for the US government decided to go back to the old model of broad curiosity and research. He did have a point though - without open ended research the facts/ discoveries that allowed targeted project teams to be successful came largely from that broad type of research
- The team Lasker had put together pushed back against that to speed up and create a War on Cancer and make a Manhattan Project of their own targeted against cancer
- During this time Farber discovered that radiation combined with actinomycin D (a nature based antibiotic much like penicillin) could be very successful in treating highly specific forms of cancer even when it metastasized
- The author (Dr. S) goes back to Carla and describes how given her acute lymphoma there were currently three steps:
    - Highly intense and short radiation to send it into remission - which would also destroy her immune system
    - Less intense, but more broad radiation to keep it that way once her immune system started to come back
    - Brain treatments via radiation and spinal taps (since the blood-brain barrier prevents normal injections from working in the brain) after to treat it potentially hiding in the brain, which is common for that form of lymphoma

Chapter 16

- Gordon Zubrod at NCI proposed a new form of group clinical trials called procedures. It would facilitate more communication between cancer researchers and make it easier to distribute patients and data instead of them competing. This greatly advanced research.
- In the 1940's there was much antibiotic research and thus a need for clinical trials that could determine the efficacy or a drug. Bradford Hill at that time first proposed randomized blind clinical trials with placebos to avoid the inherent bias of doctors. Zubrod made this a big part of his model for cancer research
- Much like they learned for antibiotics, cancer researchers saw that often multiple drugs needed to be used the to evolved resistance. This type of variety carpet bombing ensured no further growth. In fact the first true cancer treatment clinical trial was testing this. It was a huge success, finally uniting researchers.

Chapter 17

- At NCI Min Chiu Li discovered that for a certain kind of birth cancer (a cancer

obtained by babies before they are born) antifolates seemed to work. Further, it was marked by a drop in hormone levels (hcg) that indicated the presence of the cancer. The drugs didn't eliminate the hcg level completely even though it seemed the cancer was gone. Li kept pushing until the hcg level was 0 to be sure, but the medical board fired them for this as there was no qualitative effects to accompany getting the hcg level back to 0 (thus it was seemingly medically unnecessary)
- Li turned out to be right though -every single sign needs to be treated until it goes to 0, otherwise the cancer will come back.

Chapter 18
- The new rigorous and collaborative clinical trail process was starting to get slow. As more drugs and different doses were introduced, there were more possible combinations to experiment with. This slowed down everything since the number of combinations grow faster than exponentially.
- Howard Skpper used mouse models to study cancer. He found that chemotherapy in ouse models killed a fixed percentage of cancer cells each time - regardlesss of the total number of actual cancer cells. This percentage was unique and particularly to each drug. This suggested that of course multiple rounds would be necessary as one would have to repeatedly apply that percentage until the number went to 0.
- He also found that pairs of drugs were always better than a single drug since they fought cancer cell defensive evolution better than just one.
- Researchers at NCI realized that they would need to use all drugs at once and in rapid succession (called VAMP after the names of the four drugs used)

Chapter 19
- Many didn't want the VAMP trials to proceed because they sounded far too intense to use on a patient - after all each of the antibiotics are essentially poisons
- Nonetheless they managed to try. At first results seemed terrible, then amazingly everyone started to recover until the cancer was gone.
- The problem was that some of these patients would later come back with head issues. Scientists found that this was due to the cancer reappearing in their brain - a place their antibiotic drugs couldn't reach. So it seemed cancer ran and hid in the 'last' place it could.

Chapter 20
- Thomas Hodgkin was an anatomist back in 1850 London. He did pathological anatomy by organ instead of by disease or some other metric. This led to him discovering what would turn out to be Hodgkin's cancer, a lymph node cancer
- The cancer, unlike others, spreads locally from place to place (unlike other cancers that can metastasize from the lung to the brain)

- Henry Kaplan in 1950 at Stanford combined their idea of a linear accelerator and radiation therapy to try and treat Hodgkins since it was perfect for a concentrated local attack
- He managed to get funding in a small warehouse in SF. He rigorously proved that in targeted super high radiation at infected AND contiguous sites could truly cure the disease
- He was successful due to highly rigorous and selective trials and followed the principle of using facts about the disease to tailor the medicine - that is, exploiting the uniqueness of each disease as a vector for attack rather than going to broad. This would become an important principle later

Chapter 21

- Other scientists tried multiple-drug chemotherapy and found it successful in late stage Hodgkins disease
- Doctors thought the next step would be:
  - Even more multiple drugs
  - Getting some of those drugs into spinal fluid or some way to break the blood-brain barrier (or using radiation)
  - The duration of chemotherapy needed to be longer
- Donald Pinkel first tried the above at the newly founded St Judes in the 60's

Chapter 22

- After proving out chemotherapy with leukemia and Hodgkins, doctors started using it in mass in the following decade (60's+)
- Scientists had known for a while that certain organic compounds and radiation could cause cancer. This was known as the somatic theory of cancer (carcinogens mess up cell structure and functionality, thus leading to cancer)
- However, Peyton Rous found in the 20's that cancer could be transmitted from chicken to chicken by transplanting tumors or even just the bile from them (devoid and filtered of cells). This suggested some cause was inside of the cell.
- Eventually they found that a virus could be responsible for causing cancer in some cases in animals. They eventually discovered this in humans when they found the Epstein-Barr virus (EBV).
- In the late 60's however funding was drying up for cancer from a political perspective. So fundraisers decided to go for a more public approach - a moonshot cure for cancer that would be billed much like the recent moon landing.

Chapter 23

- The War on Cancer became bolder when a large Times ad addressed Nixon saying that he could cure cancer by investing more in it
- Cancer was a good metaphor for the times. American society has finally

avoided external threats in prior decades and by the 70's was worried about decaying growing within - much like the sociopolitical issues of the time
- Eventually this led to political funding in the form of the Kennedy/Javits bill in 1971 in the Senate
- This got watered down in the house a bit - there would be a war on cancer - but not a NASA for cancer. It was argued this was important for balancing NIH initiatives
- Nonetheless this felt like a bit of defeat for people like Farber and Lasker and they retreated a bit from actively working on cancer
- At this point Carla has gone into full remission

Chapter 24

- Geoffrey Keynes eventually proved Halsted wrong and showed that radical surgery to stop breast cancer could be replaced with minor surgery combined with minor post-surgical radiation
- Keynes gave a talk at the Cleveland Clinical that George Crile heard that brought Keynes better theories to the USA. He agreeed and saw in research that radical surgery was useless since cancer often didn't radiate outward from the primary tumor and expand. It could turn up anywhere - driven by anatomy and circumstance and luck
- Developments in statistics helped Keynes and Crile price their theory through the development of methods to prove a negative claim (Neyman and Pearson)... preciously doctors had only worked with positive claims (that a drug helped - not that a given therapy didn't)
- Unfortunately these statisticians showed that to prove a negative claim you needed a "powerful" trial with MANY patients. This was a catch-22 though. To arrange such a trial you needed other doctors to agree with you. But how could you get others to agree without proving it through a trial? Radical breast cancer surgery was so ingrained due the glorification of surgeons it was hard to get them to try an alternative
- What caused change to happen was women themselves. The rise of feminism and the horror of radical surgery led to women rejecting it and doctors had to start to pursue alternatives

Chapter 25

- Cisplatin was a drug produced by running an electrical current through platinum that damaged dna and prevented cell replication
- It was found to be extremely effective in testicular cancer but had extreme nausea affects. Back then there were almost no antiemetics, so many people used marijuana instead
- All of this success continued to promote chemotherapy's research style of testing random drugs that simply worked - without more research being done to actually understand the internals of cancer and why certain drugs worked

- Patients started to pushback on the intense side effects of chemotherapy though

Chapter 26

- Charles Huggins, a urologist, noticed that depriving dogs of testosterone could make prostate cancer largely go into remission. Cancerous prostate actually appeared to need it more than regular cells. This was one of the first attacks on the biology of cancer instead of a carpet bombing strategy like chemotherapy
- It was even found that artificial estrogen could be given to such men and see a similar remission response - a form of chemical castration
- It only led to temporary remissions, but was still a good starting point
- They similarly found that in women removing ovaries could cause similar remissions for breast cancer (about 2/3 of the time) - this worked because it reduced/removed the estrogen supply
- Later in the 1960's doctor's discovered that some breast cancer cells lack a estrogen receptor - explaining why the above only worked part of time
- It was difficult to test this though given that ovary removal was no longer accepted by that time and they had yet to find an 'anti-estrogen' (testosterone did not work)
- They eventually found such a chemical while developing birth control and it was proven (tamoxifen)

Chapter 27

- Gianni Bondadonna conducted the first trials to prove that breast cancer was 50% remission versus 66% remission by doing chemotherapy rounds after surgical removal. This stunned people. He had to do it in Italy because no one in America would do it - partly because surgeons despised the notion that follow up work had to be done. Their pride had actually slowed down research.
- Similar finding were found for tamoxifen.
- Finally researchers saw that by understanding the biology of cancer they could better treat it and without side effects
- During this time Palliative Care naturally evolved. Cecily Saunders invented this in England. It took decades after to make it to America.

Chapter 28

- Eventually they tried to quantify the progress of cancer medicine, treatment, etc.
- They found it was very hard to measure. For example, earlier testing might suggest an increase in survival time or could be equally explained by the cancer just being detected more early and survival time not actually increasing. It was hard to eliminate all of these types of biases. Researchers needed a way to 'normalize' stats to account for such biases.

- This was eventually solved using age adjustment - normalizing for age so that age was held constant. Different age groups are weighted differently according to the overall population distribution.
- The results were that over 1962 to 1985 cancer had actually increased (this was possible due to thinks like smoking, etc.)
- Other researchers showed that this wasn't necessarily the case when one didn't just count death - but saved years (i.e. saving a child provided 50 years of life whereas saving an older person might just be 10 years). By including this difference the stats looked not as bad.
- All of this served to point out that disease stats are highly subjective because we have to define the right metric - and that's often extremely hard
- But there was one clear standout point from the research - clearly treatment alone couldn't stop cancer. Much like any disease (and as was seen with Tuberculosis and Polio) prevention was the only way to truly stop it - a curing treatment alone wouldn't stop cancer.

Chapter 29

- In the 1700's doctors began to notice cancer cases isolated to specific industries. The most common example of the time was chimney sweeps. It would of course turn out the such soot was a carcinogen (cancer causing substance). It was notable since if often occurred in younger (children) chimney sweeps
- The existence of man-made carcinogens suggested that much cancer could be prevented by simply removing or avoiding said substances
- Political pressure has since caused much prevention. For example child labor laws and the Chimney Sweepers Act of 1788 all worked to prevent expose of children to carcinogens.
- They eventually found this to be true for tobacco (especially chewing). However such evidence as largely disregarded. It became even more spread when cigarettes were invented during the wars. Much like a virus, this disease "tobacco causing cancer" spread through society much like any "regular" virus would. In fact it became so popular it was hard to tell it was a disease - as almost everyone was infected.
- This led to many decades of a rampant tobacco cancer epidemic - that can in many ways be viewed no differently than a terrible flu

Chapter 30

- By the 1940's many considered the idea of cigarettes causing cancer ridiculous
- In an effort to largely disprove that scientists ended up finding that it actually and undeniably did have a causal link to cancer. Although in their first papers they only established a link - not a necessarily caudal one
- Around this time a scientists famously demonstrated evolution in live action by

successively selecting for moths in a nearby forest and studying successive generations (for example he'd kill purple moths and watch evolution show that line dying out). Researchers wanted to use the same methodology to prove cancer was caused by cigarettes. But they weren't sure where or how to find subjects.
- Doll and Hill got lucky in that there was a detailed doctors database that recorded things such as death etc of doctors. Doll and Hill reached out by mail to all 60,000 doctors in the database about their smoking habits and over 40,000 responded.
- After a few years of waiting the data showed indisputably that cigarettes cause lung cancer

Chapter 31
- As these links became clearer the large tobacco industry pushed back aggressively. Their best tactic was funding more research to investigate the cancer-cigarette link. This suggested that there was still scientific debate to be had - but there wasn't. The statistics were already clear. But this was enough to fool the average person.
- Scientists increasingly demonstrated this causal link by showing things like second hand smoke and tar causing rats to become ill - but the public largely rejected the science
- To help prove this scientists more rigorously came up with standards for cause when a literal direct link couldn't be observed to make it more clear to prove
- Doctor's wondered how to stop such a 'pandemic' when medicine wasn't necessarily the fix - but people taking specific action. So doctors were forced to go to politicians since the public couldn't be convinced and they were too easy to manipulate via advertising (sound familiar?)

Chapter 32
- The smoking-cancer link was further developed by Oscar Auerbach when he showed the progressive nature of lung cancer through layers of lung tissue (much like a fossil)
- This was eventually reviewed by a small team of scientists tasked by the government with finding a link between cancer and smoking and if such a thing was true/existed
- The surgeon general at the time sought to change opinions by starting another official inquiry into the smoking-cancer link. It was already medically clear (and had been for a decade) - but doing this round of testifying and inquiring would be helpful to reiterate that to the public and reframe the issue and ignite public outcry. Their final report would overwhelming show and declare a cancer-smoking link.
- Unfortunately there was little politicians could do legally to control the tobacco industry. Ultimately, they snuck this through the backdoor by

targeting the FTC (which was largely underused back then). They said that the FTC couldn't allow tobacco companies to make the outrageous claims in their massive ad industry. Thus even though cigarettes themselves couldn't be directly regulated - their advertising could. This is how the tobacco warnings on the box came to be. Congress nonetheless diluted the warning as Southern states depended on tobacco revenues and many of their constituents refused to believe the science (what's new)

- This was eventually retried in court using an obscure law that said both sides of a debate had to presented fairly on public tv - this eventually led to a ban on cigarette commercials.
- The tobacco industry tried to fight back by inspiring doubt of the scientific claims, however the anti-tobacco lobby fought back hard with fear and graphic warnings. The tobacco industry stood no chance. This finally gave for the public to not view this as a scientific debate, but as an emotional one with real human victims through the fear ads and graphic warnings.
- Further legal fights would happen. Often tobacco companies would evade trouble by arguing when sued in court that the consumers would have been stupid to not know the risks of smoking. And they usually won. It wasn't until a lawyer argued that their client did know the risks - but it was so addictive they couldn't stop. Further, if the the makers knew all the bad things and still sold it - they should be held responsible. This forced the tobacco companies legal documents and personal knowledge on the matter into public sight. It showed that these companies had known about the addictive and cancer risks for years and actively tried to squash any such research from getting out.
- Over the next 20 years, smoking rates fell.
- Later in the 90's states started filing cases against tobacco companies for the health costs they started to incur due to the lung cancer epidemic they had caused. This led to a massive settlement that reformed the industry.
- Nonetheless, tobacco companies merely went to other countries and developed new products. As of late, rates of plateaued.
- It is nonetheless surprising to doctors that in a country such as America cigarettes can still largely be bought anywhere with relative ease.

Chapter 33

- This method and success in the proof of artificial carcinogens led doctor's to look for others. They looked for clusters of specific cancers that tended to concentrate in certain professions. This is how they discovered mesothelioma and asbestos.
- Similar things were found for certain hormonal medication like DES, carcinogens that would only act upon in future generations
- The next step was understanding carcinogens
- The first way this was done was by studying bacteria. Some bacteria like salmonella need a certain gene present in their DNA to survive in a Petri dish

with only one kind of sugar. Naturally through evolution though some bacteria would evolve this gene and manage to survive and form colonies in the dish. In theory one could thus test for mutagens (things that cause DNA mutations) by exposing separate Petri dishes to different chemicals and seeing how many colonies formed. More colonies will form in the dish that undergoes more mutations because they'd be more likely to evolve the gene necessary to survive and eat that one kind of sugar. Thus one could now scientifically test to what degree a substance could cause mutations.

- Scientists compiled data and found that most mutations happen to be carcinogens as well
- They found viruses to be carcinogens as well - especially HBV
- Other odd things were found using the same techniques. They found a cause of gastritis to be h pylori - a bacteria that strangely grew I the stomach. When it was discovered there was no viable way to directly prove it caused it. The researcher eventually injected themselves with it to prove it. But it was also a carcinogen because the repeated inflammation it caused often led to stomach cancer.Eventually a drug was created to kill the bacteria. It worked, but it only reduced cancer rates in younger people - thus showing that one had to act fast.

Chapter 34

- George Papanicolaou from Cornell was studying cervical cells in animals and humans. His research wasn't very useful until he noticed that when taken from a patient with local cancer, the cells were often very strangely designed and shaped - a clear indicator of the cancer. This could serve as a potential indicator for forms of cancer - thus now known as a Pap smear (thus the name)
- At first the technique wasn't found to be very useful - why not just do a biopsy?
- Not much was done with it for the next few decades until Papanicolaou realized it's true value. He could use the progressive deformation of the cells to put a timeline on the cancer and determine how far along it was by looking for early 'predecessor cells'. It was a simple treatment that allowed for early preventative care.
- They rolled this out on a national scale and found many instances of cancer. But more importantly they found many cases of 'pre-cancer' in asymptotic individuals. These asymptotic individuals were often decades younger than the symptomatic ones.
- In the early 1930's a scientist in Berlin began the first true studies into the use and development of mammography - another useful preventative/early-diagnostic for cancer that would later become one of the primary methods of preventing cancer and save millions of lives. Unfortunately before it could take off the Nazi's came to power and the scientist had to flee.

- Decades later it would be studied again and tested.
- A good screening test must do the following, so it's very hard:
  - Not over-diagnose (false positives)
  - Not under-diagnose (false negatives)
  - Increase chance of survival - but not just any survival (image two twins are the given an option of screening. One accepts and it detects cancer in 1990 and the other declines. The other only detects it in 1999. However they both die of cancer in 2000. Did over survive 5 years or did they survive the same? Was the screening worth it), this forces us to add the next:
  - Improve mortality rate
- The first trial for mammography-based screening was partly possible to be setup using health insurance programs from employers. It allowed scientists to get specific data on people largely in the same demographic. After 8 years it appeared to be a huge success and the program was launched everywhere nationwide.
- However after further inspection the study was deemed inconclusive because the control non-trail group was never informed - creating a potential bias and preventing researchers from fixing questions post-facto as those non-trial group could never be found (example of such is whether they had already had cancer which they had apparently forgot to ask and now couldn't fix)
- Many more studies were done in following years but they all had some fatal flaw that undid them. It was an extremely difficult statistical process as per the above standards for screening.
- A final good study in Sweden finally showed that overall mammography screening was not worth it. However, upon further inspection they found there were cases where it was. Specifically, women over 55 saw a 20% reduction in cancer death.

Chapter 35

- There is an important touch doctors need when working with patients. Specifically they need to give them important information without dressing it up - but do so in a way that the patient understands and finds acceptable. Good examples in book.
- Previous limits on chemotherapy were dictated by bone marrow cells prior to the mid 80's. Chemotherapy couldn't be any more intensive without destroying the fragile bone marrow
- They started to work around this through blood marrow transplants afterwards to remove that limit. At first they used other's and then they used saved copies of the person's own.
- Researchers eventually tried this new aggressive therapy and it appeared to work
- It was during this time in the 80's that aids broke out. It was first noticed by

pneumonias appearing in young men that it normally shouldn't because of high white blood cell count. This suggested something was attacking white blood cells - aids.
- Another symptom of aids at the time actually was cancer that could appear due to the weakened immune system (Kaposi's sarcoma)
- Cancer and aids were linked in many ways. In fact the first aids ward 5A was much like the first true cancer ward that Farber helped create
- A cause for aids was only found in France in 1983, 2 years after the outbreak
- They said they'd likely have a vaccine for aids in 2 years in 1984

Chapter 36
- Doctor's continued to have fantastic success with the bone marrow autologous transplant combined with mega-dose chemotherapy into the early 90's
- Many HMO's at the time didn't want to pay for coverage of a seemingly investigative treatment (even though it appeared to be working). This resulted in many successful lawsuits against said HMO's and they started to change their ways. The public backlash of denying coverage (especially after the work in the AIDS epidemic promoted the idea of trying more experimental ideas on people that were dying anyways) forced them to change. It even got to the point where some states made it law to cover such procedures.
- This ironically made it hard to run clinical trials since no one wanted to risk being in the control group
- By the end of the 90's doctor's were even more convinced of the success of the technique
- However also in the late 90's reports started coming out showing that it wasn't effective. All of the successful data had come from one doctor and group in South Africa.
- People went to South Africa to investigate and found all of their data covered in errors and fraud. They later admitted their errors and then literally disappeared.
- By 1994 cancer was still not defeated but many inroads were made

Chapter 37
- In further investigations of a root cause of a cancer it appeared to be chromosome related as chromosomes would generally be all messed up in cancer cells
- It was hard to reconcile this evidence though with the fact that viruses could cause cancer
- There was a strong basis in the chromosomal theory though as Mendel had demonstrated that inherited traits come through them (he didn't know about chromosomes specifically, but new that it did happen through something called genes... even though he didn't come up with that specific term)

- Thomas Morgan Hunt later in 1910 saw that often inherited traits were link (the presence of one meant another). This led to the idea that genes were hosted on chromosomes.
- So genes were transmitted to each generation through chromosomes. But it turns now it can also happen between two organisms through bacteria - even a dead one that was just ‘gene code’ - DNA
- They then found that genes carry instructions to build proteins - the main functioners of the cell
- The proteins could interact with other proteins or outside chemicals to create biological reactions and scaffolding and circuits of action
- A gene is a blueprint to build a protein
- RNA is the working form of this blueprint - it is through that which the gene is translated into a protein. This copy of the gene is the gene’s “message”
- This better understanding helped show scientists that in some cases cancer was genetic and this hereditary

Chapter 38

- Scientists later noticed that some viruses can actually manipulate body dna and thus cause cancer
- They believed this was possible through a special ability called reverse transcription - it could convert RNA back to DNA since how else could a virus made only of rna make a lasting impact? These types of viruses would be known as retroviruses
- Thus the thinking was this could alter a cells dna to turn on a gene that would cause it to keep growing when it wasn’t supposed to - cancer
- However it turned out that there weren’t really all that many viruses that caused cancer like this - only a few and it wasn’t super prevalent. It did cause HIV though

Chapter 39

- Cancer researchers now saw that viruses weren’t the main (although were a possible and rare) cause of cancer - the gene they added to cause cancer was real though. Thus now researchers had to find out what specifically was the viral gene that led to such a mutation that caused cancer
- Using the virus they isolate this as *src* or sarc (for sarcoma)
- It was a gene that built a protein that tagged other proteins with a small chemical known as a phosphate group. It served like a molecular “on-switch” or “tag”. These switches/tags could eventually create a chain reaction leading to overall state change within the cell.
- Src was so potent that it would seemingly just tag everything it could. It would jus turn on a bunch of switches
- Upon further investigation scientists found that this src gene was everywhere in every animal - not just a rare gene found in a rare cancer causing virus.

They weren't the exact same - but were very similar. The regular ones were far better regulated and not "always on".
- The theory was then that this viral, cancerous src may have evolved from the regular src gene. This made sense given that retroviruses constantly go between RNA-DNA-RNA and that eventually they would pickup and mess up a gene like src.

Chapter 40
- Further research would show that certain forms of cancer could be explained by a chromosomal mishap. Such as for CML where the head of chromosome 22 and 9 get swapped
- Another example of such biological reasoning about cancer is childhood retinoblastoma (eye cancer). It came in a hereditary and sporadic form. The hereditary form always happened in both eyes and onset fast. The other sporadic form was not nearly as fast and was always in one eye. It turned out that the sporadic form required two genetic changes to cause and the hereditary require one genetic change to cause it. This gene was known as *Rb*. This made sense given the new genetic model of cancer. It turned out though that unlike src, Rb didn't cause cancer. It was a cancer suppressor. Thus the cancer happened when Rb was messed with.
- Thus there are two mechanisms for cancer: Destroying cell replication control genes or letting loose cell replication genes. Think jammed accelerators and missing brakes

Chapter 41
- Scientists now knew more about how cancer worked but had yet to isolate a cancer-causing gene (oncogene) in an actual cancer cell.
- The plan was to find them much like they identified carcinogens and mutagens - transfer genes from cancer cells to normal ones and see which grow cancer colonies in a Petri dish
- They did this and eventually found *ras*. It was much like src - a cancer inducer
- However, such an experiment wouldn't work quite as expected for finding a cancer surpassing gene like Rb because the technique worked on finding growths not suppression's. It was eventually isolated to chromosome 13 but that was all that was known.
- The plan to identify it was to use the fact that in retinoblastoma two mutations were necessary. Those two mutations were unlikely to happen in the same part of the gene. It would often happen to different parts of the gene on the two chromosomes (humans have 2 copies of each chromosome). However, occasionally it would happen in the same part. If one found enough of these instances, then they could pin down the exact location. A scientist with a large enough collection of test tumors could do this.
- Eventually they found the Rb gene.

- But they also found that it wasn't mutated in just cancer cells. In fact it could be found throughout the body.
- Eventually using mouse models they were able to show that mutations in these genes literally caused cancer

Chapter 42

- Scientists next found that there was a natural genetic progression of cancer as the mutations that led up to it was a gradual and multistep process. The mutation to hit the acceleration was required, but so was the additional two mutations to stop the "brakes" (ras mutations followed by Rb mutations).
- Scientists eventually got to the point where they could see how the gene influenced protein chains (i.e. how the protein in assembled than affected other proteins) and thus affected the macro behavior of the cell
- From these reactions scientists were able to begin to understand how other symptoms of cancer, besides unregulated cell growth, fit together. This was because the protein chain reactions often had other downstream affects on the body.
- An example of this was the blood vessel growth near tumors - which tumors happen to use for a blood supply. Another example was metastasis itself.
- Thus from a biological perspective, the story of cancer was largely assembled
- They boiled down cancer to:
    - Self-sufficiency in growth signals: Cancer cells will continually grow on their own accord by virtue of ras/myc mutations
    - Insensitivity to growth-inhibitor signals: Cancer cells inactive tumor surpassing genes such as Rb
    - Evasion of programmed cell death: Cancer cells inactivate this pathway
    - Limitless replicative potential: Cancer cells tend to activate gene pathways that make them largely immortal
    - Sustained angiogenesis: Cancer cells get their own blood supply from blood vessels
    - Tissue invasion and metals: Cancer cells eventually develop the ability to travel throughout the body

Chapter 43

- In in 1998 the people running the Jimmy found located the true "Jimmy" (not his real name). He came back and visited the same cancer ward 50 years later. At this point the story had really come full-circle.
- Starting in the late 90's and early 2000's more success against cancer was seen as mortality rates had declined by about 1 percent every year for cancer in general - for fifteen straight years. One notable area of much success was breast cancer - which improved by 24%
- With the new biological understanding of cancer though, it was time to make more powerful/targeted drugs than the carpet-bombing style of treatment in

chemotherapy drugs

Chapter 44

- Up until the late 20th century most cures to cancer were limited to local cancer that could be handled with surgery/radiation or chemotherapy drugs that broadly destroyed the cells ability to divide by damaging division mechanisms or DNA itself
- The biology of cancer discovered in the 1980's created new points of attack, namely:
  - Target radical growth genes - not 'braking' genes
  - The fact that growth control pathways are tightly regulated in normal cells compared to cancer cells could be an avenue for attack
  - The growth pattern and rapid generations of cancer lets it accumulate other mutations that could be used to stop it
- Eventually doctor's would start coming up with drugs that exploited this such as transretinoic acid that can serve to bind the behavior or proteins in certain cancers
- Another example is an antigen that binds to a protein created by a cancer gene that effectively halts it. This only works on proteins from genes that partially hang outside the cell member (which are rare, but do exist)

Chapter 45

- Recombinant DNA was a technology developed in the late 70's that allowed genes to be engineered and manipulated and transferred between organisms
- This technology was bought by Genentech
- Previously it was very hard to create protein based drugs because of the difficulty in creating proteins or harvesting them from animals (1 pound of insulin per 8000 pig/cow pancreases)
- With recombinant DNA bacteria could be given a human gene and produce the protein corresponding to that gene - making protein based drugs much easier to produce
- Genentech eventually produced insulin, clotting proteins, and HGH
- Scientists found a gene known as Her-2 which was overactive in breast cancer and led to aggressive cancer. It was a gene that promoted cell division that was so powerful it could create copies of itself throughout chromosomes, further amplifying its effects.
- Scientists also found a way to easily create antibodies (proteins that fuse to specific targets on bacteria and viruses to kill them) using an immune cell connected to a cancer cell (the immune cell provided the antibodies and the cancer cell acted as a factory for them).
- They eventually showed in a mouse model how an antibody for Her-2 could be used to stop the cancer it caused
- They now technically had all of the things needed for a potential cancer cure

(though for a specific type)
- Genentech was interested in funding it though due to its complexity and they struggled to get any funding at all for this new technique/treatment
- They worked to make a human version of the treatment by 'humanizing' the protein that worked in a mouse so that it would be accepted by the human immune system - it would later be called Herceptin
- They struggled to get a trial, but through a series of lucky events managed to get one off and saw some early success

Chapter 46
- After the initial success many wanted to join the clinical trials and be given the drug, but the Genentech wanted to exercise caution. Unlike many universities or hospitals they had no compassionate use program*
- Outrage from patients and protests on Genentech's campus eventually forced their hand into expanding and adding compassionate use for their experimental drug
- Later clinical studies would find it extremely effective in both late and early stage breast cancers

Chapter 47
- Scientists found that leukemia (CML) was caused by Bcr-abl in much the same way src worked
- Scientists to see if they could control such genes that encode for kinases that serve as molecular phosphate taggers. They wanted a drug to block said kinases
- Eventually they discovered drugs that could target specific kinases produced by different genes like src or Bcr-abl
- Thus they could in theory cure cancers caused by that
- Success was seen in initial trials but once again it was hard to get that brought to true clinical scale trials needed to green light it due to the corporate parent not wanting to sponsor it further
- Eventually it was pushed through and was a big success - known as Gleevec

Chapter 48
- Scientists did notice rare cases where patients would relapse after Gleevec whereby the cancer would become resistant to it
- This happened because cells evolved so that the binding antibody in it wouldn't work. Scientists could come up with new drugs that worked with cells that evolved out of using the typical binding point
- This suggested maybe there was no true cure for cancer and it was a perpetual cat and mouse game of cancer cell evolution versus drugs/ treatment
- In later years graph and social network theory would show that social

networks largely dictate whether those engage in certain behaviors (such as smoking) - this suggests a new avenue for tackling carncinogens

Chapter 49

- Research into Cancer continues with large scale efforts like the Cancer Genome Atlas - to completely genetically sequence all forms of cancer
- Using this researchers can see how many types of mutations it takes to cause certain cancers
- The lower the number the more likely simple drugs are to work, naturally
- Mutations can thus be classified into ones that occur but contribute nothing and others that do. This can be teased out with statistics
- Often mutation pathways are more important than what it mutated

Chapter 50

- While research still continues on cancer we are at the point where we can start asking questions like can cancer ever be cured or what is the best way to continue to tackle it. Many people the current goal should be to eliminate early death from cancer before seeing if it could be fundamentally eradicated or anything like that