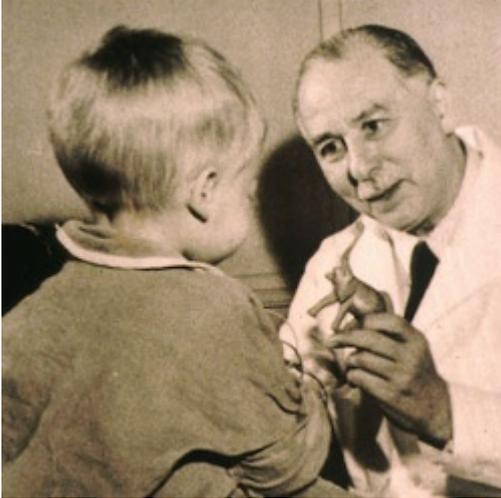


# When Cancer Strikes Back: Fighting Drug Resistance



By Christopher Gerry — July 23, 2019



Credit: Public Domain/Wikipedia [1]

Imagine you're a firefighter trying to prevent a house from burning to the ground. After many hours of hard work, you've rescued the family, saved their pet chinchilla, and extinguished every visible ember—a job well done.

Wouldn't it be strange if the blaze came roaring back the following day? At first, you might think that little Johnny hadn't learned his lesson about playing with matches, but then you realize that something strange is going on. Not only is this new fire burning hotter and spreading faster than the one from the day before, but it also doesn't seem to care if you drench it with torrents of water.

In oncology, this type of scenario is terribly common. [Cancer recurs](#) [2] so frequently that we forget how strange and unique of a phenomenon it is; nobody complains that their case of the flu “came back” after 6 months, or that their broken leg “relapsed.” And when cancer does come back, it sometimes does so in a form that is [unresponsive to therapies](#) [3] that had previously sent it into remission. It may even show up in an organ that had previously been cancer-free<sup>1</sup>.

When relapse occurs, it's very likely that not all of the original cancer cells had been extinguished. Even a handful of cells that remain after the first round of treatment can grow back into full-blown disease faster than you might expect.

To demonstrate how dramatic this can be, consider a single surviving cancer cell that divides once per day into two identical copies (which also divide once per day, and so on...). We'd only have about 100 cells after a week, but the population would exceed 1 billion after a month, and after 2 months it would exceed a billion billion (>1 quintillion). The average human body contains *only* a [few dozen trillion cells](#) [4], so this exponential growth model doesn't explain cancer behavior perfectly<sup>2</sup>, but it does show that even undetectable levels of cancer can pose a threat.

While it's no surprise that cancer grows quickly, it's a bit more perplexing that a weeks-long chemical onslaught could leave any survivors—if it killed >99.99% of the targeted cells, why didn't it take care of the rest? And when a tumor does come back, why does it sometimes not respond to drugs that worked the first time?

The answers to both of these questions are buried in the cancer's genome. As I explained [previously](#) [5], tumors are often heterogeneous mosaics comprising many cell types, each of which contains their own set of genetic mutations. Some of those mutations protect cells from cancer therapies and allow them to survive otherwise lethal bombardments<sup>3</sup>. When the shelling is over, only drug-resistant cells are left behind to grow and divide. Therefore, the recurring tumor will be composed entirely of cells that can't be touched by the therapeutic strategy that had previously worked so well—in essence, the drug has selected for cancer cells that are hard to kill.

To combat such a rapidly evolving foe, pharmaceutical companies have invented medicines designed to exploit weaknesses that [a cancer's newly built set of defenses](#) [6] haven't yet addressed. Returning to our firefighter scene from the beginning of the article, this is akin to dropping your firehose and picking up a carbon-dioxide-based fire extinguisher. The cancer will sometimes be resistant to second- and third-line therapies, but any success will provide the patient with precious additional time.

Some drugs tend to be *more* effective against recurrent cancer. [Cancer immunotherapies](#) [7]<sup>4</sup>, for example, unleash the power of the human immune system to identify and destroy cancer cells. Because relapsed cancers often contain many genetic mutations, the immune system is more likely to recognize them as invaders that are different from the rest of the body.

Tumor heterogeneity, exponential growth, drug resistance — doctors will continue to grapple with these interconnected, fundamental aspects of cancer biology for the rest of human history. Let's build an arsenal, then, that has the equally heterogeneous capabilities of a Swiss Army knife rather than investing in the elusive [silver bullet](#) [8]. We may not be able to kill a werewolf or a vampire, but we'll remain fully rooted in the awe-inspiring banalities of reality.

## Notes

(1) This situation is different from the formation of a second tumor that has nothing to do with the first. Though it may seem unlucky to suffer from two distinct cancers in a single lifetime, the alternative scenario — cancer cells spreading to another part of the body — is likely indicative of an aggressive disease and a worse prognosis overall.

(2) It incorrectly assumes, for example, that no cells die, stop dividing, or alter the rate at which they divide.

(3) Cancer cells can acquire these resistance mutations either before (intrinsic resistance) or during (acquired resistance) treatment. The timing of when the mutation was acquired, however, is often less important than the exact molecular mechanism by which it confers drug resistance.

(4) Which won James Allison and Tasuku Honjo the Nobel Prize in 2018.

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**Links**

[1] [https://en.wikipedia.org/wiki/Chemotherapy#/media/File:Sidney\\_Farber\\_nci-vol-1926-300.jpg](https://en.wikipedia.org/wiki/Chemotherapy#/media/File:Sidney_Farber_nci-vol-1926-300.jpg)

[2] <https://www.cancer.org/treatment/survivorship-during-and-after-treatment/understanding-recurrence/what-is-cancer-recurrence.html>

[3] <https://www.cancerresearchuk.org/about-cancer/what-is-cancer/why-some-cancers-come-back#resistant>

[4] <https://www.smithsonianmag.com/smart-news/there-are-372-trillion-cells-in-your-body-4941473/>

[5] <https://www.acsh.org/news/2019/07/17/more-meets-eye-how-tumors-morph-cellular-mosaics-14162>

[6] <https://www.the-scientist.com/features/how-cancers-evolve-drug-resistance-31742>

[7] <https://www.cancer.org/treatment/treatments-and-side-effects/treatment-types/immunotherapy.html>

[8] <https://www.acsh.org/news/2019/06/30/rethinking-our-goals-war-cancer-14124>