What will success look like in the war on cancer?

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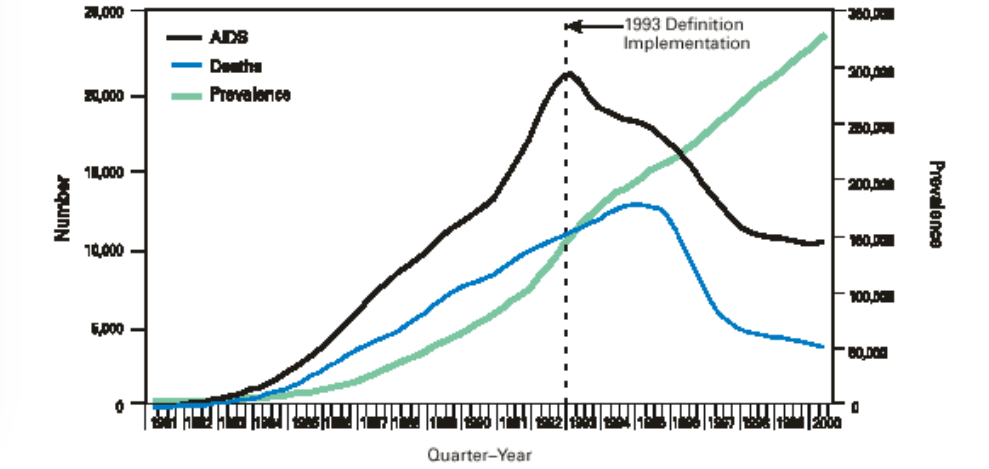
What will success look like in the war on cancer? When we **begin with the end in mind**, it helps us focus on what we want to achieve, understand better how this success can be attained and create processes to do so. The goal of our **strategic plan** is to reduce US cancer deaths from the present 600,000 per year to 100,000 per year by 2030. But how will this happen?

Historically, medical success has three phases. First, there is a long period of increasingly greater understanding of the disease and discovery of new treatments and prevention measures but with a limited improvement in death rates. Later, refinement and coordination of these new treatments and a better understanding of prevention measures cause dramatic improvements in the death rate. Finally, with treatment largely successful and prevention more effective, there are only small improvements in the death rate and a focus on reducing the side effects of treatment.

Our success in treating HIV / AIDS illustrates these three phases. The blue line below shows increasing deaths from 1981 (when it was first discovered) to 1995, followed by a dramatic drop in deaths through 1997, followed by a small decline, see **MMWR 2011**. Of note, the drop in deaths is due not only to improved treatment, but also to a reduced incidence of HIV / AIDS due to more effective prevention activities. Without treatment, most patients die within 10-15 years from exposure (**Lancet 2000**).

FIGURE 1. Estimated AIDS incidence*, deaths, and prevalence, by quarter-year of diagnosis/death — United States, 1981–2000



For childhood leukemia, there were also three phases in treatment success, as shown by the graph below of deaths in England and Wales, see **Shaw 2007**. The death rate increased until the early 1960's when the relative 5 year survival was close to zero, then decreased dramatically until the late 1990's when the relative 5 year survival rate was 70-80%, and has since flattened out. For childhood leukemia, there is no known cause or prevention strategy. Incidence has risen slightly, for unknown reasons.

For cancer in the United States, the leading causes of death are lung cancer, colorectal cancer, pancreatic cancer and breast cancer, which together account for 277,210 (45.6%) of the 608,570 projected cancer deaths in 2021. To reach our goal of only 100,000 annual deaths, there will need to be major reductions in the cancer death rates at these sites.

Deaths in 2021 (projected) and 5 year relative survival

1	Lung cancer	131,880	21%
2	Colon cancer	52,980	65%
3	Pancreatic cancer	48,220	10%
4	Breast cancer	44,130	90%
5	Prostate cancer	34,130	98%
6	Liver cancer	30,230	20%
7	Leukemia, including AML	23,660	64%
8	Non Hodgkin lymphoma	20,720	73%
9	CNS tumors	18,600	33%
10	Bladder cancer	17,200	77%
11	Esophageal cancer	15,530	20%
12	Kidney cancer	13,780	75%
13	Ovarian cancer	13,770	49%
14	Uterine cancer	12,940	81%
15	Myeloma	12,410	54%
16	Skin	11,540	93% (melanoma)
17	Stomach	11,180	32%
18	Oral cavity & pharynx	10,850	66%
19	Soft tissue	5,350	65% (a)
20	Gallbladder	4,310	19% (b)

Sources: **Cancer Facts & Figures 2021**, Tables 1, 7 and 8, (a) **Cancer.org**, (b) **Cancer.org**.

For the past 70 years we have been slowly accumulating new knowledge with small improvements in treatment and minor reductions in overall cancer deaths, but at some point, these improvements will coalesce into substantial reductions. Our **strategic plan** focuses on reducing gaps in important knowledge and increasing collaboration of research activities to get to the “dramatic improvement” phase.

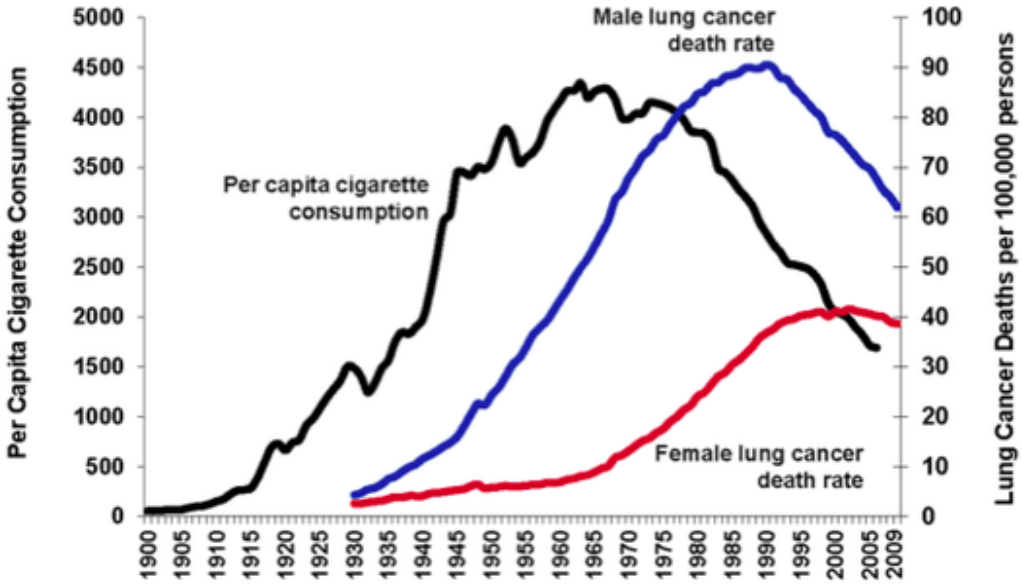
Other processes, including the development of cancer, also follow these three phases. During the malignant process, our cellular networks slowly accumulate minor variations with no apparent clinical or microscopic changes. This is followed by bursts of activity leading to obvious premalignant or malignant changes (**Cross 2016**). Once malignant, the cancer may become more aggressive (dedifferentiation) or accumulate only minor changes. Similarly, in evolution, the theory of punctuated equilibrium describes prolonged periods of apparent stasis (i.e. no new species) followed by bursts of new species (**Eldredge & Gould 1972**). During the "quiet" periods and after the "burst" phase, minor changes in the genetic code are accumulating, albeit without being noticed.

The theory of self-organized criticality, which also describes earthquakes and stock market crashes, helps us understand these phases (**Bak, How Nature Works 1999**). Many systems, both biologic and sociological, are networks poised at a critical state in which small disturbances typically cause no network changes, occasionally cause small network changes and rarely set off a cascade of changes in the initial network and those it interacts with. By analogy, individual grains of sand dropped on a sandpile usually have no apparent impact, occasionally cause small avalanches and rarely cause the entire sandpile to collapse. Dropping a single grain of sand with no apparent impact causes small structural changes in the sandpile that ultimately may enable an additional grain to set off an avalanche. According to Kauffman, these "minor" changes build up connections between elements in the network until a "phase transition" occurs in which so many connections exist that the network elements act together as a whole, instead of as individual elements. When a large enough number of "reactions" are catalyzed, a vast web of reactions will suddenly crystallize and produce dramatic change (**Kauffman, At Home in The Universe**, page 58).

For cancer research, individual researchers typically study short segments of the "web" of activity that constitutes cancer. When enough segments are understood, and there are enough connections made between their work, we anticipate that this web of collaborations will produce an explosion of new ideas and more effective treatments.

In contrast, the theory of gradualism proposes that major changes occur due to the steady accumulation of small changes that produce visible differences. Gradualism is logical and predictable and was promoted by Darwin (**Gould 1983**), but it does not accurately describe evolution, malignant progression or the resolution of disease (**Sun 2018**).

The acceleration of prevention activities will also reduce cancer deaths, but this typically has a long lead time. For cigarette smoking, one of the most important preventable causes of cancer deaths, reductions in lung cancer deaths in men, only began 20 years after the groundbreaking **Surgeon General's Report on Smoking and Cancer**.



Source: American Cancer Society

Knowing what success in the war on cancer is likely to look like, we can continue to emphasize the attainment and accumulation of small successes and collaboration between scientists, instead of relying on the discovery of a miracle drug or treatment.