

FINAL 6/17/19

### Jim's View: Why Basic Science?

There are many means by which the results of our scientific enterprise provide a public good that well-justifies the expense involved. The Editors of *FEBS Letters*, having heard one of my lectures at the Collège de France relating to this subject, encouraged me to use this format to summarize my approach with the thought that it might be useful to some of you.

I will discuss this in a series of three Jim's View articles: the present essay takes a broad historical view of the extraordinary impact that the basic medical sciences have had on the human condition over the past century. The next essay attempts to identify the key ingredients that enable scientists to produce transformative outcomes, focusing on the decades of fundamental research into cholesterol that yielded the statin drugs. The final essay in this series appraises the prospects and challenges for sustaining such productive basic sciences.

#### Basic microbiology controls infectious disease

Figure 1 shows that life expectancy remained unchanged at about 30 years until the mid/late 19<sup>th</sup> century. What happened? The answer is clear: institutionalized biomedical research began.

Modern biomedical research has its roots in French microbiology and German chemistry, dating from approximately the mid-1800s. By the turn of the 20<sup>th</sup> century the connection between sanitation and public health had been well-recognized, leading to sanitation of the

water supply and hand-washing and sterilization during surgical procedures. In particular, by the mid of the 19<sup>th</sup> century Pasteur had discovered that microbes do not spontaneously generate and therefore can grow only by spreading, and specific microbes began to be linked to specific infectious diseases, as were filterable agents (viruses). The immune system had been discovered and successfully harnessed with the first set of vaccines.

This triumph of science over disease culminated in 1928 with the discovery by Fleming of the first antibiotic, penicillin. The impact of these collective developments was dramatic (Fig. 2). Infectious disease – the single greatest limit on our lifespan – could now be controlled to a remarkable degree.

### Basic physiology, biochemistry, genetics, and cell biology combine to tame cardiovascular diseases

Thanks to antibiotics, more people could live into their fifties and beyond, and as a result heart disease and stroke became major killers, as atherosclerotic plaques and vascular damage generally increase progressively with age. People my age well remember that in the 1950s and 60s our family members and friends died relatively young of heart attacks with depressing regularity.

But this began to change, beginning mainly in the 1970s. By the turn of the 21<sup>st</sup> century, the death rate from cardiovascular disease had fallen dramatically (Fig. 3). This stemmed in large part from dramatic advances in prevention accruing from controlling high blood pressure (1960s-1990s) and elevated cholesterol (1980s – 1990s), although certainly many important advances in vascular and cardiac surgery also contributed significantly.

The precisely targeted drugs that control blood pressure came from the explosion in understanding of basic physiology of hormones and receptors in the first half of the 20<sup>th</sup> century, leading to increasingly safe and effective treatments by the second half. This progressive march of basic science to understand the body's control mechanisms was a major achievement of physiology.

Similarly, the successful control of high blood cholesterol in most people came with the development of a new class of drugs, the statins. The story of how this happened was a triumph of basic biochemistry and cell biology and illustrates much about the pre-conditions for success of our enterprise. The first statin drug was approved in 1987.

I will defer to the next installment of this series to delve in the details.

### Basic molecular biology, genetics and immunology combine to accelerate the control of cancer

With cardiovascular disease under far better control, people lived yet longer. Not surprisingly, due to accumulated mutational load, cancer gradually took over as the major cause of death in wealthy countries.

However, the tide is beginning to turn, and the key insights making this possible have come from fundamental research. The story actually began in 1910 when Peyton Rous discovered that a certain cancer in chickens could be transmitted between animals by a filterable agent, i.e. a virus. With the advent of modern molecular biology in the 1970s the cancer-causing genes of this and other viruses could be pinpointed. This soon enabled Michael Bishop and Harold Varmus to discover that viral oncogenes were derived from normally-required cellular counterparts, thereby forging the transformative connection between virology, intracellular signal transduction, and cancer.

The concurrent discovery of monoclonal antibodies by Kohler and Milstein in the 1970s (in the course of basic research to establish the clonal basis of the extraordinary specificity of the adaptive immune system) introduced a new and versatile weapon that also fueled the then-nascent biotechnology industry.

The substantial completion of the first human genome sequence in 2000 opened many new opportunities for development of targeted therapies. These gene sequences could be translated with regularity into actionable targets because of the three prior decades of fruitful basic research – a “golden age” for cell biology - that had elucidated the principal receptors and intracellular signaling pathways governing cell growth, cell death, cell differentiation, and cell division, alterations in which are among the principal causes of cancers.

The results have already been tangible and impactful, as evidenced from the marked increase in cancer survival rates in recent years (Fig. 5). Going forward, basic insights into how the immune system is regulated, most notably from research pioneered by Allison and Honjo, have already led to the development of very promising first- generation immunotherapies, accelerating this gratifying trend.

### The next major public health challenge for basic science: cost-effective treatment of diseases of aging

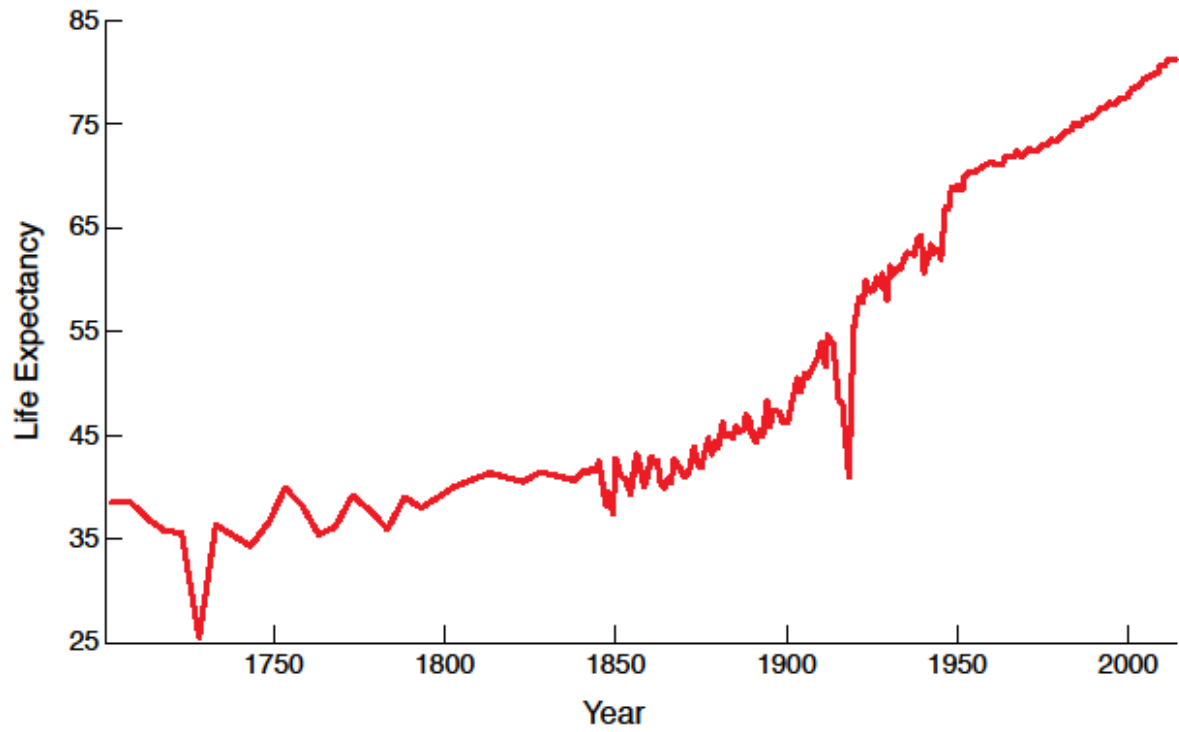
Predictably, the dramatic increase in cancer survivorship (Fig. 6) will result in an even older population, and this in turn is expected to accelerate the prevalence of dementia (Fig. 7), currently the most daunting challenge for basic science. David Baltimore and colleagues (1) have forwarded compelling arguments that most neurodegenerative diseases are best viewed as diseases of cell biology,

and therefore that renewed focus on this and related basic sciences is required to open up new avenues for translational research. This need seems all the more compelling in light of the recent serial failures of clinical trials of one drug candidate after another targeting the canonical A $\beta$  pathway.

Other chronic diseases of aging are also outstanding challenges, and here immunology is likely to be center stage. These include diabetes/metabolic syndrome and a wide variety of chronic immune-inflammatory states. The sheer prevalence of these conditions, combined with the escalating costs of new treatments, poses an existential economic challenge to the current care model. This means that basic science will – in a way it has never before been challenged to do – need to provide radically less expensive alternative treatments based on technologies that do not currently exist or are only in their infancy (2,3).

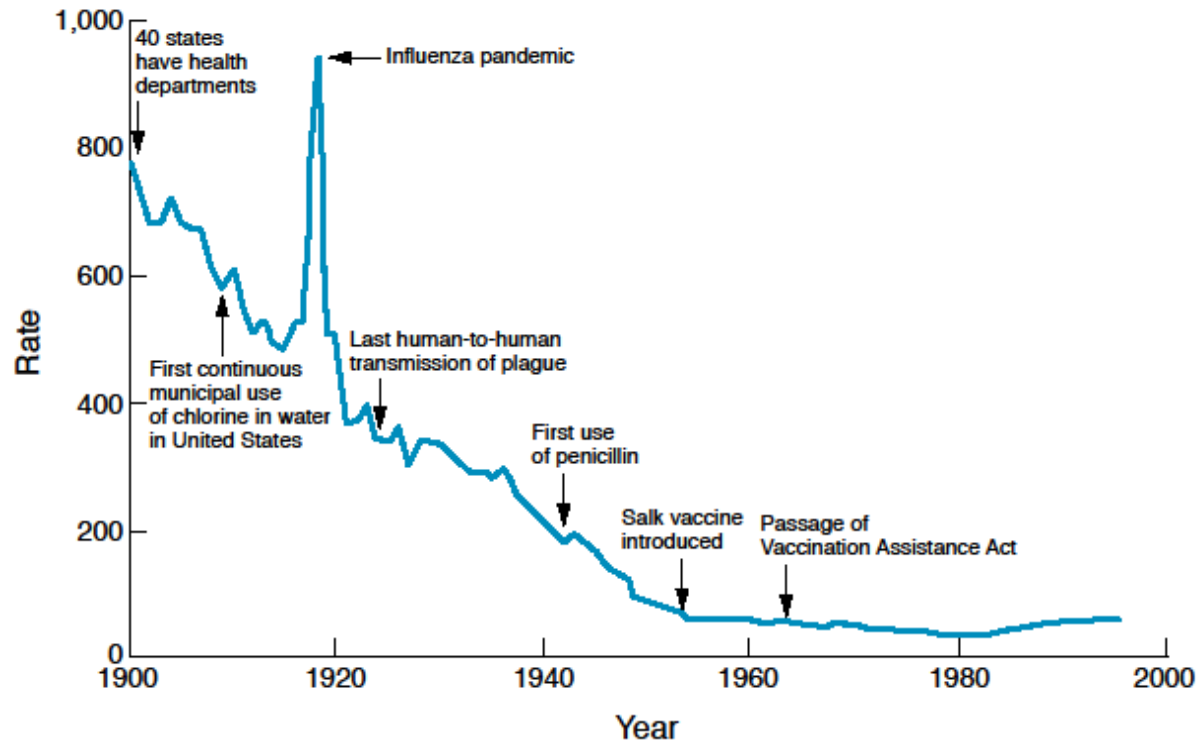
### References

1. Kosik, K. S et al. Science 353:872-873 (2016)
2. Greiner, V. et al. iScience 12:369-378 (2019)
3. Coterio, V. et al. Nature Comm. 10 (2019)



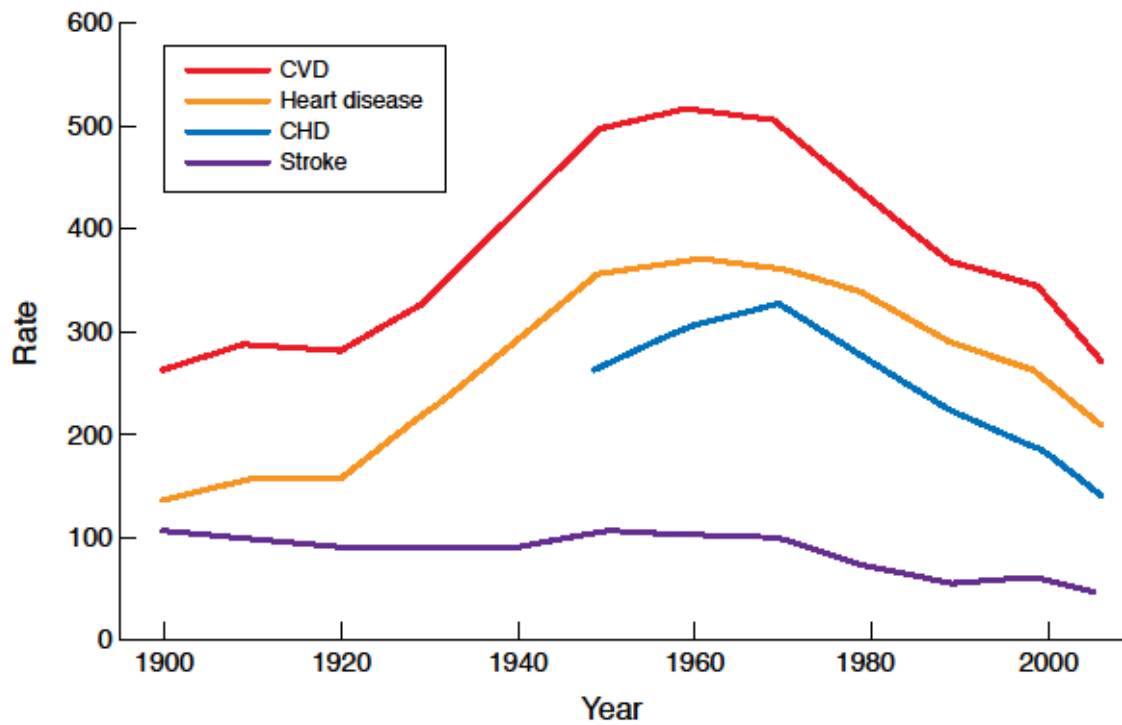
Source: OurWorldinData.org (<http://ourworldindata.org/life-expectancy>)

Figure 1. Life expectancy from the 18<sup>th</sup> century to the present.



Source: US Center for Disease Control (CDC) <https://www.cdc.gov/healthywater/drinking/history.html>

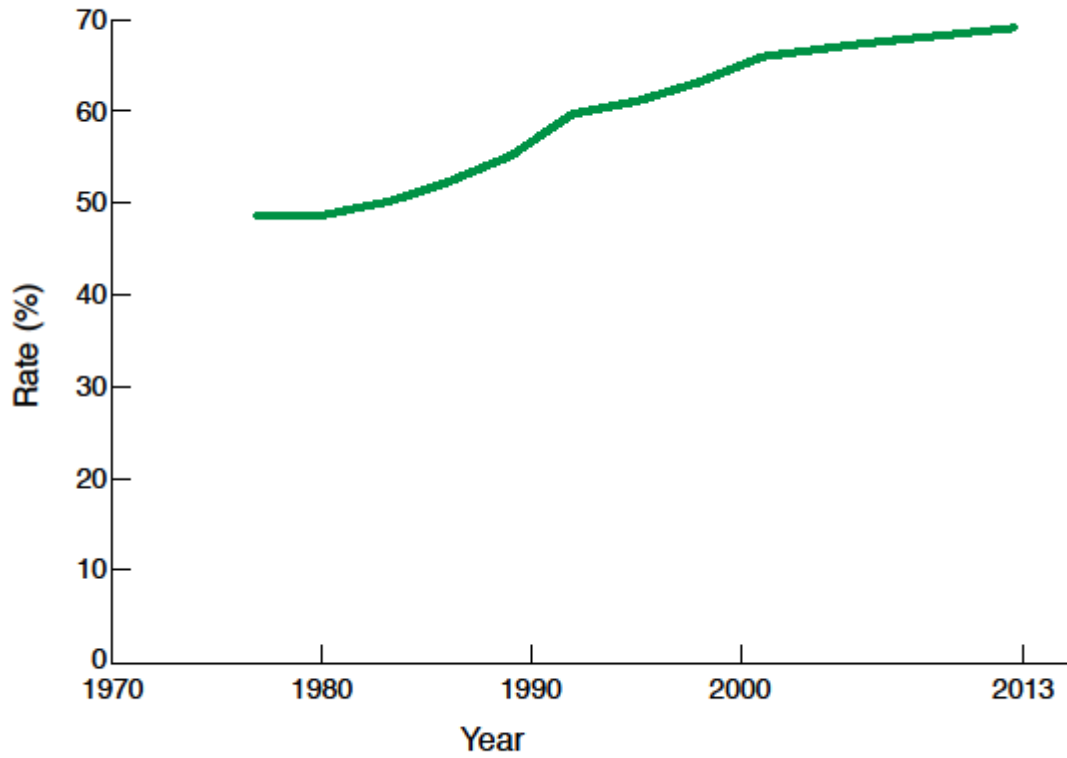
Figure 2. Historical death rates per 100000 population for the US during the 20<sup>th</sup> century.



Source: US National Institutes of Health (NIH) [Index of files/images/factbook/2012\\_nhlbi.nih.gov](http://files/images/factbook/2012_nhlbi.nih.gov)

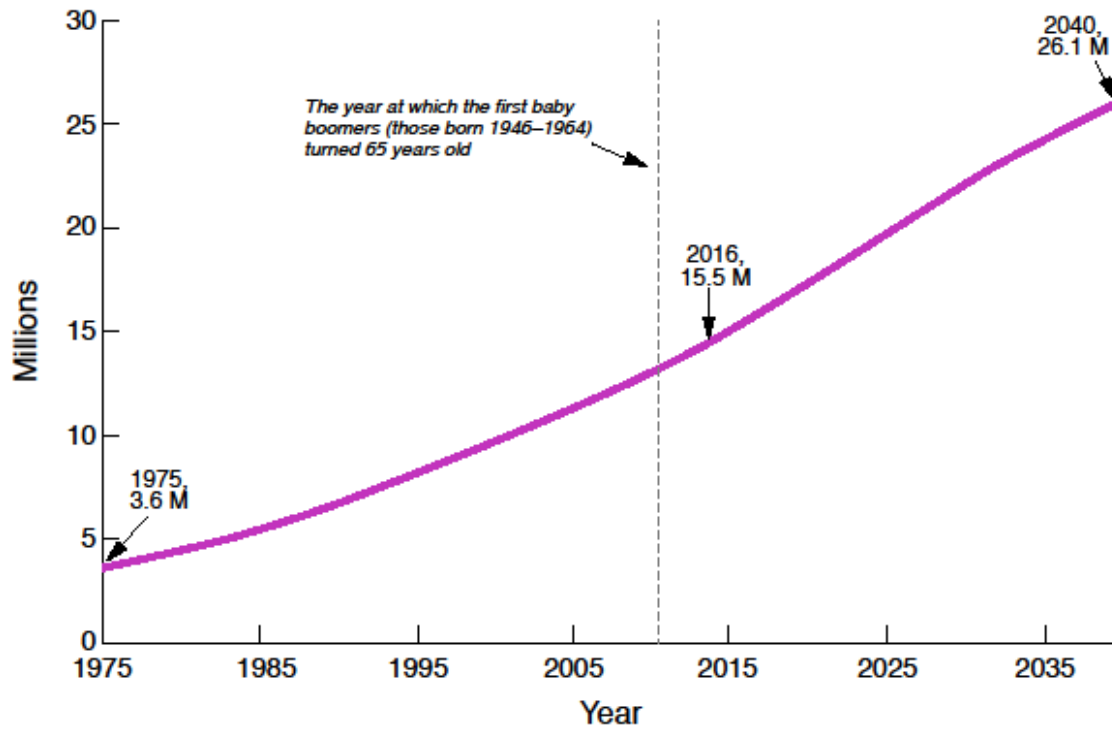
Figure 3. Historical Death Rates (per 100,000 population) due to cardiovascular diseases (CVD) during the 20<sup>th</sup> century





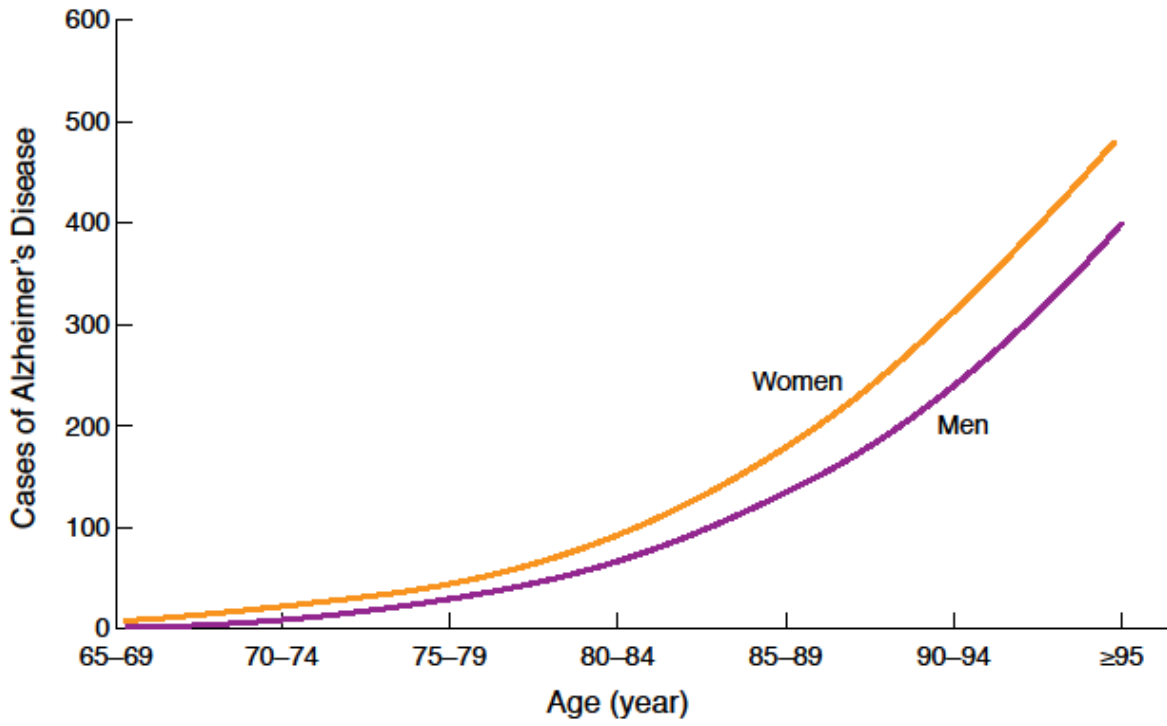
Source: US National Cancer Institute and <https://ourworldindata.org/cancer>

Figure 4. Survival rates for cancer during the latter 20<sup>th</sup> and early 21<sup>st</sup> centuries



Source: US National Cancer Institute

Figure 5. Projected cancer survivorship.



Source: New England Journal of Medicine <https://www.nejm.org/doi/full/10.1056/nejm2003ra020003>

Figure 6. The number of cases of Alzheimer's Disease per 1000 population as a function of age.