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Editorial Review

Does modern medicine increase life-expectancy: Quest for the Moon Rabbit?

ABSTRACT

The search for elixir of immortality has yielded mixed results. While some of the interventions like percutaneous coronary interventions and coronary artery bypass grafting have been a huge disappointment at least as far as prolongation of life is concerned, their absolute benefit is meager and that too in very sick patients. Cardiac specific drugs like statins and aspirin have fared slightly better, being useful in patients with manifest coronary artery disease, particularly in sicker populations although even their usefulness in primary prevention is rather low. The only strategies of proven benefit in primary/primordial prevention are pursuing a healthy life-style and its modification when appropriate, like cessation of smoking, weight reduction, increasing physical activity, eating a healthy diet and bringing blood pressure, serum cholesterol, and blood glucose under control.

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"What is the goal of medical treatment: Is it alleviating discomfort or lengthening lives?"

1. Introduction

Mortality has tormented human consciousness since time immemorial and humankind has perpetually searched for a therapy that extends life, the so-called Philosopher's Stone. In this quest, the human race has been only partially successful; the life-expectancy has certainly increased but only up to a certain point. "Nobody has yet achieved even modest life extension beyond the apparent upper limit of about 120 years". Thus, along this road, there have been some successes but mostly disappointments. Typically, when a "new therapy" is introduced, there is a lot of hope but as its use increases, its side-effects also become apparent, which starts a whole new drive toward next generation of this therapy which is safer and more effective, but then ever newer side-effects come up again and this cycle goes on and on, something like "*Carrot and the Horse*." Further, the effects of a new therapy are more remarkable when disease has already occurred (secondary prevention) and already reduced life-expectancy as a result of this disease; the more severe/serious the disease, the greater possible benefit of the therapy. However, although effective therapy may reduce the mortality arising of this disease, it practically never brings it back to normal, "*the Zenos's Paradox*." Recently, advanced technology has provided us with two highest-profile treatments for coronary artery disease (CAD): coronary artery bypass grafting (CABG) and percutaneous coronary interventions (PCI). Each intervention in itself promised a lifesaving relief and consequently was embraced enthusiastically by physicians and even lay public. Both these techniques indeed often provide rapid, dramatic reduction of the alarming pain/angina associated with the disease. Yet, when it comes to prolonging life, their track-record is near dismal, providing little or no improvement in survival rates over standard medical and lifestyle therapies except in the sickest of the patients. Further, these procedures are also associated with significant side effects. "Doctors generate better knowledge of efficacy than of risk, and this skews decision making," says David Jones Ackerman professor of the culture of medicine.[1] But why blame only physicians, even "patients are wildly enthusiastic about these treatments," he says. "There 've been focus groups with prospective patients who have stunningly exaggerated expectations of efficacy. Some believed that angioplasty would extend their life

expectancy by 10 years! Angioplasty can save the lives of heart-attack patients. But for patients with stable coronary disease, who comprise a large share of angioplasty patients, it has not been shown to extend life expectancy by a day, let alone 10 years – and it's done a million times a year in this country.''

So are there any interventions at all which can increase the expectancy of life, particularly in context of cardio-vascular conditions?

2. History of increase in life-expectancy

Worldwide life-expectancy at birth was 30.9 years in 1900, 46.7 in 1940, 61.13 in 1980.[2] As seen, there was a dramatic improvement in life-expectancy after 1940 which could be attributed to three factors:

1. A wave of global drug and chemical innovations: penicillin, streptomycin, vaccines, discovery of DDT, etc.
2. Spread and availability of medical and public health technology to all, including poorer countries.
3. Change in international status (value) of health which practically became a ''right,'' upgraded from mere ''desirable.''

While early improvement in life-expectancy was a result in control of infectious diseases, subsequent improvement occurred as a consequence of focus on life-style diseases. From 1991 to 2004, life-expectancy in US improved by 2.33 years mostly by medical innovation (discovery and availability of new drugs) but also addressing problems like smoking and obesity.[3] In context of CVS diseases, mortality from heart disease in the US fell by more than half between 1950 and 1995, with a resultant increase in life-expectancy of approximately 3½ years, half to two-thirds of which has been attributed to coronary care units, treatment of hypertension, and medical and surgical treatment of CAD.[4,5]

3. Approaches to improving life-expectancy

Improvement of life-expectancy with any maneuver essentially depends on:

Severity of disease – Baseline mortality is the most important factor operative on lifespan-gain from any procedure. Diseases with a higher baseline annual mortality rate demonstrated more lifespan gained. Thus, therapeutic maneuvers provide more survival benefit in secondary prevention than primary or primordial prevention.

Duration for which intervention is applied – age of the patient.

4. Primordial prevention – healthy individual

4.1. *Caloric restriction*

Caloric restriction (CR) is the only consistently reproducible experimental means of extending lifespan. Laboratory experiments show markedly decreased morbidity in laboratory mammals that are fed to only 80% full.[6] Indirect human proof comes from Okinawa, a region in Japan which boasts one of the longest life expectancies for its population in the world as also having a significantly large population of centenarians (living within the region) despite being one of the poorest regions in the country (being the bottom ranked in socioeconomic indicators for Japan). This is attributed to diet, high levels of physical activity, and strong cultural values that include good stress-coping abilities. Among the peculiarities of culture, Okinawa culture embraces Hara Hachi Bu, which means to eat only until 80% full.[7] Further, studies on the oldest living natural population in the world, the Seventh Day Adventists living in California, support these findings.[8] Long-term human trials of CR are now being done. More recent work reveals that the effects long attributed to caloric restriction may be obtained by restriction of protein alone, and specifically of just the sulfur-containing amino acids cysteine and methionine.[9,10]

4.2. *Increased physical activity*

Undertaking regular exercise (jogging) increases the life-expectancy of men by 6.2 years and women by 5.6 years, as per data from the Copenhagen City Heart study presented at the EuroPRevent2012 meeting. It showed that between one and two-and-a-half hours of jogging per week at a ''slow or average'' pace delivered optimal benefits for longevity.[11]

4.3. *Metformin*

A study by Bannister and co-workers revealed that patients with type 2 diabetes mellitus (DM) initiated with metformin monotherapy not only had 38% better survival than those with DM and treated with sulphonylurea (0.62, 0.58–0.66), but unexpectedly also survived 15% longer than even matched, non-diabetic controls (0.85, 95% CI 0.81–0.90). This brings out an interesting prospect of metformin as first-line therapy and may imply that metformin may confer benefit even in non-DM.[12]

4.4. *Geroprotectors*

Experimental proof of this class of drugs comes from sirolimus. It is an immune-modulator (also the drug in drug-eluting stent) which was found to lengthen the mices' lives by up to 14%. Likewise, everolimus was found to partially reverse the immune deterioration that normally occurs with age in a pilot trial in people over 65 years. The drug acting by inhibiting a protein called mTOR (interestingly mTOR also seems to be affected by calorie restriction) improved participants' immune response and is involved in sensing the level of nutrients available within cells, shifting cells into energy-conserving mode, which has anti-aging effects, including that on the immune system.[13]

In addition to rapamycin analogs, resveratrol, found in grapes, and pterostilbene, a bio-available substance found in blueberries, have also shown favorable response.[14] Scientists estimate that these drugs could increase life-expectancy by 10 years.

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