

# Commentaries

## The Epidemiology of Life and Death: A Critical Commentary

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### Introduction

It is now approximately three billion years since the first appearance of life and death on this planet. Early studies identified life and death as major causes of morbidity and mortality, respectively, but further advances did not occur until recent times, when the tools of epidemiology were developed. The goals of this brief overview are to discuss the important studies that have led to our current concepts of life and death, to highlight deficiencies in existing knowledge, and to suggest directions for future research.

### Methodologic Issues

Variation in death rates in different epidemiologic studies has long been a source of controversy, with prominent authorities hypothesizing that differences in disease incidence or case-fatality rates were responsible. A careful review has led us to an alternative explanation: *differential case ascertainment bias*, owing to discrepant methods of case definition and ascertainment. For example, close scrutiny of the methods used in the National Death Interview Survey<sup>1</sup> suggests that the investigators obtained low death rates because they ascertained death by structured interview ("Are you dead?") and excluded nonresponders from the analysis.

A more quantitative approach to the ascertainment of death was employed in the British National Death Study.<sup>2</sup> In the first phase of this study, a heart rate lower than 1.96 standard deviations below the mean was taken as presumptive evidence of death. Very consistent results (death rate approximately 2.5 per cent) were obtained. With continued funding, the group became more sophisticated, and expanded their measurements to include temperature, blood pressure, respiratory rate, and cerebral blood flow. The resulting discriminant function analysis was able to distinguish between marathon runners and corpses significantly better than would be expected by chance alone ( $N = 12,039$ ;  $p = .049$ ). A recent American study yielded similar results, although the coefficient for cerebral blood flow failed to achieve statistical significance.<sup>3</sup>

A conference was sponsored by the National Institute of Death in an attempt to develop a consensus regarding a uniform and unambiguous standard for case definition. The following compromise was eventually worked out, and was adopted into the third death studies manual (DSM-III):

"Death shall be defined as the ultimate state of the final common pathway that emerges subsequent to a terminal morbid event, culminating in the eventual biocessation of animate bioprocesses."

To further clarify the definition, the term *biodeath* was proposed. (The term "htrib", coined because death and birth are essentially the same process, differing only in direction, was the preference of a dissenting minority.<sup>4</sup>)

### Non-experimental Evidence

**Temporal Relationships**—It is widely appreciated that inference of a causal relation requires documentation of the temporal sequence of the phenomena being investigated. This principle applies to the study of life and death no less than in other areas. Recently there has been considerable excitement in this field, because a breakthrough has been achieved in the mathematical modeling of migration (Lemming, Lemming, Lemming and Miettinen; personal communication). When the effects of migration are eliminated, a close correspondence between birth rates and death rates emerges, but with a variable induction period, ranging from less than a day to over 100 years. In the US, this induction period averages 78.3 years in females, and 70.1 years in males.

**Transmission**—The mode of transmission of death has been the subject of intense scrutiny. The seminal work in this area is that of Bakker and Hart,<sup>5</sup> who demonstrated that in certain lower primates death (or at least loss of viable life) could be transmitted through sexual activity.

Recently, investigators at three institutions independently reported the discovery of an antibody marker for persons at risk for death.<sup>6-8</sup> This promises to be an especially exciting development in a field previously lacking substantial opportunities for bench research.

**Genetic Factors**—The clustering of life and death in families raises the possibility that genetic factors might be important.<sup>9</sup> Fisher<sup>10</sup> noted that in most cases of death, the proband's parents had previously died; for probands that were still living, invariably the parents had at one time been alive. This strong familial component was more recently observed by Wallace,<sup>11</sup> who used a segregation analysis of Southern blots, and confirmed by Maddox,<sup>12</sup> who obtained separate but equal results.

**Social Supports**—Syme<sup>13</sup> suggested that social support could interact with the usual association between life and death. Ames<sup>14</sup> had previously noted that as the number of *Salmonellae* on a culture plate was increased, a given dose of antibiotic became less toxic. Syme postulated that the enhanced resistance to the antibiotic was due to social support among the *Salmonellae*. Using this *Salmonella* model, Syme, *et al*,<sup>13,15</sup> have performed an elegant series of experiments in which the interventions included centrally located coffee and donut homogenates as well as facilitation of sexual interactions using bacteriophages. These results indicate that social support can play an important role in mitigating life stress among gram-negative rods. However, before assuming these

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results are generalizable to high-risk elderly humans, it would be prudent to await additional studies (using gram-positive cocci, for example).

### *Experimental Evidence*

The controversial University Group Death Project (UGDP) was the first major clinical trial to address the question of life and death.<sup>16</sup> The UGDP found excess mortality in the treated group, which was most directly related to that group's higher death rate. Similar findings were reported in the Monetary Resources For Investigators Trial (MRFIT), although the effect was restricted to red-haired dwarves with baseline EKG abnormalities.<sup>17</sup> Both studies have been criticized by Steinfein,<sup>18</sup> who felt that the published descriptions of the methods used to hire the janitorial staff were inadequate.

After the somewhat disappointing UGDP and MRFIT, there was considerable relief at the publication of the LRC-BPPT (Living Research Clinics Biodeath Primary Prevention Trial).<sup>19</sup> To overcome the familiar and frustrating problem of live subjects reluctant to cross over to the dead group, the investigators cleverly selected a medication so vile that those assigned to take it found creative new ways to die. Unfortunately, this led to an overall statistically insignificant difference in total mortality, even with the use of a one-half-tailed test of significance. Therefore, it appears that a definitive determination of whether the association between life and death is causal must await subsequent investigations.

### *Conclusions*

We have come a long way in the last few billion years, but much work remains to be done. Although at this point life appears to be the most important predictor of eventual death, many questions remain. In the coming years we hope further to elucidate the cofactors that impinge on the interaction between life and death, provided that publication of this review does not lead to our own (premature) demise.

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