Mortality Abstract

ESSENTIAL HYPERTENSION, 
CONSERVATIVELY TREATED, CIRCA 1950s

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Reference

Abstract
Natural history studies of minimally (conservatively) treated essential hypertension are rare and have generally suffered from small numbers, unusual case mix (severity spectrum bias), short or erratic follow-up, meager data collection for co-variables, and lack of standardization of registration criteria. Sokolow and Perloff followed 439 people aged 20-69 for a minimum of five years or until death. The group was assembled from among 627 consecutive people accepting referral from the general medical outpatient clinic of UCSF to the hypertension clinic during an entry period from 1946 to 1953. Participation was based on referral for persistent hypertension (>150/90 on at least three occasions) and stratification according to standardized resting (“near basal” but not casual) enrollment blood pressure also >150/90. 137 people were excluded from the study for secondary hypertension, prior sympathectomy or adrenalectomy, treatment with drugs, or age over 69. Those enrolled were tabulated according to multiple variables for later assessment against outcome. The group experienced an overall 36.7% 5-year mortality rate.

Follow-up
The minimum duration of follow-up was stated to be 5 years. Exposures were derived from the cumulative mortality curves and various rates calculated from the 5-year data given. Follow-up was said to be “92% complete,” but it was 100% (to death or 5 years) for the 439 study participants, and 89.6% (439/489 + 51) for the non-excluded registrant pool. Of those 51 persons declared to be “lost to follow-up before end of 5-year study period,” there is no information on how many withdrew in each interval, or on what effort was made to ascertain deaths or outcomes among those withdrawn, so proportional exposures, and any deaths, contributed by these lives cannot be calculated.

Methods
The mortality curves published in the study allowed for estimation of interval deaths and mortality rates, and the age and sex composition data permitted calculation of “mean q”. Centennial US Life Tables for 1949-51, male and female, were used as the basis for expected mortality. Interval, cumulative, aggregate and geometric rates for mortality and for survival were calculated, and comparative mortality ratios (MR), survival ratios (SR), and excess death rates (EDR) were then derived. From the age/sex composition data, the average age for males was 45.6; for females was 46.7; and for both sexes combined was 46.4. But the “mean q-primes” for males, females, and both sexes combined yield “actuarial ages” of 50, 51 and 50 respectively. “Mean q” was used as the basis for expected mortality and advanced one year for each annual interval.

Results
Given the “astronomical” overall 5-year cumulative mortality of 36.7% in a cohort of 46 years mean age, it is no surprise that mortality ratios here for “untreated” essential hypertension in the 1950’s are also quite large (aggregate mean average mortality ratio for the 5-year period was over 1,000% for males, over 750% for females). This is also well illustrated by comparing any of the annual interval “experienced” mortality rates, with those “expected” for a male or female of similar age (e.g., “observed” male year-two “q” is .1333, while “expected” would have been .0119). Likewise, the EDR’s were substantial for each of the 5 years studied and for both sexes, harshest in year-one (EDR = 255 for males, 110 for females) but still substantial for year-five (EDR = 106 for males, 35 for females). See Table A

Medical Risks (1976) reported excess mortality results from three other studies conducted prior to the use of anti-hypertensive drugs. A Mayo Clinic study conducted between 1940-1960 reported 5-year survival on 631 people. Palmer & Muench studied 453 private patients between 1935-1952 for variable observation periods (1.1 to 9.7 year d/E data). Smithwick reported 5-year survival on 619 hospital-evaluated and “medically-treated” patients between 1939-1955. Their mortality figures, stratified according to grades 1-4 severity of hypertension (somewhat differently defined by the different studies), are shown in Table B. The mortality data for Sokolow & Perloff are overall fairly “comparable,” recognizing, of course, the definitional differences in “hypertensive severity grade,” selection, age/sex composition, and follow-up.

Excess death rates and mortality ratios for the subjects of Sokolow & Perloff’s study were somewhat worse than those
reported for comparable ages in the *Build and Blood Pressure Study* 1959 (entry period 1935-1954) when judged by initial blood pressure reading, probably reflecting effects of selection (e.g., insured lives) since treatment was not a difference. Sokolow & Perloff’s “Grade I” hypertensives, which lumped together those with initial blood pressures (as defined) of a quite broad range (150-200/90-120), experienced a mortality ratio of 440%. The 1959 *Study* showed mortality ratios ranging from 150-370% for more segmented subsets of initial bp range for individuals of comparable age. It is important to remember that until the 1959 *Study*, there was little consensus as to where a cutoff line (even 140/90) could arbitrarily but reasonably be drawn between acceptable (“normal”) and unacceptable (“risky”) blood pressures. Although the *Blood Pressure Studies of 1925 and 1939* of The Society of Actuaries had shown a direct and continuous relationship between mortality among insured lives and level of blood pressure at entry, clinicians and underwriters even in 1960 were still skeptical about the harm of mild to moderate hypertension. This may be one reason why Sokolow & Perloff defined “grade I” so broadly.

EDR’s and MR’s for the subjects of Sokolow & Perloff’s study were substantially worse than those reported for durations 0-2 and 2-5 of the *Blood Pressure Study* 1979 for any bp group, including the Study’s Group F (>167/>97). This comparison, of course, can only be made qualitatively, given the differences in time period, cohort composition, and other key variables. The 1979 *Study* was also interesting for its persistent finding of the continuous nature of mortality risk related to blood pressure, with significant excess mortality even at “mild” levels of blood pressure elevation above “average”. The 1979 *Study* was also valuable for first showing the dramatic effects on mortality reduction which resulted from the treatment of hypertension, many forms of treatment by then being available.

Other Interesting Findings by Sokolow and Perloff

- men constituted 32.6% of the study group (women 67.4%), but men comprised 51% of the Class III or IV hypertensives.
- cumulative mortality was higher for men than women, beginning immediately in year 1 of follow-up, and final cumulative mortality was 55% for men, 28% for women at the end of the 5th year.
- no significant correlation of mortality was found with age, but mortality did rise progressively over the 5 years with:
  a) severity of initial blood pressure elevation
  b) extent of hypertensive retinopathy (Keith-Wagener grade)
  c) degree of radiologic cardiomegaly
  d) severity of electrocardiographic LVH, and
  e) progressively higher class of overall hypertensive end-organ involvement and severity.
- Class I patients (enrollment BP 150-200/90-120 and minimal hypertensive organ system abnormality) had 11% 5-year mortality, while patients with malignant hypertension, renal failure, or congestive heart failure (Class IV) had an 84% 5-year mortality.
- 49% of all male deaths and 42% of all female deaths occurred in the first year (45% of all deaths occurred in year one.) This finding is not explained.
- early deaths in patients with mild hypertension were found to be largely due to atherosclerotic complications or noncardiovascular causes, and not directly due to “hypertensive causes.”
- none of 26 patients with greater than 30% cardiac enlargement survived 5 years.
- even at equivalent grades of severity, men had a higher mortality.
- the average age of men at enrollment was 45 and at death was 51; the average age for women at enrollment was 47 and at death was 50.
- there were unexpectedly long survivals in the more severe classes of severity, just as there were unexpected early deaths in the mild classes of severity.
- patients with severe involvement in one organ system generally had advanced grades of involvement in other organs; those with mild involvement of one or more organ systems had a relatively low 5-year mortality rate, while those with moderate or marked involvement of one organ system had a high mortality; and those with multiple systems showing advanced disease had the highest mortality of all.
- overall mortality among obese patients was significantly lower than among non-obese, a finding said to be shown in other studies, but of unclear explanation and puzzling significance.
Table A
Comparative Mortality, Conservatively Treated Hypertension, By Duration

<table>
<thead>
<tr>
<th>Interval</th>
<th>Exposure Person-Yrs</th>
<th>No. of Deaths</th>
<th>Mortality Ratio</th>
<th>Conf. Limits**</th>
<th>Mean Obs.</th>
<th>Annual Mort. Rate</th>
<th>Conf. Limits**</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Start-End t to t+∆t</td>
<td>Obs. d</td>
<td>Expec* d'</td>
<td>100d/d' MR</td>
<td>95% CI(MR)</td>
<td>Obs. q</td>
<td>1000(q-q') 95% CI (EDR)</td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-1</td>
<td>143</td>
<td>38</td>
<td>1.56</td>
<td>2,400%</td>
<td>1,700-3,300%</td>
<td>.266</td>
<td>.011 255 177-353</td>
</tr>
<tr>
<td>1-2</td>
<td>105</td>
<td>14</td>
<td>1.25</td>
<td>1,120%</td>
<td>615-1,880%</td>
<td>.133</td>
<td>.012 121 61-211</td>
</tr>
<tr>
<td>1-3</td>
<td>91</td>
<td>13</td>
<td>1.18</td>
<td>1,100%</td>
<td>585-1,880%</td>
<td>.143</td>
<td>.013 130 63-230</td>
</tr>
<tr>
<td>3-4</td>
<td>78</td>
<td>4</td>
<td>1.11</td>
<td>360%</td>
<td>100-920%</td>
<td>.051</td>
<td>.014 37 9-117</td>
</tr>
<tr>
<td>4-5</td>
<td>74</td>
<td>9</td>
<td>1.15</td>
<td>785%</td>
<td>360-1,490%</td>
<td>.122</td>
<td>.016 106 40-216</td>
</tr>
<tr>
<td>1-5</td>
<td>348</td>
<td>40</td>
<td>4.69</td>
<td>855%</td>
<td>615-1,770%</td>
<td>.115</td>
<td>.014 101 69-143</td>
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<tr>
<td>0-5</td>
<td>491</td>
<td>78</td>
<td>6.25</td>
<td>1,250%</td>
<td>990-1,560%</td>
<td>.159</td>
<td>.013 146 113-186</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-1</td>
<td>296</td>
<td>35</td>
<td>2.16</td>
<td>1,620%</td>
<td>1,130-2,300%</td>
<td>.118</td>
<td>.007 111 75-157</td>
</tr>
<tr>
<td>1-2</td>
<td>261</td>
<td>11</td>
<td>2.01</td>
<td>545%</td>
<td>270-950%</td>
<td>.042</td>
<td>.008 35 13-68</td>
</tr>
<tr>
<td>2-3</td>
<td>250</td>
<td>11</td>
<td>2.08</td>
<td>530%</td>
<td>265-1,330%</td>
<td>.044</td>
<td>.008 36 14-70</td>
</tr>
<tr>
<td>3-4</td>
<td>239</td>
<td>16</td>
<td>2.15</td>
<td>745%</td>
<td>425-1,210%</td>
<td>.067</td>
<td>.009 58 29-100</td>
</tr>
<tr>
<td>4-5</td>
<td>223</td>
<td>10</td>
<td>2.16</td>
<td>465%</td>
<td>225-860%</td>
<td>.045</td>
<td>.010 35 12-73</td>
</tr>
<tr>
<td>1-5</td>
<td>973</td>
<td>48</td>
<td>8.4</td>
<td>570%</td>
<td>430-765%</td>
<td>.049</td>
<td>.009 40 28-57</td>
</tr>
<tr>
<td>0-5</td>
<td>1,269</td>
<td>83</td>
<td>10.56</td>
<td>785%</td>
<td>630-975%</td>
<td>.065</td>
<td>.008 57 44-73</td>
</tr>
</tbody>
</table>

* Basis of expected mortality is 1949-1951 U.S. Decennial Life Tables
** 95% confidence limits based on Poisson distribution

Table B
Excess Mortality in Conservatively Treated Hypertension, Comparison of Four Studies

<table>
<thead>
<tr>
<th>Series</th>
<th>No of Pts</th>
<th>Observed</th>
<th>Mortality Rate</th>
<th>No of Pts</th>
<th>Observed</th>
<th>Mortality Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>P</td>
<td>Avg. Ann. 1000q</td>
<td>Excess 1000(q-q')</td>
<td></td>
<td>Avg. Ann. 1000q</td>
</tr>
<tr>
<td>Grade 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>52</td>
<td>.894</td>
<td>22</td>
<td>14</td>
<td>74</td>
<td>.955</td>
</tr>
<tr>
<td>P</td>
<td>40</td>
<td>.583</td>
<td>60</td>
<td>40</td>
<td>70</td>
<td>.759</td>
</tr>
<tr>
<td>S</td>
<td>42</td>
<td>.760</td>
<td>53</td>
<td>49</td>
<td>36</td>
<td>.890</td>
</tr>
<tr>
<td>S&amp;P</td>
<td>25</td>
<td>.840</td>
<td>34</td>
<td>21</td>
<td>56</td>
<td>.911</td>
</tr>
<tr>
<td>M</td>
<td>134</td>
<td>.617</td>
<td>92</td>
<td>70</td>
<td>145</td>
<td>.808</td>
</tr>
<tr>
<td>P</td>
<td>29</td>
<td>.523</td>
<td>95</td>
<td>70</td>
<td>59</td>
<td>.560</td>
</tr>
<tr>
<td>S</td>
<td>136</td>
<td>.530</td>
<td>119</td>
<td>110</td>
<td>126</td>
<td>.750</td>
</tr>
<tr>
<td>S&amp;P</td>
<td>45</td>
<td>.600</td>
<td>97</td>
<td>84</td>
<td>131</td>
<td>.863</td>
</tr>
<tr>
<td>Grade 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>105</td>
<td>.316</td>
<td>206</td>
<td>191</td>
<td>46</td>
<td>.462</td>
</tr>
<tr>
<td>P</td>
<td>99</td>
<td>.320</td>
<td>278</td>
<td>248</td>
<td>102</td>
<td>.401</td>
</tr>
<tr>
<td>S</td>
<td>103</td>
<td>.250</td>
<td>242</td>
<td>229</td>
<td>47</td>
<td>.450</td>
</tr>
<tr>
<td>S&amp;P</td>
<td>40</td>
<td>.350</td>
<td>189</td>
<td>196</td>
<td>66</td>
<td>.606</td>
</tr>
<tr>
<td>Grade 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>53</td>
<td>.061</td>
<td>428</td>
<td>418</td>
<td>22</td>
<td>.190</td>
</tr>
<tr>
<td>P</td>
<td>32</td>
<td>.089</td>
<td>889</td>
<td>880</td>
<td>22</td>
<td>.263</td>
</tr>
<tr>
<td>S</td>
<td>88</td>
<td>.030</td>
<td>504</td>
<td>495</td>
<td>41</td>
<td>.300</td>
</tr>
<tr>
<td>S&amp;P</td>
<td>33</td>
<td>.090</td>
<td>381</td>
<td>368</td>
<td>43</td>
<td>.209</td>
</tr>
</tbody>
</table>

1. Adapted from Medical Risks (1976) Table 8-5
2. Follow-up period was 5 years, except for variable follow-up periods in Palmer and Muench’s groups (see Table 8-5 for detail)
3. Mayo Clinic series
4. Palmer and Muench
5. Smithwick’s series
6. Sokolow and Perloff

See text for description of formation of these series
ANATOMY OF AN ABSTRACT

MICHAEL W. KITA, MD

The Sokolow and Perloff article was selected for abstract preparation in The Advanced Mortality Methodology Workshop (1990) because of its abundance of reported data in tabular and graphical form. If Checklists A & B of “Finding Suitable Articles” (JIM 22 (4): 288) are applied to this article, it meets all of the minimum—and many of the optimal—data criteria and thus satisfies the essential criteria for abstraction suitability.

One might argue that this older and somewhat dated article lacks timeliness and, therefore, “worthiness” for any abstraction effort, but its value stems from other factors than simply its publication date. Look at the table in “Potential Value of a FU Article” in Part I of “Guidelines for the Evaluation of Follow-Up Articles and Preparation of Mortality Abstracts” (hereafter called “Guidelines”) elsewhere in this issue of the Journal. Sokolow & Perloff’s article would be deemed to have “A” grade potential value due to the large number of observed deaths (161) and the relative paucity of previous mortality studies of untreated hypertension in a general population. Also, the abundance of reported information in the article was further enhanced by the multitude of ways in which it was stratified and tabulated. Such an article can provide useful MR & EDR data, subset by subset and characteristic by characteristic, from its abundantly segmented tabular data on hypertensive impairment. It can also serve as an “expected” population (i.e., untreated hypertensives) for some future mortality abstract, subject to the usual limitations of comparability.

So, having selected the article for an abstract, the abstraction process began with a tabulation of the observed experience. Worksheets for this purpose do not look like final published tables. When one looks at completed abstracts and the data displayed in its tables, left to right, it is not in the order in which it was derived. Rather, the final display attempts to group data for some purpose—ease of comparison, commonality of type (e.g., all the mortality data shown together), etc. The actual stepwise sequence in which data is generated, column by column, generally proceeds in the manner outlined by Bob Pokorski (JIM 20 (4): 31-32 or 34-36) and worksheets need to be constructed accordingly.

Since cumulative mortality curves (Q) were supplied in the original article, these were used to derive interval deaths (d) by taking caliper measurements and making appropriate numerical conversion (see JIM 20 (4): 34). Cumulative survival (\(P = 1-Q\)) could be tabulated, followed by interval survival rates (\(p_i\)). Interval mortality rates (\(q_i\)) could be calculated from exposure data (NER, number exposed to risk) presented elsewhere in the article (\(d/E\)) or by calculation (\(q_i = 1-P\)). Mean mortality rates (aggregate means, using all the available exposure data; and geometric means, taken as the 5th root of the 5-year cumulative survival) could then be calculated for the study period.

Tabulating “expected” mortality experience posed two challenges — choosing an appropriate yardstick or reference population, and deriving suitable \(q'\) values for comparison with observed experience. Because the entry period ran from 1946-1953, straddling the 1950 census, and because the cohort represented a general population, the 1949-51 Decennial U.S. Life Tables were chosen as the yardstick (see “Guidelines,” Part II, “Expected Mortality”). These tables afforded expected population mortality by age and sex, and were used after an unsuccessful attempt to locate a California 1950 Life Table (since all the study participants were California residents). U.S. Decennial Tables were found in a city library (Portland, ME). Had these tables not been available, a later Decennial Table (e.g., 1959-61) might have been used, understanding that some differences would arise owing to secular trend toward improvement in general population mortality between 1950 and 1960, which would tend to exaggerate slightly the resulting MR’s and EDR’s. Alternatively, a U.S. Abridged Life Table for the year representing the mid-point of the study might have been chosen. Abridged Tables are rendered annually. But abridged tables have the disadvantage of presenting \(q'\) data in 5-year increments of age, instead of annually by age, and therefore require aggressive interpolation. It was decided that the 1949-51 Decennial Tables were reasonable to use as a basis of comparison. (Since one of the obstacles to mortality abstract preparation is defining and locating appropriate expected tables, one of the ongoing goals of ALIMDA’s Committee on Morbidity/Mortality is to make the most commonly-required reference tables more readily available, through The Research Center, or by some other means.)

Having selected a reference table, what \(q'\) should be chosen for the comparison group? Because the study did not include year-by-year information on the changing composition of the surviving study members (e.g., age and sex distribution annually, correcting for deaths), a “mean \(q'\)” was calculated using the time-zero composition information supplied and the calculation method described by Pokorski (JIM 20 (4): 27). Of interest, the “mean \(q'\)” was about three to four years different from the “\(q'\) for the mean age”, a phenomenon that Singer has previously noted (see “Guidelines”, Part II, “Expected Mortality”). In other words, the mean age of males in the study, from the composition data, was 45.6. This corresponds in the Decennial Tables to a “\(q'\) for that mean age” of about 0.0074 (7.4 deaths/1000/year). The “mean \(q'\)” for the males in the study, based on the weighted contributions of the cohort composition, is .0109 (10.9 deaths/1000/yr) which corresponds to a tabular (Decennial Table) age of 50 (i.e., when you look up 0.0109 under annual mortality rate for males in the 1949-51 Decennial Tables, it corresponds to that expected of 50-year-old men or q’50).

Having calculated mean \(q'\), the next step is to create a complete “expected table” from the mean \(q'\) of the base or starting year (i.e., duration 0-1 year). As described in the Abstract (under “Methods”) I chose to advance the “mean \(q'\)” one year for each elapsing year of the study. In other words, I used \(q'51\) for years 1-2, \(q'52\) for years 2-3, and so on. Singer notes (“Guidelines”, Part II, “Expected Mortality”) why this may sometimes give falsely high later-duration \(q'\), and, therefore, risks understating eventual MR’s and EDR’s. In general, for an impairment like hypertension, older individuals with the impairment tend to die off faster (earlier) than younger persons, leaving the younger people to become over-represented among the interval’s survivors. Young people have lower expected mor-
mortality rates and when these rates are contributed to the weighted “average” of the “mean q” of the next interval, the result is something less than a whole year advance of mean q’. Had the authors provided exact information about the changing composition of the cohort as aging and die-off occur, the exact q’ could have been calculated for each interval. Without this knowledge, “mean q’” must be progressed interval by interval in some fashion. In this study, advancing the mean q’ one year for each successive one-year duration turned out to be comparable to an 8% per year rate of advancement. For this type of impairment (moderately severe hypertension), this mean age (about 46), and this age range (20-69), a 5% per year rate of progression might have been a better refinement, but the effect on the EDR’s would have been negligible, and on the MR’s only modest.

Having established q’ for each interval, d’ (q’xE) and p’(=1-q’) can be calculated, and P’(p’1 x p’2 x p’3 etc.), and Q’(1-P’) can be derived.

At this point, one has in one’s worksheets a table of values for “observed” experience, and a corresponding table for “expected”, and it is a simple matter to decide what measures of comparative interest to derive and display. In general, because risk estimation and actuarial pricing relate to it, MR’s and EDR’s are the comparative mortality parameters of greatest interest, both as interval and summary statistics, and for their pattern over durations of interest. Suggestions for best data capture/tabular display are given in “Guidelines”, Part II,” Tables Based on Life Table Data.” One interesting observation in this study concerns the difference between aggregate mean (q̄) and geometric mean ̄q results. Had geometric mean observed and expected mortality rates been used as the basis for creating EDR’s and MR’s, the (annualized 5-year) results would have shown similar EDR’s but a higher MR for the geometric-mean results. This is largely due to the pattern of mortality, reflected in the number-exposed-to-risk, interval by interval, which aggregate-mean data preserves, and which geometric mean data sacrifices to the simplying assumption of constant mortality rate. Here, the striking first-duration mortality (an effect seen in other studies with high early mortality, like cancer and MI’s) was a significant factor in the difference.

The numerical value of the data reported, and how many decimal places to carry them to are subject to conventional “rounding” rules. (JIM 20: (4): 34, 44). The final “task” of the abstract ought to be calculation of confidence intervals for the key results (e.g., MR’s, EDR’s), an exercise highly recommended as part of worksheet preparation, but not typically reported (owing to space limitations, as much as anything) unless the spread or variance is so broad as to make the summary statistic (e.g., an MR) of doubtful validity, or questionably different from standard (100%). Methodology for this is given in Medical Risks (1990) pp. 1-4 to 1-6. Table A of the hypertension abstract shows how such 95% confidence intervals would look. Because there were fewer than 100 deaths in any duration, the confidence limits were derived from the asymmetric Poisson distribution, and so are not symmetrical about the MR’s and EDR’s as they would have been if the normal distribution had applied. Also, when, as in duration 3-4, male, Table A, the 95% confidence interval for the EDR includes 0 excess-deaths, then the observed EDR of 37 may not be significantly different from zero, except by chance.

Mortality abstracts may not be a highly regarded or rewarded “business” activity of the medical director, although they could be if conducted on the “right” impairments relative to the insurance focus of one’s company. But they can be rewarding in more ways than just the personal satisfaction of completing one. They can generate data permitting more enlightened underwriting and potential competitive advantage. They can generate data to support an underwriting derision. But they can also be of academic and medical value, refining what we know about prognosis and outcome. Most of all, they need to be done. They can, as in this example, furnish possible “expected” data for future studies and comparisons. More commonly they can provide an update of the retrospective and historical information that “experience” data necessarily represent.