# After Office Hours

## Clinical research in ancient Babylon: Methodologic insights from the Book of Daniel

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**Around 600 BC, Daniel of Judah conducted what is widely regarded as the earliest recorded clinical trial. His trial compared the health effects of a vegetarian diet with those of a royal Babylonian diet over a 10-day period. The strengths of his study include the use of a contemporaneous control group, use of an independent assessor of outcome, and striking brevity in the published report. Weaknesses include probable selection bias, ascertainment bias, and confounding by divine intervention. Although Daniel probably never achieved tenure, he did get "learning and skill in all letters and wisdom ... and understanding in all visions and dreams" (well before Freud). Despite the trial's dramatic findings, over 4 centuries elapsed before publication of Daniel's results. Daniel apparently perished, then published.** ***(Obstet Gynecol 1995;86:1031–4)***

Experts have suggested a 32-point structured format for reporting randomized trials,[1] to improve the quality of this type of research. To demonstrate the usefulness of this format, I used it to evaluate the earliest known report of a clinical trial.[2] In this trial,[3,4] Daniel and three colleagues compared the immediate health effects of a vegetarian diet with those of a rich diet, including meat and wine, enjoyed by the Babylonian royalty.

1. *State the unit of assignment.* The trial allocated participants to two treatment groups with the individual being the unit. Four young men from Judah (Daniel, Hananiah, Mishael, and Asariah, also known as Belteshazzar, Shadrach, Meshach, and Abednego) comprised one treatment arm, and an unspecified number of Babylonian youths comprised the other.

2. *State the method used to generate the intervention assignment schedule.* The experimental group self-selected their exposure, a vegetarian diet. No random assignment occurred. Randomization is important to avoid selection bias and both known and unknown confounders[5]; subsequently, confounding played an important role in this trial's results.[6] The trial did, however, feature a contemporaneous comparison group.

3. *Describe the method used to conceal the intervention assignment schedule from participants and clinicians until recruitment was complete and irrevocable.* Assignment to treatment groups was transparent, raising the strong possibility of selection bias, as has been documented in the modern literature.[7] Large treatment effects, as seen in this trial, are more common when the allocation schedule is transparent.

4. *Describe the methods used to separate the generator and executor of the assignment.* Not applicable. Daniel both generated and executed the treatment assignments with the willing complicity of a steward (Melzar) appointed by the chief eunuch, Ashpenaz. The trial was a secret, because discovery might have led to the death of Ashpenaz. King Nebuchadnezzar had made the chief eunuch responsible for the well-being of Daniel and his colleagues; Ashpenaz considered the vegetarian diet potentially dangerous to the trial participants and, hence, indirectly to himself.

5. *Describe an auditable process of executing the assignment method.* Adequate records of the allocation of participants in the active treatment arm have survived for over 2 millenia. However, reconstructing events in the Book of Daniel is challenging because the clinical trial in chapter 1 was recorded in Hebrew, whereas other chapters are in Aramaic or Greek.[8] Deciphering trials not published in English remains problematic today.

6. *Identify and compare the distributions of important prognostic characteristics and demographics at baseline.* Limited data are available concerning baseline characteristics of those in the experimental arm. None, however, suffered from acne; the king had ordered Ashpenaz to bring from Israel certain "youths without blemish, handsome and skillful in all wisdom, endowed with knowledge, understanding learning and competent to serve in the king's palace, and to teach them the letters and language of the Chaldeans."[3] The Chaldeans were the intelligentsia of Babylon; they taught astrology, mathematics, and magic, for which Babylon was famous.[6] No information is available concerning participants in the other treatment arm, except for their chronic exposure to the king's "rich food."[3]

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7. *State the method of masking.* Not applicable. Even a double-dummy approach would not avoid distinguishing between the vegetarian and royal diets. Whereas the revised standard version of the Bible[3] describes Daniel's diet as one of "vegetables," the King James version[4] reports more specifically that the diet consisted of "pulse." Unrelated to cardiac activity, "pulse" refers to the seeds of peas, beans, lentils, and similar plants bearing pods. A modern equivalent may be succotash, invented by the North American Indians.

8. *State how frequently care providers were aware of the intervention allocation, by intervention group.* The steward Melzar was aware of treatment allocation; whether the chief eunuch knew is not clear. Nebuchadnezzar presumably was blinded (even to the existence of the trial). Melzar apparently skirted any requirement Nebuchadnezzar might have had for the protection of human subjects.

9. *State how frequently participants were aware of the intervention allocation, by intervention group.* All members of the active treatment group knew their assignment, although it is not clear that participants in the comparison group were even aware that they were participating in a formal trial. Lack of blinding in the experimental group could have led to overcompensation on the part of participants regarding exercise, weight reduction, or personal grooming, which would not have occurred in the control group.

10. *State whether (and how) outcome assessors were aware of the intervention allocation, by intervention group.* The steward Melzar was the outcome assessor for both treatment groups, and he was aware of the intervention allocation for both. Blinding the evaluator to treatment allocation is highly desirable, but the steward might not have accepted this condition, given that his survival (and that of his boss) depended on the trial's outcome. Here, both the evaluator and the investigator had an urgent interest in the trial's outcome, raising the strong possibility of ascertainment bias.

11. *State whether the investigator was unaware of trends in the study at the time of participant assignment.* This information is not available. Because of the trial's short duration (10 days), this deficiency may be unimportant.

12. *State whether masking was successfully achieved for the trial.* Not applicable.

13. *State whether the data analyst was aware of intervention allocation.* The outcome assessor also served as the data analyst, and he knew the treatment assignments. The lethal consequences of an unfavorable assessment of the vegetarian diet probably heightened the potential bias toward favoring the "new treatment."[1] Again, ascertainment bias is likely in this situation.

14. *State whether individual participant data were entered into the trial data base without awareness of intervention allocation.* No blinding was done.

15. *State whether the data analyst was masked to intervention allocation.* See no. 13.

16. *Describe fully the numbers and flow of participants, by intervention group, throughout the trial.* Full accounting of the four participants in the experimental arm is available; the report provides no information on participants in the comparison group.

17. *State clearly the average duration of the trial, by intervention group, and the start and closure dates for the trial.* The trial lasted 10 days. Because of the favorable outcome, the steward continued the vegetarian diet for Daniel's group for the entire 3 years of their preparation for service to the king.[3]

Biblical scholars disagree on the exact dates of the trial, which reportedly took place in the "third year of the reign of Jehoiakim king of Judah."[3] One commentator reports that the Jewish nation fell in 586 BC and the Babylonian empire ended in 539 BC, when Cyrus, King of Persia, conquered Babylon.[9] Another places the trial in either 606 or 597 BC.[10] Nevertheless, the author of the Book of Daniel did not publish these results until the time of Antiochus IV Epiphanes, which was most probably around 168–165 BC.[8,10] Delay in publication of research findings is not a new problem: Daniel apparently perished, then published.

18. *Report the reason for dropout clearly, by intervention group.* No dropouts occurred in the experimental arm, and no details are available concerning the other group.

19. *Describe the actual timing of measurements by intervention group.* The steward apparently performed all evaluations simultaneously: "At the end of ten days it was seen that they [Daniel's group] were better in appearance and fatter in flesh than all the youths who ate the king's rich food."[3] This feature helps to avoid bias.[1] Paradoxically, "fatter" refers not to skinfold thickness but to attractiveness.[4]

20. *State the predefined primary outcome(s) and analyses clearly.* The a priori hypothesis was that a 10-day course of vegetarian food would result in an improvement in physical appearance: "Then let our appearance and the appearance of the youths who eat the king's rich food be observed by you. . . ."[3] However, the definition of the primary outcome measure was not clear, specific, or measurable. No interim analyses occurred, despite the high stakes involved.

21. *Describe clearly whether the primary analysis has used the intention-to-treat principle.* The report describes no deviations from the assigned treatment in the experimental group, so compliance with the regimen was presumably complete. Daniel and his colleagues would have avoided food that violated Mosaic law or that had been offered to idols.[10] Hence, all those assigned to the

experimental group were appropriately analyzed with the group to which they had been originally assigned. No information is available concerning the comparison group.

22. *State the intended sample size and its justification.* The sample size was one of convenience. Regrettably, the small number of participants in the experimental group (four) severely limited the power of the trial to show a significant difference, a common deficiency even today.[11] For example, with "appearance" as a dichotomous outcome variable, to detect a relative risk of 2.0 with an outcome rate of 50% in the unexposed group and four participants in each arm, the power ($\alpha = .05$) would be less than 1%.[12] With 20 Babylonians and the four men from Judah, the power would still be only 24%.

23. *State and explain why the trial is being reported now.* The trial ended as planned, and confirmatory evidence grew during its 3-year extension.[3] Written during the oppression of Antiochus IV Epiphanes, the Book of Daniel gives hope to those suffering from persecution.[8] Although he belonged to a conquered people, Daniel had great power and influence in Babylon. An innovator in other areas, Daniel interpreted dreams centuries before Freud.

24. *Describe and/or compare dropouts and completers.* No dropouts occurred in the experimental arm, and no data are available for the comparison group.

25. *State or reference the reliability, validity, and standardization of the primary outcome.* No definition is available for the "appearance" outcome variable. Given the subjective nature of such a determination and the potentially lethal consequences for the outcome assessor, ascertainment bias seems likely.

26. *Define what constituted adverse events and how they were monitored by intervention group.* This was not explicitly stated. However, at the trial's completion, those in the control group did not fare as well as did those in the experimental group. The latter received "learning and skill in all letters and wisdom; and Daniel had understanding in all visions and dreams." When Nebuchadnezzar tested Daniel and his colleagues, he found them "ten times better than all the magicians and enchanters that were in all his kingdom."[3] The prospect of better outcomes remains a powerful inducement for volunteers in clinical trials today.

27. *State the appropriate analytical techniques applied to the primary outcome measure(s).* Not done. The trial clearly antedated modern statistical theory, and, presumably, few software packages were available for an abacus or other computers of the day. However, at the trial's conclusion, Daniel and colleagues were better in appearance than "*all* [emphasis mine] the youths who ate the king's rich food."[3]

28. *Present appropriate measures of variability (eg, confidence intervals for primary outcome measures).* Data provided do not allow these calculations to be made.

29. *Present sufficient simple (unadjusted) summary data on primary outcome measures and important side effects so that the reader can reproduce the results.* A numerator and denominator were available for the experimental group only.

30. *State the actual probability value and the nature of the significance test.* Not done; see no. 27.

31. *Present appropriate interpretations (eg, not significant, no effect; $P < .05$, proof).* Despite the small sample size and short treatment course, the trial's author found the evidence of benefit compelling, as did the steward.

32. *Present the appropriate emphasis in displaying and interpreting the statistical analysis, in particular controlling for unplanned comparisons.* Not applicable.

## Discussion

Daniel's trial anticipated the essence of the scientific method: an experimental group exposed to the factor of interest compared with contemporaneous unexposed controls. However, after Daniel's study, clinical experimentation languished until the 16th century, when Pare compared a "bland digestive" to boiling oil (the standard treatment) for battle wounds.[2] In his famous 1747 study, Lind followed Daniel's precedent of a small dietary trial in preventing scurvy among British sailors. Despite six different treatment arms and a total of only 12 participants, citrus fruit supplementation was strikingly effective. The trial led to effective prophylaxis and the nickname "limeys" for British seamen.[2]

In the 1600s, several thousand years after the Babylonian trial, van Helmont first suggested a *randomized* controlled trial.[13,14] He proposed, "Let us take out of the hospital, out of the camps, or from elsewhere, 200 or 500 poor People that have Fevers, Pleurisies, etc. Let us divide them into halfes, let us cast lots, that one half of them may fall to my share, and the other to yours: . . . we shall see how many funerals both of us shall have."[13,14] Because van Helmont's challenge was not accepted, he failed to win the 300 florins he was prepared to wager on the outcome.

Although randomization in agricultural trials began in the 1920s, Hill[15] was first to use the powerful technique of randomizing participants in clinical trials. In Daniel's trial, randomization would have avoided the selection bias and the confounding that apparently occurred. Several nutritional skeptics[6,10] have noted that, "Ten days is too short a time for any natural effect of a difference in diet; the noticeably healthier appearance of the four youths must be attributed to divine approval of their loyalty."[6] Divine intervention was

associated with the predictor variable (vegetarian diet) and caused the outcome (healthy appearance).

By contemporary standards,[1] Daniel's trial had numerous deficiencies. However, many of these weaknesses persist in clinical research today.[16,17] Indeed, some modern investigators have drawn causal inferences without the use of appropriate controls.[18] Similarly, the published report of this trial[3,4] would not meet contemporary standards of peer review.[1] In the author's defense, he had no "Instructions for Authors." On the other hand, he was concise: The entire account runs less than a page of printed text[3] (presumably longer when handwritten on clay tablets).

Examples from the Bible illuminate human behavior; the Book of Daniel is no exception. After thousands of years, excellent clinical research still brings great rewards[19]—and much fun. Although contemporary investigators who conduct excellent studies[1] may no longer gain "understanding in all visions and dreams," they may well be "ten times better than all the magicians and enchanters" who use inferior research methods.[20]

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