APPENDIX-L

Radiation "Hormesis" : How an Illusion Can Arise from "Perfectly Good Data"

• Part 1. The Meaning and Attraction of Radiation "Hormesis"

Hormesis is the phenomenon when a poison or harmful agent is good for health at low doses, even when it is manifestly deadly at higher doses. The dose-response for hormesis is a J-shaped curve, when the poisonous agent is on the horizontal axis, and the mortality rate is on the vertical axis. The MortRate DECLINES between zero dose and some small dose of the poison, and thereafter, as dose rises, so does the MortRate.

Obviously, radiation hormesis would be a welcome phenomenon, if real. Such an attractive concept inspires hope and speculation.

Unfortunately, we and others have shown (in Appendix-B, for example) that there is NO dose of ionizing radiation which is either harmless or beneficial with respect to carcinogenesis (and mutagenesis). However, Cancer causes "only" 23% of the deaths in the USA, and Ischemic Heart Disease causes "only" 22% (Chapter 39, Part 4).

Suppose that OTHER causes of death were, somehow, reduced by exposure to low-dose radiation? Such speculations often refer to the fact (not in dispute) that radiation exposure stimulates measurable responses at the cellular level. For instance, concentrations of some enzymes temporarily increase and others decrease. In the search for radiation hormesis, a large literature has developed around such "adaptive" responses --- for example, discussions in Gofman 1990 (Chapter 35) and in UNSCEAR 1994 (its "Annex" B).

• Part 2. A Demonstrable Cause of a Spurious J-Shaped Dose-Response

We expect to see some epidemiologic studies showing the J-shaped curve, with radiation exposure on the horizontal axis and MortRates on the vertical axis. If a study produces several curves including the J-shaped type, ALL must be published and none hidden. We do not pre-judge a J-shaped curve to be spurious, but --- like every other wished-for curve --- it deserves especially rigorous scrutiny with respect to potential pitfalls.

One potential pitfall is a weak or non-existent "blinding" procedure. Exposure-status and health-status should not be known by the SAME decision-makers, when radiation doses (which are likely to be rough estimates) are assigned to participants, or when radiation doses are "revised" for certain participants, or when certain participants are thrown out of the study completely.

But the topic of this appendix is a wholly separate pitfall, which also could produce a spurious J-shaped dose-reponse.

Medical Care: Control-Group vs. Exposed-Groups

Any variable which causes the control group to have a higher MortRate, than the baseline MortRate of the study-population, can result in a J-shaped curve. Can this happen, even though proper matching is one of the fundamental rules of epidemiologic research?

Yes it can, despite the best intentions. Part 3 will demonstrate how it can happen, by using "Medical Care" as the variable which may turn out NOT to be properly matched.

Medical Care and MortRates

We begin with the proposition that medical services do reduce some types of mortality dramatically. This is almost beyond dispute.

When I was a senior in medical school and an intern in medicine (1946-47), the revolution in managing a number of very prominent infectious diseases was evident before our eyes. Pneumonias which were considered to be "in the lap of the gods" with respect to recovery, became treatable with full recovery. Syphilis became successfully treatable beyond any expectations. Tuberculosis first became more treatable (by lung collapse), and later highly successfully treatable with antibiotics. Tuberculosis sanitoria closed their doors all over the country. Dreaded streptococcal and meningococcal infections yielded to a variety of antibiotics. Rheumatic fever deaths and deaths from rheumatic heart disease became vastly more rare, as the underlying infections were managed with antibiotic prophylaxis and therapy.

It was during my internship period that some of the dreaded subacute infectious diseases began yielding to prolonged therapy with penicillin. Subacute bacterial endocarditis --- previously 90-95% fatal --- became curable, if caught before appreciable valvular damage had occurred. My wife was cured in 1948 of a post-partum fulminant bacteroides funduliformis infection, by ten million units of penicillin daily --- at a time when the medical experts pronounced that the disease was 95% fatal if it did not respond to 500,000 units of penicillin daily.

Fatal, infectious complications of trauma and surgery, for otherwise non-fatal disorders, became less common. For diabetics, too, the bacterial infections which had been such a common and often fatal complication of the disease, became more manageable and less of a menace. Meanwhile, surgery began to develop the ability to manage, increasingly, many congenital heart malformations and other disorders --- aided in no small measure by advances in the use of blood and other fluids.

However, medical advances ALONE do not determine the death-rate in a population-sample. AVAILABILITY of medical care --- and on a timely basis --- is another factor which affects specific MortRates. Long before work-related health insurance became common, there were some corporations and institutions which established "health preservation" programs, and even installed medical facilities right at their "plants." Indeed, in 1954, I organized the industrial medical facility at the Lawrence Livermore Laboratory. We instituted a policy of complete medical examinations for everyone, at intervals of approximately 1.5 years. For those engaged in particularly hazardous work, the exam frequency was greater. There is no doubt that such examinations did pick up manageable diseases, for which therapy made a difference in outlook.

Overall, with respect to non-malignant disease, there is little doubt that the more medical care exists for a U.S. population sample, the lower will be the death rate on an age-adjusted basis. Indeed, the proposition is consistent with the studies in Section 3 of this book (Chapters 23-38).

• Part 3. The Illusion of Hormesis --- due to Unmatched Medical Care

Suppose that an epidemiologic study is undertaken to assess the effect of radiation exposure upon mortality rate (from all causes combined). For such a study, investigators generally seek plenty of participants who have doses appreciably above normal, from occupational or medical irradiation.

For our illustrative demonstration, we can gloss over the many difficulties in such a study. For example, we will assume that reliable and comparable estimates of accumulated dose (medical + non-medical) exist for all participants, individually. The participants with the lowest accumulated doses (no one has zero dose) are designated to be the control-group, and the remaining participants are designated as the study-group. The study-group, sorted by individual accumulated radiation dose, can be divided along its dose-continuum into ten groups of progressively higher dose.

Somehow (a word which reflects more "glossing-over"), the participants in each dose-group and in the control-group are well-matched with each other for age, gender, occupation, smoking habits, nutrition, and other variables which can affect the MortRates --- except for one variable: MEDICAL CARE. Suppose it turns out that the control-group has less medical care, or worse medical care, than the study-group, but the analysts do not realize it. What can happen?

Illustrative Numbers and a J-Shaped Curve in Figure L-1

For purposes of comparison, we will call the All-Cause MortRate observed in the control-group "unity" (1.00). Thus, a MortRate 15% below the control-group's MortRate would be 0.85, and a MortRate 15% higher than the control-group's MortRate would be 1.15. In the tabulation below Figure L-1, the control-group is called dose-level 0, and its observed MortRate (in Column D) = 1.00 .

Now, thanks to the "extra" medical care, each part of the study-group will have an All-Cause MortRate which is 15% lower than the MortRate of the control-group. The value of 15% is purely illustrative. In Column C below Figure L-1, we enter 0.85 as the effect of "extra" medical care upon the MortRate in the study-group.

And thanks to the extra accumulated doses of ionizing radiation, each part of the study-group will have a higher MortRate from Cancer and Ischemic Heart Disease than the control-group. To illustrate the point, suppose that in the first dose-group, radiation is sufficient to increase the All-Cause MortRate by 10% above the MortRate observed in the control-group, and by an additional 10% in each successively higher dose-group --- as shown in Column B of the tabulation presented below Figure L-1. Although the 10% value is purely illustrative, the expectation of an increase in the study-group --- due to fatal cases of radiation-induced Cancer and radiation-induced Ischemic Heart Disease --- is based on real-world evidence.

The NET observed All-Cause MortRate is the product of two factors: The elevation by radiation, and the decrement by better medical care. Column D calculates the product of Column B times Column C. The results are depicted by the graph of Figure L-I.

Hormetic Illusions: A Realistic Pitfall in Epidemiology

There it is: The J-shaped dose-response. A little extra radiation appears to make the All-Cause MortRate fall BELOW the rate in the control-group --- a spurious hormetic effect, because the harm from even the lowest level of extra radiation is present in Column B. The hormetic illusion is produced by the fact that the control group and the study-group are not matched for medical care.

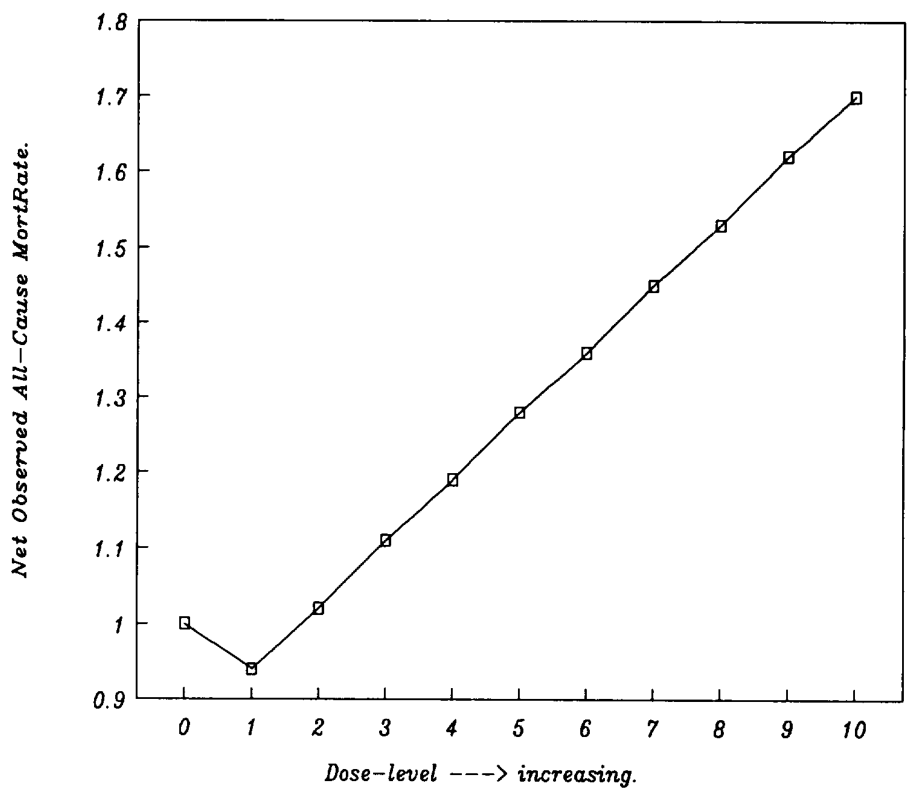
The same problem --- less, or less effective, medical care in the control group --- could also produce a J-shaped dose-response in a similar study concerning death only from Cancer (or IHD). Moreover, the problem could produce a dose-response with the SAME MortRate in the control-group and at dose-level 1 --- which would be a threshold illusion instead of an hormetic illusion.

If the hormetic illusion can arise out of "perfectly good data" having nearly IDEAL conditions for an epidemiologic study, then the hormetic illusion is a realistic pitfall in the ACTUAL world of epidemiology --- where matching for socio-economic factors may not assure comparable medical care, where reliable and comparable estimates of accumulated radiation dose (medical + non-medical) almost never exist, and where a general population serves rather often as the control-group for a relatively particular study-group.

>>>>>>>>>>

Figure L-1.
How the Hormetic Illusion Can Arise from "Perfectly Good Data."

• Below the graph, "perfectly good data" match the circumstances described in the Text, Part 3. The control-group and the irradiated study-group are perfectly matched with each other on all variables --- except medical care. The study-group is divided into ten dose-levels. The horizontal axis shows the dose-levels from Col.A, where 0 is the control-group. The vertical axis shows the net observed death-rates from Col.D, where unity (1.00) is the death-rate observed in the control group.
• The J-shaped dose-response depicts a spurious hormetic effect. The harm from even the lowest extra dose of radiation is present in Col.B, below. The hormetic illusion is produced by a failure to match the control-group and the exposed groups for medical care.



Related text = Part 3.

Col.A Dose-Level	Col.B Change in MortRate due to Extra Radiation	Col.C Change in MortRate due to Extra Medical Care	Col.D Net Obs. MortRate = B times C
0	1.00	1.00	1.00
1	1.10	0.85	0.94
2	1.20	0.85	1.02
3	1.30	0.85	1.11
4	1.40	0.85	1.19
5	1.50	0.85	1.28
6	1.60	0.85	1.36
7	1.70	0.85	1.44
8	1.80	0.85	1.53
9	1.90	0.85	1.62
10	2.00	0.85	1.70