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Professor Joshua Lederberg  
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Dear Dr. Lederberg:

This is not exactly fan mail, although I do look forward to your pieces in the Sunday Washington Post. You have a curiously detached style which invariably leaves me wanting to argue points; but no doubt that is part of the game.

I believe your recent remarks on "Pill Heralds Biological Changes"--that was the headline--do not engage the ultimate in what may be the long-term aspects of the problem-hazard associated with its clinical usage in the female. As presented in your column, it seems that you are considering thrombosis to be a long-term effect in women using the pill. Presumably it occurs while they are still on the drug, not years after they have ceased taking it, and if this is true, a pharmacologist would tend to classify thrombosis as a delayed drug reaction. Of course, one recognizes that this classification is more descriptive than explanatory and is not inherently discriminative.

Our work with radiation effects, which appears many years after an exposure, may conform more closely with the usual definition or concept of "long-term effects." The word "chronic" is rather too general to express the idea of a lengthy, seeming disconnection between cause and response. Of course, many of the biologic processes that appear as the clinical response are no doubt building up during this "latent" period.

Our concern with long-term effects has been condensed into the following questions: Is employment in nuclear energy facilities and laboratories associated with any discernable change in employee morbidity and/or mortality patterns? This question must be raised despite the fact that the typical exposure here is zero exposure or quite low-level continued or repeated exposures above background.

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This question must be dealt with by retrospective epidemiological procedures and to that end we have contracted with Dr. Thomas Mancuso, Research Professor, School of Public Health, University of Pittsburgh, to carry out these studies if he finds usable for such an analysis the available data on some millions of man-years at risk. He is presently in the early-middle of this investigation. Not unexpectedly, he has had to invent many new techniques as he has gone along, and these may turn out to be the most important product. At the very least, we expect him to tell us how to set up our occupational health services so as to accumulate proper prospective data on this question.

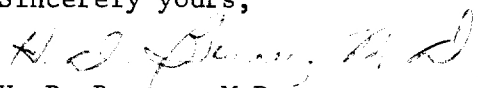
Concurrently, Jim Neel is concerned with the genetic aspects of long-term radiation effects and, of course, the Atomic Bomb Casualty Commission is directly involved with learning what are the long-term effects in another kind of irradiated population.

I have briefly described our problem in order to make the point that the long-range hazard in the pill-takers should be sought perhaps 20 to 40 years after they have stopped taking the pill. We have good experimental data in animals to suggest what long-term radiation effects should be looked for, but are there similar intimations from toxicologic studies of the pill?

Is it not reasonable to suppose that this chemical, which intrudes on the ovulation-menstrual cycle and feeds back to the pituitary, could also upset other pituitary-endocrine gland cycles? This, if it were to happen, could result in long-term effects in the context that we have been using the word. Are there data from animal experiments to rule out such reactions? Are there plans to search for such presumed reactions in women 10 or more years in the future? We can testify to the difficulties in trying to investigate such questions retrospectively.

If this letter causes you to ruminate about the special problems, techniques, and philosophy that must be developed in order to deal with long-range effects, it will have accomplished a purpose. Perhaps you may choose to write about the problem. In any case, you may be assured that there are numbers of medical, ethical, moral, social, financial, etc., considerations associated with, or more likely dependent on, the logic to be evolved in this long-term effects quandry. I am convinced that experimental controls in the conventional sense are not possible.

Sincerely yours,



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