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February 25, 1994

**The Honorable David A. Kessler, M.D.
Commissioner
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857-1706**



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Dear Dr. Kessler:

You may be aware that Samuel Epstein made public the contents of his February 14 letter to you on bovine somatotropin. He did so at a panel discussion on the environmental causes of breast cancer at the Association for the Advancement of Science meeting in San Francisco earlier this week. Copies of his letter were available in the press room.

As you must know, because of your agency's critical evaluation of BST, Epstein has made similar accusations in the past. The NIH panel convened to review the scientific data on the human safety aspects of BST, after listening to Epstein for well over an hour, concluded that his arguments were without merit.

As a member of that NIH panel, I feel obliged to comment on his most recent allegations. The numbering corresponds to the points in Dr. Epstein's letter.

1. The most recent evaluation of data on milk IGF-1 concentrations reported by the Fortieth Meeting of the Joint FAO/WHO Expert Committee on Food Additives in 1992, concluded that, " however, the most definitive and comprehensive studies demonstrate that IGF-1 concentrations [in milk] are not altered after rbST treatment. Additionally, IGF-II concentrations in cow's milk are also not affected by rbST treatment."
2. Epstein is correct — pasteurization does not destroy IGF-1. However, the high heat used in the preparation of infant formula does inactivate IGF-1.
3. IGF-1 is normally present in the gut to some extent since it can reach the small intestine via pancreatic or biliary secretion, thus bypassing the stomach. Nonetheless, as with almost all proteins, gut IGF-1 is eventually inactivated by proteolytic digestive enzymes.
4. It is true that there may be some protein leakage in the immature infant gut; however, the IGF-1 content of human colostrum is significantly higher than that of whole cow's milk, from supplemented or unsupplemented cows. Furthermore, the American Academy of Pediatrics guidelines do not recommend cow's milk feeding during the neonatal period and up to 12 months of age.

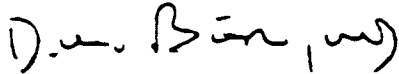
5. Epstein has misinterpreted Monsanto's data in the *Science* paper authored by Drs. Juskevich and Guyer. First, there was no increase in serum IGF-1 concentrations by oral gavage while there was an increase in systematically treated animals. The body weight change cited by Epstein was not consistent in that it only occurred in one dose and only in males. The size of this effect was compounded by a typographical error in which the weight gain (g/day) of the control group was cited in the text as 7.29 when it was actually 7.92. This body weight change was not repeated in the Eli Lilly gavage study even at doses five times higher than the Monsanto study. There was a slight increase in tibial length in orally gavaged males, but this was not corroborated by an increase in tibial epiphyseal width and was not evident in females. The Eli Lilly study utilizing oral IGF-1 doses ranging up to five times higher than the Monsanto study detected no effect of oral IGF-1 on measures of growth. Since there were no consistent changes in hematology, clinical chemistry, urinalysis parameters, organ weights or body weights in orally gavaged animals that were consistent with systematically dosed animals, it was concluded that oral IGF-1 up to a dose of 2 mg/kg was orally inactive. To put this into perspective, an oral dose of 2 mg/kg in a 10 kg infant equates to a milk consumption of 5 metric tons of milk per day using a milk IGF-1 concentration of 4 ng/ml. The NIH Consensus panel reviewed at length the data in the *Science* paper and concluded that these data do not support the hypothesis that IGF-1 has systemic activity when given by the oral route.
6. Epstein is correct. In fact, the bovine and human IGF-1 molecules are identical. However, Somatotropin is required to stimulate IGF-1 production and bovine somatotropin is inactive in humans because the human receptor interacts only with human somatotropin. The molecular structure of the IGF-1s may be very similar or indeed identical, but the structure of the somatotropins are significantly different.
7. Bovine somatotropin has no action on human breast epithelial cells, since it does not interact with the human somatotropin receptor on breast or any other human cell membrane.
8. It is true that IGF-1 is a mitogen and causes cell division. This is one of its normal functions.
9. I am aware of no substantive evidence in the world's scientific literature that IGF-1 causes malignant transformation of normal human breast epithelial cells. If this were true, then at the very least, there should be a high incidence of breast cancer in patients with acromegaly. I know of no such association. IGF-1 has been transfected into mammalian breast cancer cells with the result that these malignant cells become more differentiated – suggesting just the opposite of what Epstein is hypothesizing.

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10. **Essentially all malignant cells produce IGFs.**
11. **The most recent data indicates that there are no increased IGF-1 levels in milk and bovine somatotropin is inactive in humans who lack receptors for the bovine form. BST cannot stimulate any IGF-1 production in humans.**
12. **If this were true, then human colostrum, human breast milk, and indeed, all milk would be incriminated as a cause of breast cancer.**

In summary, I can only conclude that Epstein has no scientific basis for his claims regarding bovine somatotropin and IGF-1. I hope that the FDA will issue a strong statement reassuring the women of this country that they and their children have nothing to fear regarding the nation's milk supply.

Sincerely,



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