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LETTERS

Myoblast Transplantation

I appreciate Larry Thompson's balanced presentation of the issues surrounding my myoblast transfer work (News & Comment, 24 July, p. 472). Thompson obviously made a real effort to listen to all points of view. I also appreciate his recognition of the most important point—whatever the criticism of specific studies, myoblast transfer is a treatment of important potential value.

I would like to correct a few errors in the article that are of particular concern. First, I did not "set up" the two institutional review boards (IRBs) that approved my study. They existed long before I approached them to review my study, and neither the Cell Therapy Research Foundation (CTRF) nor I have any ties to them. Second, the number of patients in the study (32) did not exceed the number of patients approved by the IRBs. The Food and Drug Administration's (FDA's) observations in this respect were in error, and CTRF has provided material to the FDA to set the record straight. I agree that exceeding the number of patients approved by an IRB would be a serious breach of professional ethics, and I would not do so.

Third, I did not in any way select data when analyzing the study's results. Our analysis was conducted according to the method established in the protocol. As the article points out, some data included in the computer print-out were not recorded as isometric contractions. The computer recorded every contraction that occurred; we included in our results only those maximal contractions that were physiological, not those involving involuntary muscle cramping. This was not data selection that could bias the results; it avoided bias by using only the contractions the study was designed to assess.

Fourth, the characterization of the FDA's inspection as an "investigation" is misleading. The FDA conducts such routine inspections when it learns of new therapies that have not previously been regulated.

Finally, I am puzzled by the assertion that parents of children receiving treatment are unhappy with our study. The parents of the patients in this study have been most supportive and have urged CTRF to move faster than we thought appropriate.

I realize that some critics will continue to argue that I have moved too far too fast. I must respectfully disagree. Children are dying for want of an effective treatment for Duchenne muscular dystrophy. This is why I have pushed forward as quickly as good science will allow.

Peter K. Law
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I would like to point out several errors in Thompson's article. To my knowledge, all the families participating in the lower body clinical trial conducted by Peter K. Law have given their full support to his work. This study is based on 23 years of animal research as well as 2 years of work in human clinical trials. In the first study in which the extensor digitorum muscle was injected, Law found myoblast transfer to be a safe procedure. He also performed several biopsies on the extensor muscle after myoblast transfer and indeed found dystrophin present. Robert Miller and George Karpati also found dystrophin to be present in their myoblast clinical trials and have confirmed the safety of myoblast transfer. In addition, Jacques Tremblay performed myoblast transfer, again affirming the safety of the technique. The families of these children involved in the clinical trials being conducted by Law, Miller, and Jerry R. Mendell, as well as the families of children with Duchenne muscular dystrophy, wish this research to be ongoing, without interruption.

The inspection by the Food and Drug Administration (FDA) was not requested by parents of the children either involved in a clinical trial or anxiously awaiting their ability to participate in such a trial. The FDA inspection, while routine, was initiated because the Muscular Dystrophy Association asked Congressman William H. Natcher (D–KY) to write Health and Human Services Secretary Louis W. Sullivan and the National Institutes of Health (NIH) and request such an evaluation. In a meeting in September 1991 with members of the NIH, Charles McCarthy, then director of NIH's Office for Protection from Research Risks, indicated he had received and placed on file such a letter.

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Response: Most of what Law says is covered in Thompson's article. With regard to the institutional review boards, the article said that he had set up his own boards based on assurances from several experts in the field. If this statement was wrong, Law had ample opportunity to correct it before publication, but he specif-

ically declined to answer questions about the boards. As for the contention of the families of Law's patients, we deeply sympathize with their plight. The Food and Drug Administration (FDA) told Thompson that it had received complaints about Law's foundation both from physician-scientists and from parents of children with the disease. The FDA has clarified its statement and has indicated that the families who complained had considered Law's treatment and rejected it. *Science* regrets the error.—***The Editors***

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Carcinogenicity of Butadiene

Philip H. Abelson's editorial (19 June, p. 1609) "Exaggerated carcinogenicity of chemicals" is more a legal brief than an editorial. Any and all evidence that suggests 1,3-butadiene is not likely to be carcinogenic in humans is emphasized, while a large body of evidence that it is indeed carcinogenic for humans is ignored. Butadiene is carcinogenic to Swiss mice without the murine leukemia virus and to Sprague-Dawley rats in spite of metabolic and pharmacokinetic differences. Butadiene-induced mouse neoplasms contain K-ras oncogenes and inactivated tumor suppressor genes, similar to those in humans. The preliminary study by B. J. Divine (*1*) showed a clear increase in lymphopoietic cancers and leukemia. The finding of overall lower cancer mortality is consistent with the healthy worker effect. Other studies also show that butadiene is a human carcinogen. If trillions of dollars and loss of competitiveness and jobs are really at stake, the readers of *Science* deserve a more careful review of the literature.

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1. B. J. Divine, *Environ. Health Perspect.* **86**, 119 (1990).

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Abelson's editorial contains an unbalanced and cursory review of 1,3-butadiene toxicity and of the recent National Institute for Occupational Safety and Health (NIOSH) risk assessment of butadiene (*1*). A thorough review of the metabolic, toxicologic, and epidemiologic data for butadiene is available (*2*). The NIOSH risk assessment was based on a recent National Toxicology Program study (*3*), in which $B6C3F_1$ mice were exposed to butadiene concentrations of 6.25 to 625 parts per million (ppm), a range which overlaps that of actual occupational exposures (*2*). In order to evaluate the sensitivity of our risk estimates to modeling assumptions, we applied time-to-tumor models under several assumptions. None of these models led to the 100% predicted response at 2 ppm that was implied in the editorial.

Abelson's statement that, after exposure to 10 ppm butadiene, mice retain 10 times more of it than rats, and 33 times more than monkeys, is not an accurate summary of the data in (*4*). Of greater importance is the requirement for metabolic activation to observe genotoxicity (*2*), which suggests that butadiene metabolism is a more meaningful measure of dose than ^{14}C retention. Percent metabolism in rats and mice is similar and is independent of exposure concentration in the range of linear kinetics (*4*). We assumed that this would also hold for humans. Although cryogenic trapping data suggest that primates produce smaller quantities of genotoxic metabolites than do rodents (*4*), the validity of this comparison is questionable because of protocol differences between mouse and monkey experiments and the nonspecificity of the cryogenic trapping (*2*).

Abelson's interpretation of interspecies differences in epoxide hydrolase activities and in urinary metabolites is misleading. A recent analysis concluded that epoxide hydrolase is not the major enzyme involved in the elimination of butadiene monoepoxide in mice, rats, and humans (*5*). Urinary metabolites measured at high concentrations (8000 ppm) (*6*) are not relevant to estimating risks at low concentrations.

The epidemiological evidence for the carcinogenicity of butadiene is stronger than was suggested in the editorial. A study by B. J. Divine (*7*), cited as negative evidence, actually reported a 2.3-fold statistically significant excess of lymphosarcoma. Abelson did not point out studies (*8*) which found evidence of excess lymphatic and hematopoietic neoplasms.

Both toxicologic and epidemiologic data support our concern that butadiene may produce cancer in occupationally exposed humans and that the current Occupational Safety and Health Administration's Permissible Exposure Limit of 1000 ppm may not be protective.

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Abelson argues that "a searching review of the risk assessment methodology of the regulatory agencies is overdue." To support his thesis, he chose the case of 1,3-butadiene, a monomer used extensively in the production of synthetic rubber. On the basis of an epidemiologic study of a population of butadiene workers employed by Texaco that found no overall increase in cancer mortality (*1*), Abelson states that butadiene is not a potent human carcinogen. He argues that the results of positive animal bioassays of the carcinogenicity of butadiene (*2*) should be discounted.

In his review of the Texaco study, Abelson does not mention that, despite the overall deficit in cancer mortality [observed in relatively fit populations of industrial workers (*3*)], there was a striking and statistically significant excess in mortality from cancer of the lymphatic and hematopoietic system. This excess was most strongly evident in production and maintenance workers (who are regularly exposed to butadiene) and in black workers. Also, Abelson does not mention a study of 12,113 rubber workers in the United States and Canada (*4*) that also found excess mortality from lymphatic and hematopoietic malignancies despite an overall deficit in cancer mortality. The excess was most strongly evident in production and black workers, for whom the standardized mortality ratio (SMR) for these malignancies was 507 (five times greater than background). That increase reflected an SMR of 532 for lymphosarcoma, 656 for leukemia, and 482 for other lymphatic cancers.

It would be fitting if Abelson withdrew his ill-conceived and selectively researched editorial.

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