Table 1. Heights and chest circumferences (inches) of 5732 Scottish militiamen, data compiled by an army contractor and printed in 1817 (*2*).

Height	Chest circumference																Total
	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	
64–65	1	7	31	69	108	154	142	118	66	17	6	3	0	0	0	0	722
66–67	1	9	30	78	170	343	442	337	231	124	34	12	3	1	0	0	1815
68–69	1	2	16	34	91	187	341	436	367	292	126	70	13	3	2	0	1981
70–71	0	1	4	7	31	62	117	153	209	148	102	40	16	7	0	0	897
72–73	0	0	0	1	9	7	20	38	62	65	45	43	18	7	1	1	317
Total	3	19	81	189	409	753	1062	1082	935	646	313	168	50	18	3	1	5732

Table 2. Data from Table 1 reclassified and expressed in rounded percents, together with rounded percents (in parentheses) from a bivariate normal distribution with correlation .45. The means and standard deviations of the bivariate normal distribution were fixed to be $39\frac{7}{8}$ inches and $2\frac{1}{16}$ inches (chests) and $67\frac{1}{2}$ and $2\frac{1}{8}$ inches (heights) (*3*).

Height	Chest circumference						Total
	33–35	36–38	39–40	41–42	43–45	46–48	
64–65	1 (1)	6 (6)	5 (6)	1 (2)	0 (0)	0 (0)	13 (15)
66–67	1 (1)	10 (9)	14 (14)	6 (8)	1 (2)	0 (0)	32 (34)
68–69	0 (0)	5 (5)	14 (13)	11 (11)	4 (3)	0 (0)	34 (32)
70–71	0 (0)	2 (1)	5 (5)	6 (7)	3 (3)	0 (0)	16 (16)
72–73	0 (0)	0 (0)	1 (1)	2 (1)	2 (1)	0 (0)	5 (3)
Total	2 (2)	23 (21)	39 (39)	26 (29)	10 (9)	0 (0)	100 (100)

unheralded Gauss who constructed his data using techniques now considered not to have been invented until at least half a century later.

As statisticians we decry both inadequate statistical reporting and inappropriate statistical analyses. But both shortcomings are too common in the literature of the past and present to permit them alone to serve as evidence of fraud or intentional deceit. Dorfman's article has served the worthy purpose of stimulating discussion highlighting the inadequacies of Burt's descriptions. But using Dorfman's inappropriate statistical techniques to detect fraudulent data would be to condemn a major portion, if not all, of empirical science as fabrication.

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References and Notes

1. Among the other problems with Dorfman's statistical analyses are that (i) Dorfman's assumption in his reply (p. 251) that "column totals are not changed by the weighting along rows" does not follow from our proposed method of constructing the tables. It is in fact a tacit assumption of the conclusion he wishes to prove; the algebra here is irrelevant, and the conclusion that "the column totals are determined by the row totals" (p. 254) is incorrect. (ii) It is not unusual to obtain high correlations among class means of approximately multivariate normal data. For example, the correlation of the row means and the height midpoints of the Scottish data (our Table 1) is .99604, not far short of the value .99867 Dorfman (p. 252) found for Burt's means. Analogously, regression of one group of class means on another may, with data like these, produce a remarkably close fit to a straight line, like that exhibited in Dorfman's figure 1 (p. 254), where his "fabrication equation" and the means are displayed.
2. *Edinburgh Med. Surg. J.* **13**, 260 (1817). Table 1 was constructed by aggregating separate tables for 11 different regiments. The compiler of the tables is only identified as "an army contractor, a gentleman of great observation and singular accuracy." Quetelet used the chest measurements in his *Lettres . . . sur la theorie des probabilités* (1846) and other books.
3. The figures in parentheses were found from a bivariate normal distribution with chest mean $39\frac{7}{8}$, chest standard deviation $2\frac{1}{16}$, height mean 68, height standard deviation $2\frac{1}{8}$, and correlation coefficient .45. The columns were considered as corresponding to classes (0, 35.5), (35.5, 38.5), (38.5, 40.5), (40.5, 42.5), (42.5, 45.5), (45.5, ∞). The row classes were taken to be (64, 66), (66, 68), (68, 70), (70, 72), (72, 74). Apparently no Scotsmen below 64 inches or above 74 inches were admitted to the militia, so the distribution was truncated at these values and renormalized so that the sum of the probabilities for the given cells was 1.0. The bivariate normal probabilities were found from the *Tables of the Bivariate Normal Distribution Function and Related Functions* (Applied Mathematics Series No. 50, National Bureau of Standards, Washington, D.C., 1959). All standardized cell boundaries were rounded off before entering in the table, to eliminate the need to interpolate. Means, standard deviations, and the correlation coefficient were chosen as being standard fractions near sample estimates, and they may not produce the best possible fit. Incidentally, published tables are ill-suited to this purpose, and the required computations seemed laborious to us.

Chemical Carcinogens: Estimating the Risk

We would like to respond to the letter by Hooper, Harris, and Ames (16 Feb., p. 602), in which the authors comment on what they feel are ". . . several errors of fact and interpretation" in an earlier series of articles on chemical carcin-

ogens by Thomas H. Maugh II (Research News, 29 Sept. 1978, p. 1200; 6 Oct. 1978, p. 37). In particular, they express concern that one of us (P.J.G.) incorrectly inferred that a threshold exposure to vinyl chloride existed at 50 to 150 parts per million (ppm) and consequently might have underestimated the risk from exposure to low levels of vinyl chloride by ". . . more than a millionfold. . . ."

In fact, the risk estimate alluded to (*1*) (which predicts a cancer risk of 10^{-8} in workers occupationally exposed to 1 ppm vinyl chloride for 35 years) is performed without *any* assumption of a threshold. Instead this analysis incorporates pharmacokinetic principles to predict the rate of production of a reactive intermediate in vivo after exposure to vinyl chloride.

Although we believe it is possible that thresholds for chemical carcinogens exist, our research on vinyl chloride has not provided evidence showing such thresholds. Indeed, attempting to provide irrefutable evidence of absolute thresholds for chemical carcinogens is simply an exercise in futility. Because it is impossible to prove that any chemical is totally without risk, it is essential to move toward rational risk assessment based on the best available technology.

Furthermore, it is important to check *any* type of risk estimate against real data whenever possible. In the case of vinyl chloride this is possible because a survey of almost 10,000 workers occupationally exposed to vinyl chloride was recently conducted by Equitable Environmental Health, Inc. (EEH) (*2*). Exposure of these workers (which occurred before current standards were established) was great—very likely more than 200 ppm and certainly far more than 1 ppm. If Hooper *et al.* are correct in projecting a risk of 10^{-2} to 10^{-1} from exposure to 1 ppm vinyl chloride, then this group of workers, exposed to much higher doses, should have experienced several hundred to several thousand cases of hemangiosarcoma. However, the survey failed to show this—only five of the almost 10,000 exposed workers had developed this type of cancer.

A key factor in the extrapolation of the results of animal studies to humans is the role played by metabolic activation. Vinyl chloride is one of a class of chemicals in which the proximate carcinogen is generated from the parent molecule by microsomal oxidation (*3*). In general, this type of metabolic reaction occurs more rapidly in small laboratory animals than in humans. Investigators in another laboratory have studied the metabolism of vinyl chloride in several species, in-

cluding humans, and have determined that it is about 4.3 times slower in humans than in rats (*4*). Consequently, one would expect that humans should be much less sensitive than rats to the carcinogenic activity of vinyl chloride. The risk assessment of Gehring *et al.* (*1*), based on this principle, is reasonably consistent with the results of the EEH survey. Ten hemangiosarcomas are predicted from exposure to 200 ppm vinyl chloride and five were actually observed. However, the risk estimate of Hooper *et al.*, which apparently does not consider this principle, clearly cannot be reconciled with the data in the EEH report.

Hooper *et al.* also comment on the role of pathological tissue damage in the cancer bioassays of chloroform. Many investigators have reported that short- and intermediate-term exposure to chloroform is toxic to kidney and liver tissue in mice (*5*) and rats (*6*). However, in the long-term studies conducted by the National Cancer Institute (*7*) and Roe (*8*) the absence of *reported* pathological damage is very likely misleading. These studies were designed to detect irreversible toxicity, such as the induction of tumors. In each case, the chloroform was administered daily for a period of 78 to 80 weeks followed by several months of observation before the animals were killed. Consequently, any *reversible* tissue damage would probably not have been apparent in these studies. However, prolonged cell regeneration after chemical insult may be very significant in the induction of tumors. In fact, in the first published study (*9*) to link chloroform exposure with tumor induction in mice, the authors noted that liver necrosis was consistently produced by doses of chloroform that were tumorigenic. These investigators were careful to administer a dose of chloroform 24 hours before necropsy so that both short- and long-term effects could be observed.

Recent studies in our own laboratory have been concerned with the induction of tissue damage and subsequent cellular regeneration after single oral doses of chloroform to male B6C3F1 mice. We found that tissue damage could be detected microscopically in both the liver and kidney after chloroform treatment. In the liver, cellular degeneration and necrosis were present after a dose of 240 milligrams (mg) of chloroform per kilogram (kg) body weight, hepatocellular swelling was noted after 60 mg/kg, and 15 mg/kg apparently had no effect. In the kidney, necrosis was observed after both 240 and 60 mg/kg, but not after 15 mg/kg (*10*). This correlated well with the relative rates of DNA replication in these tissues, estimated by injection of ^{3}H-labeled thymidine 48 hours after a dose of chloroform (*10*). The demonstration of chloroform-induced tissue damage at tumorigenic doses is particularly noteworthy because chloroform has been tested by several investigators in the bacterial mutagenicity test developed by Ames with apparently negative results (*11*).

Thus we do not feel tissue damage can be legitimately dismissed as a factor in the carcinogenicity of chloroform. Furthermore, indications that chloroform probably lacks genotoxic activity raise serious questions about the validity of carcinogenic risk estimates based on the "one-hit" model, since the one-hit model was developed to deal with genetic events.

There is certainly no question that the test developed by Ames can give useful information about the potential of various agents to interact with DNA. However, so many complex interactions are involved in the generation of a tumor in a whole animal that it is essential to carry out a complete evaluation of the effects of chemicals in whole animals before drawing any conclusions about their carcinogenicity.

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