efficiency of human fibroblasts. In some experiments, we varied the number of cells plated per dish; Kurz *et al.* suggested that our results might therefore be an artifact of cell density ("cloning efficiency decreases at higher cell densities") rather than a consequence of the toxicity of dexamethasone. They reported that, with their methods, increasing the number of cells plated per dish from 100 to 1000 resulted in a 50 percent decrease in plating efficiency in two fibroblast strains. In our experiments, 1500 to 8000 cells are typically plated per 100-mm dish (in the absence of the drug, the range is 500 to 2000 cells). Table 2 shows that there is no decrease in plating efficiency with increasing numbers of cells plated. We had determined long before starting our CF experiments that, in the ranges given above, the number of cells plated per dish has no significant effect on the plating efficiency. Furthermore, the results in tables 1 and 2 of Kurz *et al.* were based on plating a maximum of 300 cells per 100-mm dish. We have never worked with such a low number of cells per dish because too few colonies are obtained for statistical reliability. In addition, we have performed experiments in which killing by dexamethasone was observed when nearly equal numbers of cells were exposed to various dexamethasone concentrations (Table 3). These data reveal that killing by dexamethasone is not an artifact of the number of cells plated.

Table 2. Plating efficiencies with different numbers of cells plated.

Cells per 100-mm dish	Colonies counted per replicate dish*	Plating efficiency (%)
500	43, 41, 42	8.4
1000	76, 73, 81, 80	7.8
1500	126, 123, 106, 129	8.1
2000	159, 163, 172	8.3

*Each colony had ≥ 75 cells.

Table 3. Survival of skin fibroblasts subjected to various concentrations of dexamethasone after being plated in nearly equal numbers.

Drug concentration (*M*)	Cells plated per 100-mm dish	Colonies counted per replicate dish*	Survival (%)†
0	1500	208, 200, 185, 216, 197, 207	100
10^{-10}	1500	117, 108, 134	59
10^{-9}	1500	97, 78	43
10^{-8}	1500	63, 88, 71	37
10^{-6}	2000	36, 29, 47	14

*Each colony had ≥ 75 cells. †Corrected for plating efficiency.

Although Kurz *et al.* apparently examined many relatively minor parameters in detail, they failed to establish proper colony criteria, one of the most important aspects of the survival assay method. In addition, they failed to work within the range of cell numbers specified in our reports. We believe that these factors contributed significantly to their results and invalidate their claim of having replicated our experiments. Also, inasmuch as their results were obtained with normal human fibroblasts only and not CF fibroblasts, we are concerned that their interpretations of the results were too broad.

Finally, they stated that they "know of no other evidence showing that human fibroblasts are killed by glucocorticoids." However, Weichselbaum *et al.* (*7*), who are experienced in the use of the survival assay method, recently observed killing of normal human diploid fibroblasts with glucocorticoids. Gibbs (*8*), using our method, not only found that dexamethasome kills normal human diploid fibroblasts, he found that it kills fibroblasts from obligate CF heterozygotes at a lower rate. The fact that other laboratories have confirmed our results suggests that the technique is valid when properly utilized.

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27 December 1979

Clomid Administration in Rats

We have reviewed the slides selected by McCormack and Clark (*1*) as most representative of the histologic changes that they observed after administering Clomid to pregnant rats.

Independent review of the slides by pathologists with knowledge of neoplasia in the female genital tract revealed squamous metaplasia and inflammation but no evidence of cellular atypia or neoplasia. Furthermore, there were no histologic changes suggestive of those observed in offspring born to women exposed to diethylstilbestrol during pregnancy.

We are expressing our opinion because of the implications of this animal study for humans who require Clomid for ovulation induction.

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We did not describe our findings as evidence for neoplasia; however, the teratology that we observed cannot be denied. Uteri that contain 90 to 100 percent metaplastic epithelium are not normal. Likewise, gross abnormalities, such as large uterine masses that contain necrotic remains of pups, are not normal.

We have studied hundreds of slides from both normal and abnormal tissues, and are familiar with the histology of the reproductive tract of the rodent. The abnormalities that we reported are similar to, if not identical to, those caused by neonatal or fetal exposure to estrogens (*1*). Similar findings have been observed as a result of neonatal treatment with Tamoxifen, a drug similar to Clomid that is used in the treatment of breast cancer (*2*). In our opinion and in the opinion of Chamness *et al.* (*2*) these changes are atypical and abnormal. Whether they occur in humans is unknown; however, the clinical implications remain clear.

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