4. W. H. Thorpe, *Learning and Instinct in Animals* (Methuen, New York, 1963); A. Manning, *Nature (London)* **216**, 338 (1967).
5. W. von Borel du Vernay, *Z. Vgl. Physiol.* **30**, 84 (1942); A. Borsellino, R. Pierantoni, B. Cavazzo, *Nature (London)* **225**, 963 (1969); J. C. Somberg, G. M. Happ, A. M. Schneider, *ibid.* **228**, 87 (1970).
6. T. Alloway, *Science* **158**, 1066 (1967).
7. W. G. Quinn and P. P. Sziber, unpublished data.
8. Y. Dudai, Y. N. Jan, D. Byers, W. G. Quinn, S. Benzer, *Proc. Natl. Acad. Sci. U.S.A.* **73**, 1684 (1976).
9. W. G. Quinn, P. P. Sziber, R. Booker, *Nature (London)* **272**, 212 (1979).
10. T. W. Cline, *Genetics* **90**, 683 (1979).
11. Sources of critical materials are: bolting cloth; Nitex monofilament nylon screen HD3-100 (mesh opening 100 μm), Tetko Inc., Elmsford, N.Y. Petri plates: 1013 (for training) and 1003 (for testing), Falcon Plastics, Oxnard, Calif. Odorants: 3-octanol 16448 and 4-methylcyclohexanol 16954, ICN-K&K Laboratories, Plainview, N.Y.; amyl acetate 3568, Mallinckrodt Inc., St. Louis, Mo.
12. D. Bodenstein, in *Biology of Drosophila*, M. Demerec, Ed. (Hafner, New York, 1965), pp. 275-364.
13. P. P. Sziber, L. Tomkins, W. G. Quinn, unpublished data.
14. H. Hertweck, *Z. Wiss. Zool.* **139**, 559 (1931).
15. For an ablation experiment on blow fly larvae (*Lucilia sericata*) see J. H. Welsh [*Science* **85**, 430 (1937)].
16. V. Rodrigues and O. Siddiqi, *Proc. Indian Acad. Sci. Sect. B* **87**, 147 (1978).
17. Apparently most of the larval brain is conserved through pupation. The protocerebrum and deutocerebrum (antennal lobes) and the subesophageal and thoracic ganglia retain their general morphology and most of their larval neurons. New neurons are added in all structures, however, and the entire optic ganglion complex is generated de novo during metamorphosis [(*12*, *14*); K. P. White and D. R. Kankel, *Dev. Biol.* **65**, 296 (1978)]. Axonal and dendritic branching patterns of cells may also change during metamorphosis [J. W. Truman and S. E. Reiss, *Science* **192**, 477 (1976); G. B. Casaday and J. M. Camhi, *J. Comp. Physiol.* **112**, 143 (1976)]. Larvae of *Tenebrio molitor* can be trained, and the memory is preserved through metamorphosis to be expressed in the adults (*5*).
18. S. Ward, *Proc. Natl. Acad. Sci. U.S.A.* **70**, 817 (1973).
19. Chemoreceptors in adult *Calliphora* and *Drosophila* are insensitive to 0.5*M* LiCl [C. J. den Otter, *J. Insect Physiol.* **18**, 109 (1972); G. Pollack, E. O. Aceves-Piña, W. G. Quinn, unpublished data]. Larvae are also behaviorally insensitive to this salt in chemotaxis tests. Third-instar larvae, placed on a petri dish (Falcon 1003) containing equal semicircular sectors of agarose and agarose + 0.5*M* LiCl, distributed themselves randomly; .52 ± .02 of the larvae were on the LiCl sector after 15 minutes (ten experiments).
20. We thank S. Ward for helpful discussion and S. Benzer for his observation that larvae respond to shock. We are grateful to friends in the Benzer laboratory and to M. Ginder and J. Hall for comments on the manuscript. Preliminary experiments suggesting that larvae could learn were conducted by J. P. Corsones. We used equipment made available by the Whitehall Foundation. E.O.A.-P. was a fellow of CONACYT of Mexico. Supported by NSF grant BNS 75-00474 and NIH grant GM 25578.

28 February 1979; revised 29 May 1979

Prednisone Therapy and Birth Weight

Reinisch *et al.* (*1*) reported a retardation of intrauterine fetal growth in infertile women treated with 10 mg of prednisone daily prior to conception and throughout pregnancy. These data were widely quoted in the news media and interpreted as evidence of potential danger to the offspring. Others have reported on the use of prednisone for induction of ovulation and alleviation of female infertility, but continuation of therapy during gestation was not advocated (*2*). We examined the question whether administration of prednisone to infertile women, when discontinued after confirmation of conception, will also result in a reduction of birth weight.

Birth weight and duration of pregnancy were available for 251 births (Table 1) from women evaluated for infertility in our clinic. The data permitted a comparison of offspring of mothers receiving prednisone, prednisone and clomiphene citrate, clomiphene citrate, other therapeutic modalities (for example, low-dose estrogen, human menopausal gonadotropin, human chorionic gonadotropin, thyroid hormone), or no treatment. Mean birth weights and duration of pregnancy were comparable in all groups. One-way analysis of variance and Duncan's multiple range test showed no statistical differences among means, or differences from the mean of the entire group. The median birth weight for term infants in the United States in 1975 was reported to be 7.31 pounds (*3*). In 1978, the mean weight of all infants born at Hermann Hospital, Houston, was 7.10 pounds (*4*), remarkably close to the mean birth weights in Table 1 and to those reported as controls by Reinisch *et al.* (*1*). Unfortunately, since Reinisch *et al.* failed to provide standard errors for their data, statistical comparisons could not be made.

These observations suggest that administration of low-dose prednisone (5 to 10 mg daily) for therapy of infertility, if discontinued after documentation of pregnancy, does not result in a decrease in birth weight of infants.

KEITH D. SMITH
EMIL STEINBERGER
LUIS J. RODRIGUEZ-RIGAU
Department of Reproductive Medicine and Biology, University of Texas Medical School at Houston, Houston, Texas 77025

Table 1. Mean (± standard error) duration of pregnancy and infant birth weight in relation to therapeutic management of infertile women.

Therapy	Number of pregnancies	Birth weight (pounds)	Duration of pregnancy (days)
Prednisone	103	7.22 ± 0.12	281.2 ± 1.5
Prednisone and clomiphene citrate	49	7.00 ± 0.18	280.6 ± 2.3
Clomiphene citrate	28	7.06 ± 0.20	280.2 ± 2.6
Other	12	6.72 ± 0.51	284.4 ± 3.7
No treatment	59	7.12 ± 0.13	275.6 ± 1.8
Total	251	7.11 ± 0.08	279.7 ± 1.0

References

1. J. M. Reinisch, N. G. Simon, W. G. Karow, R. Gandelman, *Science* **202**, 436 (1978).
2. R. B. Greenblatt, W. E. Barfield, C. P. Lampros, *Fertil. Steril.* **7**, 203 (1956); H. L. Kotz and W. Hermann, *ibid.* **12**, 299 (1961); W. H. Perloff and E. Steinberger, *Am. J. Obstet. Gynecol.* **88**, 439 (1964); K. D. Smith, E. Steinberger, W. H. Perloff, *ibid.* **93**, 994 (1965); E. Steinberger, K. D. Smith, R. K. Tcholakian, L. J. Rodriguez-Rigau, *ibid.* **133**, 133 (1979).
3. U.S. Department of Health, Education, and Welfare, Public Health Service, Publ. No. 78-1113 (1978), Sect. 1, pp. 1-53.
4. Houston City Health Department, Bureau of Vital Statistics (1979).

26 June 1979

The report by Reinisch *et al.* (*1*) presents the potential harm of the administration of prednisone in a dosage of 10 mg daily to pregnant women. The implication that any dosage of any corticosteroid would have comparable harmful potential is, however, unfortunate. The authors quote in their introduction two of our reports of the beneficial effects of dosages of cortisone acetate or hydrocortisone between 2.5 mg every 8 hours and 5 mg four times daily in women with ovarian dysfunction and infertility (*2*), implying that such treatment would also be potentially harmful and that it "resulted in the exposure of large numbers of fetuses to augmented adrenal hormone levels."

Cortisone and hydrocortisone are normal adrenal hormones; prednisone is not. Doses of 5 mg of cortisone acetate or hydrocortisone four times daily, before meals and at bedtime, do not raise the plasma cortisol levels above normal at any time (*3*) and hence have none of the harmful potential that is so well known for hypercortisonism. A 10-mg dose of prednisone is equivalent to 50 mg of cortisone acetate, ten times the potency of an individual dose and over twice the potency of the total daily dosage we use.

After more than 20 years of experience with administering to women dosages of cortisone acetate or hydrocortisone of 5 mg four times daily or less, we have found absolutely no evidence of hypercortisonism with any of its harmful po-

0036-8075/79/1005-0096$00.50/0

tential to either mother or child. These dosages are physiologic, and are administered to correct an abnormality and make the mother normal, in contrast to pharmacologic dosages or treatment with more potent steroid derivatives such as prednisone which introduce potential hazards.

I emphasize this point in an attempt to reassure physicians or patients who have given or taken physiologic dosages of cortisone acetate or hydrocortisone and hence might be unnecessarily alarmed by this otherwise excellent report. A more detailed discussion of the unfortunate tendency to confuse the effects of physiologic versus pharmacologic dosages of glucocorticoids was presented in (*4*).

WILLIAM MCK. JEFFERIES
Euclid Clinic Foundation, Euclid, Ohio 44119

References

→ J. M. Reinisch, N. G. Simon, W. G. Karow, R. Gandleman, *Science* **202**, 436 (1978).
2. W. M. Jefferies, W. C. Weir, D. R. Weir, R. L. Prouty, *Fertil. Steril.* **9**, 145 (1958); W. M. Jefferies and R. P. Levy, *J. Clin. Endocrinol. Metab.* **19**, 1069 (1959).
→ W. M. Jefferies, *Arch. Int. Med.* **119**, 265 (1967).
4. W. M. Jefferies, in *Controversy in Internal Medicine*, F. J. Ingelfinger, R. V. Ebert, M. Finland, A. S. Relman, Eds. (Saunders, Philadelphia, 1974), vol. 2, p. 439.

30 October 1978; revised 19 March 1979

Jefferies, who has provided much of the seminal data on corticosteriod therapy for the treatment of infertility, states that we implied that " . . . any dosage of any corticosteroid would have comparable harmful potential. . . ." Our finding of significantly reduced birth weight in full-term human offspring as a consequence of exposure to prednisone throughout gestation (*1*) was derived through the use of a fixed-effects model of analysis of variance. The constraints of this statistical model necessitate that any observed effects be ascribed to the specific manipulation under study (*2*). We could not, given our choice of design, imply that any and all corticosteroid therapies used for the treatment of infertility and maintenance of pregnancy entailed risks to the developing fetus.

It is possible, however, that the effects on birth weight observed in our study *may* generalize across various corticosteroid therapies since to our knowledge no data are available on the effects of other corticosteroids when these are compared to data for appropriate control groups. It should be noted that the effects found in our investigation would not be obvious to the physician upon inspection of the neonate at birth since 86 percent of the 119 infants studied were born at seemingly "normal" weights. Nonetheless, the comparison of prednisone-exposed neonates with their controls revealed a highly significant difference in body weight. In view of these findings, we would strongly urge investigators to reevaluate data from neonates exposed to other corticosteroid preparations during prenatal development.

In response to the comments concerning administration and side effects, prednisone was given in divided doses (2.5 mg four times per day until conception was confirmed and then 5 mg twice a day for the remainder of pregnancy), a regimen similar to that used by Jefferies. Finally, no symptoms of hypercortisonism were observed in any of the women or offspring studied.

Smith *et al.* conclude that the discontinuation of prednisone treatment to infertile women at confirmation of pregnancy does not affect the subsequent birth weight of offspring. This confirms our finding that the severity of the effects of prednisone on fetal development is related to the duration of treatment during gestation. Therefore, their data provide additional support for our view that it is exposure to prednisone during a long period of fetal development that poses potential hazards for the human neonate. It must be emphasized, however, that prednisone is administered for the treatment of a variety of maternal ailments (*3*). Any caution suggested in our report was directed not only to physicians who administer prednisone for infertility but also to those who treat such conditions as asthma, arthritis, and lupus erythematosus. These treatments are often prescribed throughout the entire course of pregnancy at higher doses than those used for infertility and pregnancy maintenance. For such conditions prednisone may be the treatment of choice, and we hoped that our report would alert physicians to the possibility that prednisone therapy may place the infant at risk.

Although the data presented by Smith *et al.* are of interest, it is unfortunate that they did not include the durations of treatment. Our providing standard errors would still not permit them to make statistical comparisons *between* experiments. The obvious similarity between the means of their samples and our control group, however, does suggest that the weights of the infants are comparable.

JUNE MACHOVER REINISCH
Department of Psychology, Busch Campus, Rutgers, the State University, New Brunswick, New Jersey 08903
NEAL G. SIMON
Department of Psychiatry and Behavioral Science, State University of New York at Stony Brook, Stony Brook 11790
WILLIAM G. KAROW
Southern California Fertility Institute, Los Angeles 90025
RONALD GANDELMAN
Department of Psychology, Rutgers, the State University

References

→ J. M. Reinisch, N. G. Simon, W. G. Karow, R. Gandelman, *Science* **202**, 436 (1978).
2. B. J. Weiner, *Statistical Principles in Experimental Design* (McGraw-Hill, New York, 1962).
3. F. G. McMahon, *Am. Fam. Physician* **10**, 132 (1974).

2 August 1979