variable down to 400 Mc/sec. Standard formulas for synchrotron emission would require about 1.5×10^{52} erg of relativistic electrons in each source. Such amounts of energy ($8 \times 10^{-3} M_\odot c^2$) are marginally obtainable from explosions of massive stars (several hundred solar masses) according to the calculations of Colgate and White (*4*). The proposal of Field (*5*), that quasars represent the earliest phase in the life of a galaxy, when supernovae occur at a rate of about five per year, is therefore pertinent.

GEORGE B. FIELD
Astronomy Department,
University of California, Berkeley

References and Notes

1. W. A. Dent, *Science* **148**, 1458 (1965).
2. M. Schmidt, *Nature* **197**, 1040 (1963).
3. V. I. Slish, *ibid.* **199**, 682 (1963).
4. S. A. Colgate and R. H. White, *U.S. At. Energy Comm. Rept. UCRL 7777* (Lawrence Radiation Laboratory, University of California, 1964).
5. G. B. Field, *Astrophys. J.* **140**, 1434 (1964).

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Forelimb Deformity in Rats: Association with Acetazolamide

Layton and Hallesy [*Science* **149**, 306 (1965)] show that administration of 200 mg of acetazolamide (but not less) per kilogram of body weight per day to the pregnant rat induces a deformity of the right forelimb in some of the offspring. As these authors point out, the only pharmacological effect of acetazolamide known up to this time is carbonic anhydrase inhibition. Their experiments, however, have certain features which lead me to believe that carbonic anhydrase inhibition is not involved in the teratogenic effects. Also, their conclusion that acetazolamide is a potentially useful tool in teratology must be tempered by the following considerations:

There is fairly compelling evidence that 10 mg of acetazolamide per kilogram produces maximum physiological carbonic anhydrase inhibition in a wide variety of systems and species [*Proc. Intern. Pharmacol. Meeting, 2nd* (1965), vol. 4, p. 155]. In the rat, this dose produces full renal effect, which is not substantially increased when the dose is raised 100-fold. Layton and Hallesy suggest that the large doses used may indeed produce other pharmacological effects, but do not raise the important question of the disposition of this drug in the rat. In this species, about 70 percent of a parenteral or oral dose appears to be metabolized to products as yet unknown, but which are not inhibitors of carbonic anhydrase [*Bull. Johns Hopkins Hosp.* **95**, 199, 277 (1954)].

The evidence that 20 times the usual dose rate for enzyme inhibition is needed to produce the deformities, combined with the fact that in the rat we are dealing with new and unknown metabolites, leads me to suggest that carbonic anhydrase is not involved and indeed the effects may not be those of acetazolamide itself. More important, and the chief point of this communication, is to indicate that further work of this type in the field of limb morphogenesis must be accompanied by studies of the metabolic products of acetazolamide in the rat.

THOMAS H. MAREN
Department of Pharmacology and Therapeutics, University of Florida College of Medicine, Gainesville

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While a metabolite of acetazolamide may be responsible for its teratogenic effect, we do not think we can dismiss the possibility that the deformities are caused by the action of acetazolamide itself, perhaps acting as a carbonic anhydrase inhibitor. The following arguments should be considered:

1) We do not agree that 20 times the usual dose rate for maximal enzyme inhibition was needed to produce deformities. The 10 mg/kg that Maren says is necessary for maximal inhibition was given as a single intravenous dose, inhibition being measured during the 30 minutes after administration. The 20 mg/kg that we found necessary was given in the diet over a 24-hour period. This, together with the extensive metabolism noted by Maren, might make this seemingly excessive amount of drug necessary to maintain sustained maximal inhibition.

2) The acetazolamide concentration in the embryo may be considerably lower than that in the mother.

3) The embryo may have an isoenzyme of carbonic anhydrase that is relatively resistant to acetazolamide inhibition.

While we agree with Maren on the importance of studying the metabolic products of acetazolamide in the rat, we think it is also important to see if other, structurally dissimilar, carbonic anhydrase inhibitors can produce this same deformity. If they do, it would seem likely that the deformity is due to carbonic anhydrase inhibition.

Finally, we find it difficult to temper our conclusion that acetazolamide is a potentially useful tool for the study of limb morphogenesis. Whether it is ultimately shown to be caused by acetazolamide itself or a metabolite, the resulting deformity, a right-sided postaxial defect of the forelimb, is so specific in its location and reproducible in its pattern that work to elucidate its mechanism must surely help uncover new findings about how a limb is formed.

W. M. LAYTON, JR.
D. W. HALLESY
Experimental Therapeutics Research,
Lederle Laboratories,
Pearl River, New York

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