organisms. An example is the intermittent galls on the green alga *Vaucheria*, caused by a rotifer [W. Rother, *Jahrb. Wiss. Botan.* **29**, 525 (1896)]. The abnormal growth of these galls is produced through the activity of "growth-hormones" secreted by the resident predator. These substances are related to if not identical with substances commonly secreted by fungus or bacterial invaders; the auxins and gibberellins are examples.

The abnormal corallites could well represent a hitherto unreported type of response to some sedentary predator—virus, bacterium, fungus, or invertebrate, which might have made three separate attacks on a single coral colony over a period of several years. I hope that Squires' article will alert others to be on the watch for similar phenomena, which may indeed have great importance in our understanding of the causes of neoplasia.

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1 June 1965

. . . From careful examination of Squires' Figs. 1 and 2, and the account in the text, it appears to me that what is described as a pathologic corallite on the specimens of *Madrepora kauaiensis* are actually colonies of the cyclostomata ectoproct belonging to the genus *Lichenopora* DeFrance 1823. Recently, I have found a few similar specimens of *Lichenopora* adherent to other bryozoans and coral in a collection, from Hawaiian waters, belonging to the Bernice P. Bishop Museum. The confusion is readily explained. Before DeFrance erected the genus *Lichenopora* in 1823, many members of this genus were referred to the *Madrepora*, a good indication of the superficial resemblance of the mineralized portions of these two animals.

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3 June 1965

White and Soule have both raised the question of the possibility that the growths on the coral *Madrepora kauaiensis* resulted from growths about other organisms. Such a result is extremely probable among the corals, for they are hosts to large numbers of crustaceans and other organisms which cause the formation of "galls." The particular instance described was believed to arise from other stimuli because of the sequential development of the abnormal corallites, steps which also suggested that there was a certain similarity between the development and neoplasia.

Because of the unique nature of the specimen, extensive dissection and sectioning were not undertaken. Examination of the exterior and interior of the specimen shows no evidence of coral overgrowth of another organism as often found in other galls. Although not diagnostically definitive, x-ray diffraction patterns obtained from septal fragments of the abnormal growths show that they are aragonite and similar to diffraction patterns from other portions of the corallum. Bryozoans differ in the crystal form of calcium carbonate utilized in their skeletal structures, either aragonite or calcite being present. Corals, on the other hand, exclusively utilize aragonite. No undoubted *Lichenopora* has as yet been available to me for x-ray diffraction analysis to rule out conclusively the possibility that *Lichenopora* was the cause of the anomalous growths.

Growths resulting from activity of growth hormones as suggested by White are indeed a possibility, and the uncertainty of the neoplasia diagnosis is indicated by the query in the title of the note. Conclusive evidence of neoplasia can, of course, rest only with histological studies of the tissues of the specimen, unfortunately unpreserved in this instance.

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2 September 1965

Quasi-Stellar Source 3C 273 B: Variability in Radio Emission

In a recent issue of *Science* Dent (*1*) has reported the very important discovery of variability in the 8000-Mc/sec radio emission of the quasi-stellar source 3C 273 B. The purpose of this note is to call attention to a numerical error in Dent's calculations which invalidates his conclusion that if the variable source emits by the synchrotron mechanism it must be much closer than the 1.5×10^9 light years assigned to it on the basis of its red shift (*2*).

Dent based his discussion on an article by Slish (*3*), who shows that below the frequency

$$\nu = [10^{33}\,\theta^{-2}\,S_\nu\,\nu^{\alpha}]^{2/(5+2\alpha)}\,B^{\,1/(5+2\alpha)} \quad (1)$$

self-absorption of synchrotron radiation will cause a rapid drop in flux. In this expression θ is the angular diameter of the source, S_ν its flux density in MKS units, α its spectral index at high frequencies ($S_\nu' \propto \nu^{-\alpha}$), and B the magnetic field in gauss. For the case $\alpha = 0$ applicable to 3C 273 B and with $S_\nu = 3 \times 10^{-25}$ watt m^{-2} cps^{-1} (cps, cycles per second), Eq. 1 gives $\theta'' = 3 \times 10^9\,B^{1/4}\,\nu^{-5/4}$ arc seconds. If we take $B > 10^{-5}$ gauss and assume that the spectrum of the variable component extends down to 400 Mc/sec (following Dent), we find $\theta'' > 3 \times 10^{-3}$ sec. This is 1/30 of the value derived by Dent. The error must be Dent's, as I derived Eq. 1 independently as a check. At the cosmological distance of 3C 273, this corresponds to a lower limit of 23 light years for the diameter of the source, a value which is just marginally compatible with the observed variability. It should be noted that this argument is based on the assumption that the source is variable at 400 Mc/sec also. The lower limit on θ based on the 8000-Mc/sec data alone (with $\alpha = 0$) is 6×10^{-5} sec, or 0.5 light years (whereas Dent found that the source would be optically thick at 8000 Mc/sec for $\theta < 2 \times 10^{-3}$ sec). We conclude that the 8000-Mc/sec data alone do not justify Dent's conclusion that the variable component cannot be due to a synchrotron source at great distance. Even the further assumption that the variable component is still strong at 400 Mc/sec is marginally compatible with such a source. Obviously any further information which can be obtained on the variability at lower frequencies will bracket the angular diameter better and permit conclusions as to the nature of the source.

A model which appears compatible with the present data consists of about 50 sources, each contributing to the flux and varying independently with periods of approximately 10 years. If each source is about 10 light years in radius, and has a magnetic field of 1.2×10^{-2} gauss, the source can be

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.

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References and Notes

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4. S. A. Colgate and R. H. White, *U.S. At. Energy Comm. Rept. UCRL 7777* (Lawrence Radiation Laboratory, University of California, 1964).
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29 June 1965

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.

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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.

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