Pannella and MacClintock (*3*) report that tidal patterns in bivalves are widespread but not always readily recognizable. In *M. mercenaria* they are expressed by groups of thin daily increments alternating with groups of relatively thick ones, forming 14-day periodic patterns. The smaller the tidal fluctuation, the thinner the increment; thus, the narrow increments are related to neap tides. In *Tridacna squamosa* tidal patterns are clearly expressed. The two kinds of daily increments, simple and complex, are present and form marked patterns with a 14-day period.

Specimens of the basket cockle *Clinocardium nuttalli* were collected on 9 July 1971 in Coos Bay near Charleston, Oregon. They were in muddy sand at about the +0.6-m tide level. Radial sections of four shells were examined by the acetate peel method (*3*). Tidal information was obtained from the U.S. Coast and Geodetic Survey tide tables for 1970. Data from the Humboldt Bay, California, reference station were corrected for Empire, Oregon.

The shell margin of *C. nuttalli* is moderately reflected. The structure of the outer layer is prismatic, and the boundaries of the growth increments are usually sharply marked by thin layers of conchiolin. These lines form a repetitious pattern of simple and complex increments (Fig. 1C) similar to the pattern observed in *T. squamosa* (*3*).

Initially, I assumed that the lines marked the boundaries of daily increments. However, it was not possible to count the number of days in a tidal cycle, because a set of lines is lost as it passes through the area of complex increments only to be replaced by a new set that is half an increment out of phase with the first. The second set of lines form the median surfaces of the complex increments of the first set, and vice versa. This results in the loss of half a day in a 2-week period. To explain this, I hypothesized that the sharp lines represent growth stoppages due to exposure at low tide. Thus, the growth increments are considered "low tide increments" with an average period of 24 hours and 50 minutes.

The tidal predictions for Empire, Oregon, for 13 June to 16 July 1970 show the mixed semidiurnal pattern of the tidal cycle (Fig. 1A). This pattern, which is particularly well developed along the Pacific Coast of North America, has two highs and two lows of unequal amplitude each day. The lows are most different during periods of spring tides. These differences are reduced and finally eliminated by the next neap tide period. At this point, two sets of low tides cross over so that the low low tides of one fortnight become the high low tides of the next.

A line drawn through the tidal cycle at the +0.6-m level shows the probable pattern of exposure experienced by the cockle during this time (Fig. 1B). During spring tides a single exposure each lunar day (24.8 hours) would produce a simple increment, and during neap tides two exposures produce a complex increment. As one set of low low tides is replaced by another during neap tides, one set of lines is replaced by another in the region of the complex lines. In both cases there is a dislocation of the phase, by about 12.4 hours or by half an increment respectively.

The date at which part of the shell was deposited can be estimated by counting the number of sets of complex lines back from the leading edge and relating this to the number of neap tide periods. This can be done easily and accurately except for a few periods during the winter months where the growth increments are so narrow that reading is difficult. A photomicrograph of part of the shell, thought to be deposited during the period 13 June to 16 July 1970, shows lines which almost exactly coincide with the predicted tidal exposures (Fig. 1C).

Clinocardium nuttalli is probably a particularly sensitive recorder of tidal exposure because it lies just below the surface of the sand. Low tide increments can also be seen in *Protothaca staminea* (Veneridae), which lives in the same area but slightly deeper in the sand. Extinction of neighboring sets of lines in the area of complex increments can be seen, but the pattern is less clearly defined than in *C. nuttalli*. Specimens of *Penitella penita* boring into nearby rock at the same tide level do not exhibit this pattern of growth.

Low tide increments were recognized only because of the peculiar nature of the mixed semidiural tides along the eastern Pacific coasts. Where diurnal or semidiurnal tides predominate alternating groups of simple and complex increments would not occur, nor would sets of lines become extinguished every 14 days. The only other place I have seen this pattern is in a photomicrograph of a thin section of *T. squamosa* (*3*). Perhaps a closer look at this animal would also reveal low tide increments.

The demonstration of low tide increments indicates that workers should be cautious about claiming daily increments in the skeletal material they are examining. Paleontologists must demonstrate that they are actually counting daily increments before they draw conclusions about the number of days in a Mesozoic month or year.

JOHN W. EVANS

Biology Department and
Marine Sciences Research Laboratory,
Memorial University of Newfoundland,
St. John's, Newfoundland, Canada

References and Notes

1. J. W. Wells, *Nature* **197**, 948 (1963); S. K. Runcorn, *Sci. Amer.* **215**, 26 (October 1966).
2. R. M. Baker, *Malacologia* **2**, 69 (1964).
3. G. Pannella and C. MacClintock, *J. Paleontol.* **42**, No. 5 (Suppl.), 64 (1968).
4. G. Pannella, *Science* **173**, 1124 (1971).
5. Supported by the National Research Council of Canada. I thank Dr. Paul P. Rudy of the Oregon Institute of Marine Biology for his hospitality and assistance and Marie LeMessurier for technical assistance and advice. Studies in Biology No. 316 from Memorial University of Newfoundland. Contribution No. 106 from the Marine Sciences Research Laboratory.

15 December 1971; revised 23 February 1972

Ergot-Induced Inhibition of Pituitary Tumor Growth in Rats

Abstract. *Daily injections of ergocornine or ergonovine, for 3 weeks, into rats carrying a prolactin- and growth hormone–secreting pituitary tumor (MtW15) induced significant regression or inhibition of tumor growth, whereas ergocryptine had no significant effect. Ergocornine caused a decrease in cells and a disappearance or pycnosis of nuclei in the tumor tissue, and a reduced concentration of prolactin in blood.*

We have observed that an ergot derivative, ergocornine, can reduce the weight of the pituitary in the normal rat and prevent estrogen from increasing size of the pituitary and secretion of prolactin (*1*). We also found that ergocornine significantly inhibited prolactin secretion by a direct action on the pituitary (*1*) and by increasing the hypothalamic content of prolactin-inhibiting factor (PIF) (*2*). Ergocornine induces regression, in rats, of mammary tumors that are induced by cacinogens (*3*) or are spontaneous (*4*). We report here that

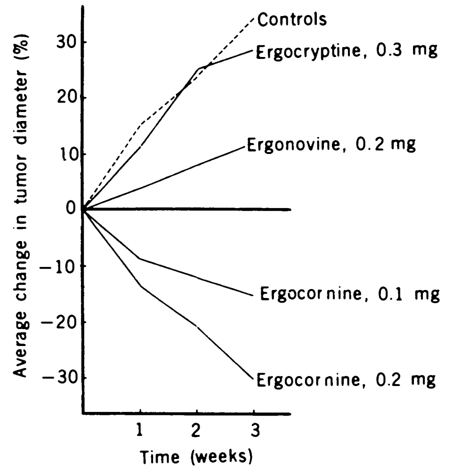

Fig. 1. Effect of three ergot drugs on the growth of a transplanted pituitary tumor (MtW15) in rats. The number of animals in each group was as follows: controls, 10; 0.3 mg of ergocryptine, 6; 0.3 mg of ergonovine, 6; 0.1 mg of ergocornine, 6; and 0.2 mg of ergocornine, 7.

ergocornine and ergonovine can inhibit growth of and prolactin secretion by a pituitary tumor (MtW15) that is known to secrete large amounts of prolactin and growth hormone.

We used two inbred female rats (Wistar-Furth) carrying the MtW15 pituitary tumor transplants (*5*). Some tumor tissue from each of the two rats was removed by sterile techniques, was minced with a small scissors in physiological saline, and was injected subcutaneously in a volume of 0.2 ml of 0.85 percent saline in the postcervical area of 50- to 55-day-old female rats of the same inbred strain. About 8 weeks later, when each pituitary tumor transplant was 1.5 to 3.0 cm in diameter, the rats were divided into five groups and were injected intraperitoneally, once daily for 3 weeks, with either (i) 0.1 mg of ergocornine; (ii) 0.2 mg of ergocornine; (iii) 0.2 mg of ergonovine; (iv) 0.3 mg of ergocryptine; or (v) the injection vehicle for the ergot drugs, 97 percent physiological saline and 3 percent ethanol (controls). Tumor diameter in each rat was measured with calipers once a week while each animal was under light ether anesthesia. Body weight was recorded weekly. At the end of the treatment period, the rats were killed and the tumors were removed; the tumors were fixed in Bouin fluid and were stained with Masson trichrome stain.

Figure 1 shows that both doses of ergocornine produced a significant regression in the average size of the MtW15 tumors, whereas in the control group the tumors continued to increase in size. By the end of the 3-week period there was a 33.6 percent gain in average diameter of the tumor in the controls, and a 14.8 and 30.6 percent loss in the average diameter of the tumor in rats injected with 0.1 and 0.2 mg of ergocornine, respectively. These differences are significant ($P < .0001$). Ergonovine significantly reduced, but did not completely inhibit, tumor growth. The dose of ergocryptine used had no significant effect on tumor growth although there was a small decrease in tumor growth during week 3. Microscopic examination revealed that the transplanted MtW15 pituitary tumors from control rats consisted of numerous cells of different size with prominent nuclei and many mitotic figures; the transplanted tumors from rats treated with ergocornine consisted of relatively few, separated, large cells with absent or pycnotic nuclei (Fig. 2). Radioimmunoassays indicated that serum prolactin was significantly reduced in the rats treated with ergocornine as compared to that in rats given the control injection (*6*). At the doses given, none of the three drugs had any significant effect on body weight, although necrosis of the tail was observed in some of the rats given the larger dose of ergocornine.

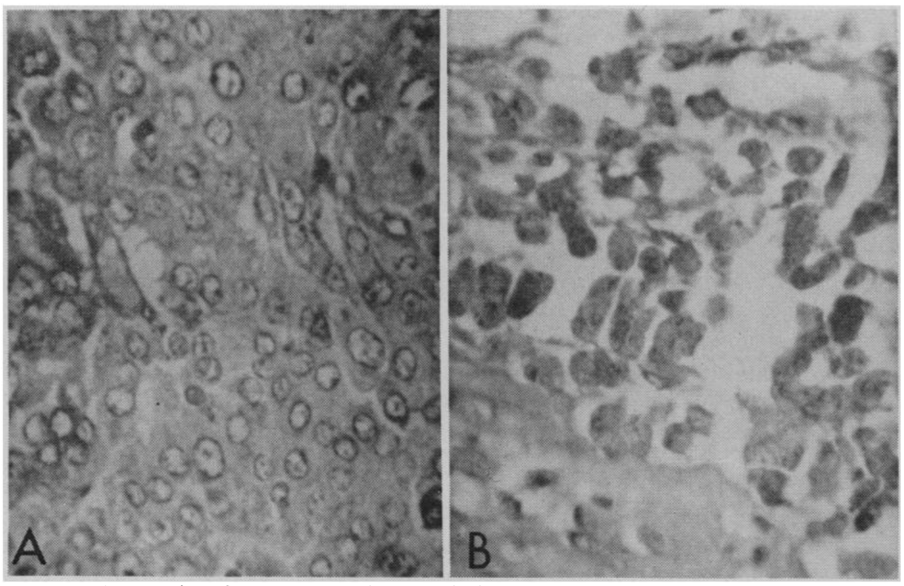

Fig. 2. (A) Section from a transplanted pituitary tumor from a control rat showing cells of diverse size with prominent nuclei and several mitotic figures. (B) Section from a transplanted pituitary tumor from a rat treated with ergocornine, showing large, separated cells with few pycnotic nuclei (× 680).

These observations indicate that ergocornine and, to a lesser extent, ergonovine can significantly inhibit growth of the MtW15 pituitary tumor. Ergocryptine was not effective at the dose used, and is less effective than ergocornine in inhibiting growth of mammary tumors (*3*). Associated with the tumor regression that was induced by ergocornine, there was a disappearance of cells, pycnosis or loss of nuclei, and a decrease in concentration of prolactin in serum. The capacity of ergocornine and ergonovine to inhibit growth of the MtW15 pituitary tumors is obviously not dependent on any direct connection to the hypothalamus, suggesting that the major action of the drugs was exerted directly on the tumor. This agrees with the observation that ergocornine can act directly to decrease the size of a normal rat pituitary gland that is grafted under the kidney capsule (*1*). Prolactin-secreting pituitary tumors have been observed in human patients (*7*), but the effect of ergot drugs on such patients has not yet been determined.

S. K. Quadri
K. H. Lu, J. Meites
Department of Physiology, Michigan State University, East Lansing 48823

References and Notes

1. K. H. Lu, Y. Koch, J. Meites, *Endocrinology* **89**, 229 (1971).
2. W. Wuttke, E. Cassell, J. Meites, *ibid.* **88**, 737 (1971).
3. E. Cassell, J. Meites, C. W. Welsch, *Cancer Res.* **31**, 1051 (1971).
4. S. K. Quadri and J. Meites, *Proc. Soc. Exp. Biol. Med.* **138**, 999 (1971).
5. The animals were provided by Dr. Jacob Furth.
6. S. K. Quadri and J. Meites, in preparation.
7. G. T. Peake, D. W. McKeel, L. Jarett, W. H. Daughaday, *J. Clin. Endocrinol.* **29**, 1383 (1969).

8. Supported in part by NIH research grants AM 07484 and CA 10771, and by a grant from Eli Lilly and Co. We thank Dr. M. Taeschler and Dr. E. Fluckiger, Sandoz Ltd., for ergocornine and ergocryptine, and Dr. J. A. Clemens, Eli Lilly and Co., for ergonovine.

30 December 1971