18. G. S. Levey, personal communication.
19. J. Fried, T. S. Santhanakrishnan, J. Himizu, C. H. Lin, S. H. Ford, B. Rubin, E. O. Griegas, *Nature* **223**, 208 (1969).
20. M. Szabo and G. Burke, *Biochim. Biophys. Acta* **284**, 208 (1972).
21. G. Burke, *Prostaglandins* **2**, 413 (1972).
22. F. Marumo and I. S. Edelman, *J. Clin. Invest.* **50**, 1613 (1971).
23. O. Hechter, in *Monographs on Endocrinology*, vol. 7, *Prostaglandins*, F. Gross, A. Labhart, T. Mann, L. T. Samuels, J. Zander, Eds. (Springer-Verlag, Berlin, 1972), pp. 83–85.
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Osteopetrosis Cured by Temporary Parabiosis

Abstract. *The excessive accumulations of spongiosa in the long bones of congenitally osteopetrotic mice permanently disappeared after a brief parabiotic union to normal littermates. Most of the bone removal was accomplished long after interruption of parabiosis. It is proposed that, during parabiosis, progenitors of competent osteolytic cells were recruited from the blood of the normal mouse.*

Signs of osteopetrosis in microphthalmic mice disappear within 6 weeks after parabiotic union is made between mutant and normal littermate (*1*). However, the parabiotic union need exist for only 2 weeks to obtain a permanent cure of the congenital bone disease.

Parabiosis was performed at 10 (six pairs) or 45 (two pairs) days of age (*2*). In each instance, the subcutaneous union was made between a mutant and normal sibling of the same sex. Two weeks after parabiosis, the animals were disjoined, and the right hind limb was amputated below the knee in order to provide a tibia for histologic examination. Two to 8 months later, when mice were 84 (six pairs) or 270 (two pairs) days of age, respectively, the animals were killed and the remaining long bones were prepared for histologic study (*3*).

At the end of the 2-week period of parabiosis, little, if any, of the excess bone had been removed from the medullary cavities of the long bones (Fig. 1, A and B). However, during the subsequent observation period when the animals were no longer united, signs of osteopetrosis vanished from the mutants (Fig. 1C). In the unoperated mutants that survived for 10 months or longer (five microphthalmic mice), spontaneous remission was never seen (Fig. 1D).

During parabiosis bone remodeling in the mutant was initiated by cells or hormones (or other factors) derived from the normal mouse. Perhaps among the mononucleated elements normally in circulation are progenitors of osteolytic cells. It seems unlikely that anything but cells could survive long after interruption of parabiosis to have accomplished the result reported here. Calcitonin and parathormone activities are elevated in the gray-lethal and microphthalmic mice (*4*). However, these endocrine effects are probably secondary to an unresponsive osseous target tissue. Primary hyperparathyroidism and hypercalcitonism in the etiology of congenital osteopetrosis in mice is not borne out by the therapeutic failure of thyroidectomy and parathyroidectomy (with L-thyroxine replacement therapy) in long-term follow-up studies (*5*).

A practical implication of the present report is that congenital osteopetrosis may be curable by an appropriate series of blood transfusions.

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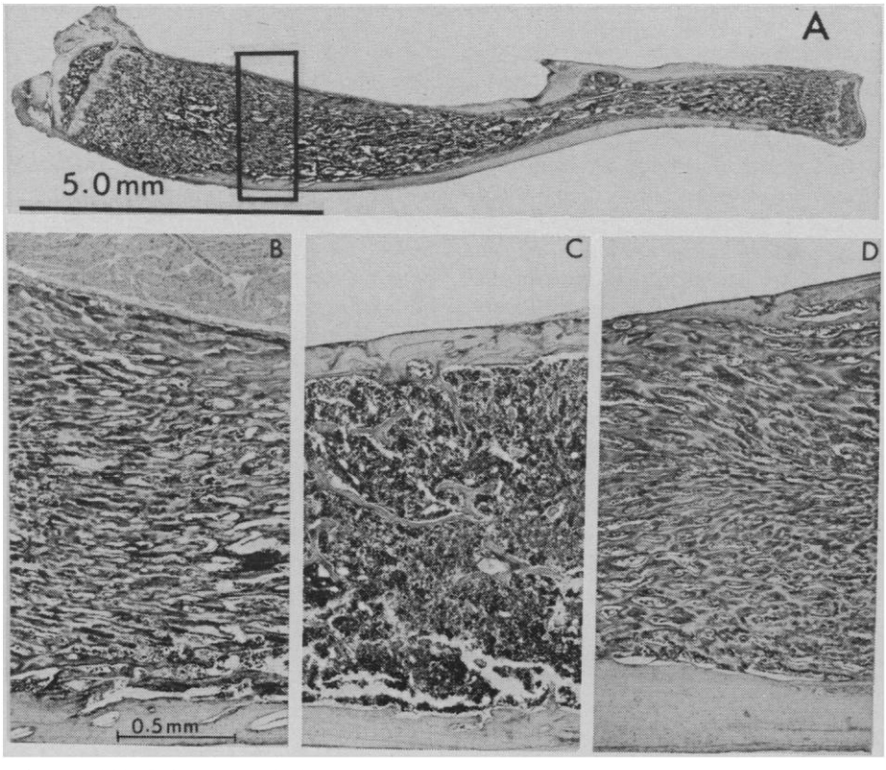

Fig. 1. (A) When parabiosis was terminated 2 weeks after onset, the amputated right tibia showed no evidence of bone remodeling. (B) Area enclosed in A is enlarged to reveal the presence of spongy bone at the interior of the shaft. (C) Eight months later the left tibia of the same mutant is of normal histologic appearance. (D) Tibia of an unoperated osteopetrotic mouse 10 months of age.

References and Notes

1. D. G. Walker, *Endocrinology* **91**, 916 (1972).
2. The mortality attending the surgical procedure was negligible provided that the animals were free of signs of intestinal and respiratory infections. The skin along the postaxillary line of incision was removed with Nair, cleansed with soap and water, and disinfected with 70 percent ethyl alcohol. The instruments and sutures were autoclaved. For the first postoperative day, the parabionts were isolated from other animals. Thereafter, each was given 1000 to 2000 units of penicillin subcutaneously, fed 0.10 to 0.20 ml of milk (Esbilac) by stomach tube, then returned to the original mother. The adequacy of lactation was assessed twice a day. If on any occasion milk was not visible in the stomach (through the transparent anterior abdominal wall) of the mutant, feeding by stomach tube was repeated, and often the original mother was replaced by a more profusely lactating foster mother. The temperature of the mouse housing was maintained at 70° to 80°C. McCollum's diet I was provided in powdered form as wet mash to cages housing mutants. When the foregoing regimen was followed strictly, the mortality of microphthalmic mice was less than 10 percent.
3. I thank C. Reather for the photomicrography, Z. Kareem for live animal photography, and S. Dobbs for the histology and animal husbandry. Supported by PHS grant AM 12491.
4. D. G. Walker, *Z. Zellforsch.* **72**, 100 (1966); *Endocrinology* **79**, 836 (1966); S. C. Marks, Jr., and D. G. Walker, *Amer. J. Anat.* **126**, 299 (1969); S. C. Marks, Jr., *J. Bone Joint Surg.* **51-A**, 875 (1969); H. M. Murphy, *Clin. Orthop. Related Res.* **65**, 97 (1971); *J. Endocrinol.* **53**, 139 (1972).
5. D. G. Walker, unpublished observations.

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