Within the uncertainty of the curves, most movement between the plates has been localized along the San Andreas fault proper for the last 6 million years. Between that time and the early Miocene, most of the plate motion was distributed between the San Andreas and San Gregorio–Hosgri fault trends. Thus the present extension of granitic basement of the Salinian block in large part is explained by right slip on faults of the Neogene San Andreas fault system, as suggested by Johnson and Normark (*34*).

S. A. GRAHAM
Exploration Department, Western Region, Chevron U.S.A. Inc., San Francisco, California 94119
W. R. DICKINSON
Department of Geology, Stanford University, Stanford, California 94305

References and Notes

1. A. K. Cooper, *U.S. Geol. Surv. Open File Rep. 1907* (1973), p. 65.
2. G. E. Weber, *Geol. Soc. Am. Abstr. Programs* **9**, 524 (1977).
3. H. G. Greene, W. H. Lee, D. S. McCulloch, E. E. Brabb, *U.S. Geol. Surv. Misc. Field Stud. Map MF-518* (1973).
4. H. C. Wagner, *U.S. Geol. Surv. Open File Rep.* (1974).
5. S. A. Graham, dissertation, Stanford University (1976), p. 510.
6. ——— and W. R. Dickinson, *Calif. Div. Mines Geol. Spec. Rep.*, in press.
7. E. A. Silver, *Geol. Soc. Am. Abstr. Programs* **9**, 500 (1977).
8. J. C. Crowell, *Geol. Soc. Am. Spec. Pap. 71* (1962), p. 61.
9. For example, see T. H. Nilsen and T. R. Simoni, Jr., *J. Res. U.S. Geol. Surv.* **1**, 439 (1973).
10. C. M. Wentworth, *Stanford Univ. Publ. Geol. Sci.* **11**, 130 (1968).
11. A. J. Galloway, *Calif. Div. Mines Geol. Bull. 202* (1977).
12. J. C. Clark, dissertation, Stanford University (1966).
13. D. C. Ross, *U.S. Geol. Surv. Prof. Pap. 698* (1972).
14. J. C. Crowell, *Geol. Soc. Am. Bull.* **68**, 993 (1957).
15. D. R. Lowe, *Proc. 24th Int. Geol. Congr.* **6**, 75 (1972).
16. J. C. Clark and E. E. Brabb, *Calif. Div. Mines Geol. Spec. Rep.*, in press.
17. E. A. Silver, *Geol. Soc. Am. Abstr. Programs* **6**, 253 (1974).
18. W. Gilbert, *Geol. Soc. Am. Bull.* **84**, 3317 (1973).
19. K. J. Hsu, *Calif. Div. Mines Geol. Spec. Rep. 35* (1969).
20. P. D. Trask, *Bull. Dep. Geol. Univ. Calif.* **13**, 133 (1926).
21. C. A. Hall, Jr., *U.S. Geol. Surv. Misc. Field Stud. Map MF-599* (1974).
22. ———, *Science* **198**, 1291 (1975).
23. E. A. Silver, J. R. Curray, A. K. Cooper, in *Geologic Guide to the Northern Coast Ranges, Point Reyes Region, California*, J. H. Lipps and E. M. Moores, Eds. (Geological Society, Sacramento, Calif., 1971), vol. 1, pp. 1–10.
24. W. R. Dickinson, D. S. Cowan, R. A. Schweickert, *Am. Assoc. Pet. Geol. Bull.* **56**, 375 (1972).
25. V. Matthews, III, *ibid.* **60**, 2128 (1976).
26. T. H. Nilsen and M. H. Link, in *Paleogene Symposium*, D. W. Weaver, G. Hornaday, A. Tipton, Eds. (Society of Economic Paleontologists and Mineralogists, Tulsa, 1975), p. 367.
27. J. Suppe, *Geol. Soc. Am. Bull.* **81**, 3253 (1970).
28. R. W. Kistler, Z. E. Peterman, D. C. Ross, D. Gottfried, *Stanford Univ. Publ. Geol. Sci.* **8**, 339 (1973).
29. For example, see S. A. Graham, *Neogene Symposium*, A. E. Fritsche, H. Ter Best, Jr., W. W. Wornardt, Eds. (Society of Economic Paleontologists and Mineralogists, Tulsa, 1976), p. 125.
30. See the dotted line in Fig. 3.
31. P. J. Coney, *Geol. Soc. Am. Spec. Pap.*, in press.
32. Modified from the curves of Dickinson *et al.* (*24*) and Nilsen and Link (*26*) in accordance with a Miocene-Pliocene boundary near 5 million years ago. For a detailed discussion see Graham (*5*).
33. T. Atwater and P. Molnar, *Stanford Univ. Publ. Geol. Sci.* **13**, 136 (1973).
34. J. D. Johnson and W. Normark, *Geology* **2**, 11 (1974).
35. Our research was supported in part by the Earth Science Section, National Science Foundation (grant DES72-01728).

23 May 1977; revised 22 August 1977

Zinc Deficiency in Murine Milk Underlies Expression of the *Lethal Milk* (*lm*) Mutation

Abstract. *The inability of nursing pups to survive on milk of mice homozygous for the recessive mutation,* lethal milk (lm), *is correlated with a reduction in zinc levels of both milk and pup carcass. Administration of zinc to pups nursing on* lmlm *dams reduces the observed mortality and morbidity. It is suggested that* lm *alters zinc transport from maternal blood to milk and that its study may provide useful information for understanding the rare human disease, acrodermatitis enteropathica.*

A recessive mutation, designated *lethal milk* (*lm*), was discovered among mice of the C57BL/6J (B/6) strain (*1*). Pups nursed on *lmlm* dams exhibit stunted growth, acute dermatitis, alopecia, and death prior to weaning. Since normal B/6 pups (*LmLm*) die when nursed on *lmlm* milk, the defect resides in the milk. Moreover, *lmlm* pups develop normally if foster-nursed on a normal dam. Genetic analyses indicate that *lm* is located on chromosome 2 and maps 9.6 centimorgans from the agouti (*a*) locus.

The effects of *lmlm* milk on newborn pups persist at all stages of lactation (*2*). We have confirmed that newborns fostered on *lmlm* dams at mid-lactation or late lactation are as severely affected as those nursed from the beginning of lactation. In addition, we have found a difference in susceptibility to the effects of *lmlm* milk with respect to the age of pups. Newborn pups are irreversibly committed to death after 3 days on *lmlm* milk, even when subsequently transferred to a normal dam. Older pups, on the other hand, having nursed on normal milk for a few days, frequently survive a 3-day period on *lmlm* milk. Nevertheless, pups of all ages display reduced weight and fur development when nursed on *lmlm* milk.

In an attempt to determine the cause of death, tissue sections from the affected pups were examined histologically. Thin sections of skin, lung, liver, stomach, bone, and muscle were prepared from 8-day-old pups nursed on *lmlm* milk. The sections were stained with hematoxylin and eosin and examined under the light microscope. Only the skin appeared abnormal, displaying focal acute dermatitis, general underdevelopment, and follicle atrophy. Furthermore, the stratum granulosum was significantly thickened and the number of hair shafts markedly reduced. All other organs appeared normal, though undersized, and no evidence of infection, allergy, or incomplete digestion of milk was observed.

Histological observations were also made of mammary glands of *lmlm* dams whose pups were close to death. In general, these glands appeared less active and smaller than those of normal B/6 mice. Moreover, we observed that *lmlm* dams frequently yield less milk.

Taken together, these symptoms are similar to those described by Mutch and Hurley (*3*) in rat pups nursed on dams receiving a postgestational zinc-free diet. This diet leads to a 50 percent decrease in the zinc content of the milk by day 18 of lactation, with only minimal effects on the other constituents. As a result, nursing pups are severely depleted of plasma zinc. Two-thirds of such animals die and all exhibit retarded growth and severe dermatitis. Moreover, total milk production was reduced by 50 percent in the zinc-deficient dams.

Because of the similarity of symptoms between the dietary-induced zinc deficiency and the *lethal milk* syndrome, we compared the concentrations of zinc in the milk of *lmlm* and normal mice. As shown in Table 1, the zinc content of the milk of mutant mice is reduced 34 percent from that of normal B/6 mice. This difference is seen throughout lactation and is reflected in the whole body zinc concentrations of 8-day-old suckling animals. However, we found no such deficiency in either the plasma of lactating *lmlm* dams or in the carcasses of adult *lmlm* females. Since adult *lmlm* females exhibit normal concentrations of total body zinc, it appears that the mutation involves reduced transport of zinc from plasma to milk. The B/6 dams maintain a zinc concentration in the milk that is ten times higher than that in the plasma,

0036-8075/78/0113-0181$00.50/0

whereas in *lmlm* animals this concentration is only three times higher. Furthermore, this mutation appears to be specific to zinc transport since the milk and plasma concentrations of another metallo-ion, copper, are within the normal range. Calcium, iron, and magnesium levels, although not shown, are also normal in *lmlm* milk.

Although the concentrations of total body zinc in pups nursed on *lmlm* dams are clearly deficient, plasma zinc levels are normal. This paradoxical result is the only feature of the *lethal milk* syndrome which we have found to differ from the symptoms seen by Mutch and Hurley (*3*) in rat pups nursed on zinc-deficient dams.

To test the hypothesis that *lmlm* milk fails to support newborn mice because of its reduced zinc content, we administered zinc glycinate, copper glycinate, or glycine to nursing pups and scored them for hair growth, development, and days of survival (*4*). The administration of zinc glycinate led to a significant improvement in pup survival (see Table 2). Seventy percent of the zinc glycinate-treated animals survived on *lmlm* milk to begin self-weaning on day 16 (*5*), and of these mice 80 percent had normal pelage. Moreover, the zinc glycinate–injected pups that did die were consistently the last to succumb and the healthiest of all animals in a litter. The zinc glycinate survivors also displayed near normal weights. This is in contrast to glycine treatment alone, which enhanced survival by 30 percent but did not correct either the fur or weight loss. Copper glycinate was completely ineffective in ameliorating the effects of *lmlm* milk.

These results suggest that the *lm* gene controls some aspect of zinc transport from maternal plasma to milk. This effect may be specific to the mammary gland because *lmlm* pups develop normally when nursed on normal milk. In addition, no effects are observed in utero and pups appear normal at birth. Lack of zinc therapy, however, leads to all of the characteristics of dietary zinc deficiency. These include extensive dermatitis and weight loss.

The *lethal milk* syndrome does not appear to alter the concentrations of any other milk constituents except zinc. We have compared the protein constituents of mutant and normal milk by both charge-separating (*6*) and size-separating electrophoresis (*7*). No differences were found with respect to kind, size, charge, or amount of milk proteins after staining with either Coomassie blue (*8*) or "Stains-all" (*9*). No differences were observed in total Lowry protein between milk of mutant and normal mice (*10*). Furthermore, *lmlm* milk appears normal with respect to fatty acids and vitamins A and D as determined by gas chromatography (*2*), and with respect to sugars and organic and amino acids as determined by gas-liquid chromatography (*2*). We found that copper, iron, magnesium, and calcium concentrations were also normal. Thus the effect of *lmlm* milk on suckling mice can be explained by a decreased concentration of zinc. It is interesting that a 34 percent reduction in a single milk component can have such

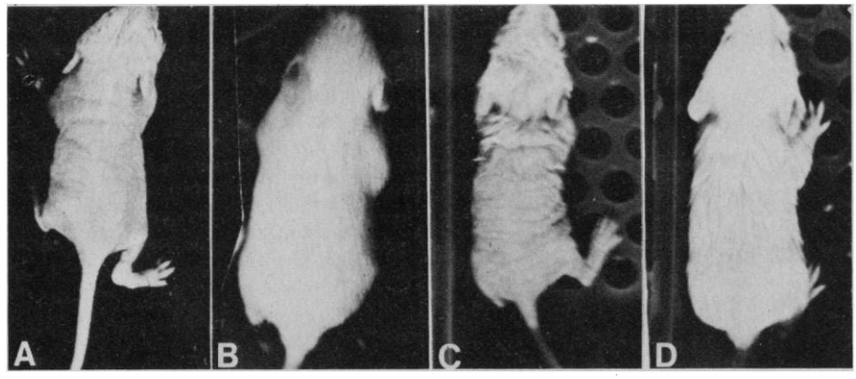

Fig. 1. Effect of zinc administration on pups nursed for 14 days by either *lmlm* or *LmLm* dams. (A) Nursed by *lmlm* dam, no treatment. (B) Nursed by *LmLm* dam, no treatment. (C) Nursed by *lmlm* dam and treated with glycine. (D) Nursed on *lmlm* dam and treated with zinc glycinate. For other experimental details see Table 2.

Table 1. Zinc and copper concentrations in mutant and normal mice. Milk was collected in vials that had been soaked in 1 percent EDTA according to the method of McBurney *et al.* (*18*). Pups were from split litters of the COX/ICR strain foster-nursed on either mutant (*lmlm*) or normal (*LmLm*) mice. Whole body values were obtained by the dry-ashing method of Menden *et al.* (*19*). All values were obtained by atomic absorption spectroscopy (*20*). Values represent the mean ± standard error of the mean. The number of samples used to obtain each value is given in parentheses.

Genotype	Zinc		Copper	
	Milk (μg/ml)	Nursed pups, whole body (μg/mg, ashed weight)	Milk (μg/ml)	Nursed pups, whole body (μg/mg, ashed weight)
LmLm	11.9 ± 1.1 (7)	770 ± 12 (5)	2.7 ± 0.5 (7)	87 ± 2 (5)
lmlm	7.9 ± 0.5* (9)	480 ± 24* (5)	1.6 ± 0.3† (9)	95 ± 5† (5)

*Significantly different from normal strain by Student's *t*-test ($P < .001$). †Not significantly different from normal strain by Student's *t*-test ($P < .5$).

Table 2. Effects of zinc and copper administration on the physical characteristics of pups nursed on *lmlm* milk and surviving to 16 days of age. Zinc glycinate, copper glycinate, or glycine were administered intraperitoneally to nursing pups on days 3, 7, and 15 postpartum. The amounts injected (4 μg of Zn^{2+} per gram of body weight, 4 μg of glycine per gram of body weight, and 0.6 μg Cu^{2+} per gram of body weight) were below known toxic levels of these compounds. Split litters of random bred COX/ICR mice were foster-nursed on both normal and mutant dams. The COX/ICR litters were large enough to provide eight pups each for B/6 and *lm/lm* dams. The pups on each dam were randomly divided into three groups receiving zinc glycinate, copper glycinate, or glycine.

Treatment of pups	Pups nursed (*N*)	Pups surviving to 16 days	Surviving pups with normal pelage (%)	Mean weight of surviving pups at 16 days (g)*
		Normal (LmLm) *dams* (N = 5)		
Zinc glycinate	10	10	100	6.5 ± 0.2
Copper glycinate	4	4	100	6.7 ± 0.2
Glycine	7	7	100	6.3 ± 0.3
Control	3	3	100	6.5 ± 0.7
		Mutant (lmlm) *dams* (N = 6)		
Zinc glycinate	20	14	79	5.7 ± 0.3
Copper glycinate	10	2	0	3.4, 3.4†
Glycine	16	5	0	4.7 ± 0.5
Control	6	2	0	3.7, 3.7†

*Mean ± standard error. †Individual values for each of two surviving pups.

deleterious effects upon suckling animals.

There are other mutations in the inbred mouse which involve metallo-ion transport. The *pallid* (*pa*) mutant involves manganese transport to the inner ear (*11*), *quaking* (*qk*) is associated with an inability to concentrate copper in the brain (*12*), and *mottled* (*mo*) produces a condition similar to the human disease, *Menke's kinky hair*, in which absorption of intestinal copper is reduced (*13*). Also, mice with *sex-linked anemia* (*sla*) exhibit a reduced ability to absorb intestinal iron (*14*). A mutation, designated *toxic milk* (*tx*), has been reported to lead to an increased accumulation of tin in the milk (*15*).

A defect in the metabolism of zinc in the milk has also been shown to underlie the inherited human disease, *acrodermatitis enteropathica* (AE) (*16*). This recessive autosomal trait, characterized by all symptoms of dietary zinc deficiency, is expressed at the onset of weaning from human milk to bovine milk or to other foodstuffs and is completely overcome by dietary zinc supplementation (*16*). Since zinc levels of bovine milk are generally higher than those of human milk, the manifestation of AE suggested to Eckhert and co-workers (*17*) that zinc of bovine milk is present in a form different from that in human milk. This suggestion was supported by their observations that most of the zinc in bovine milk was associated with high-molecular weight fractions, whereas zinc in human milk was associated with low-molecular weight fractions. Although the *lethal milk* syndrome is not identifical to AE, it may be useful for the eventual understanding of AE.

JOHN E. PILETZ
ROGER E. GANSCHOW
Institute for Developmental Research, Children's Hospital Research Foundation, Cincinnati, Ohio 45229

References and Notes

1. M. C. Green and H. O. Sweet, *Mouse News Lett.* **48**, 35 (1973).
2. M. M. Dickie, *ibid.* **41**, 30 (1969).
3. P. B. Mutch and L. S. Hurley, *J. Nutr.* **104**, 828 (1974).
4. The amounts of these compounds and the frequency of their administration were not optimized with respect to viability of *lmlm*-nursed pups, but rather were chosen to be below known toxic levels.
5. R. Rugh, *The Mouse* (Burgess, Minneapolis, 1968), p. 6.
6. M. M. Feldman and R. L. Ceriani, *Comp. Biochem. Physiol.* **37**, 421 (1970).
7. U. K. Laemmli, *Nature (London)* **227**, 680 (1970).
8. W. N. Fishbein, *Anal. Biochem.* **46**, 338 (1972).
9. M. R. Green, J. V. Pastewka, A. C. Peacock, *ibid.* **56**, 43 (1973).
10. O. H. Lowry, N. J. Rosebrough, R. J. Farr, R. J. Randall, *J. Biol. Chem.* **193**, 265 (1951).
11. L. C. Erway, A. S. Fraser, L. S. Hurley, *Genetics* **67**, 97 (1971).
12. C. L. Keen and L. S. Hurley, *Science* **193**, 244 (1976).
13. D. M. Hunt, *Nature (London)* **249**, 852 (1974); D. M. Danks, B. J. Stevens, P. E. Campbell, J. M. Gillespie, J. Walker-Smith, J. Blomfield, B. Turner, *Lancet* **1972-I**, 1100 (1972).
14. J. A. Edwards and J. E. Hoke, *Clin. Res.* **23**, 262A (1975).
15. H. Rauch, *Mouse News Lett.* **56**, 48 (1977).
16. K. H. Neldner and K. M. Hambridge, *N. Engl. J. Med.* **292**, 879 (1975).
17. C. D. Eckhert, M. V. Sloan, J. R. Duncan, L. S. Hurley, *Science* **195**, 789 (1977).
18. J. J. McBurney, H. Meier, W. G. Hoag, *J. Lab. Clin. Med.* **64**, 485 (1964).
19. E. E. Menden, D. Brockman, H. Choudhury, H. G. Petering, *Anal. Chem.*, in press.
20. W. Slavin, *Atomic Absorption Spectroscopy* (Interscience, New York, 1968), p. 65.
21. We thank M. Green and J. Womack of the Jackson Laboratory for their generous gift of the *lm* mutant stocks. We also thank H. Petering, J. Partin, J. McAdams, W. Scott, and R. Akeson for their constructive suggestions and technical assistance. This work was supported by USPHS grant AM 14770.

27 June 1977; revised 25 August 1977

Assembly of Type C Oncornaviruses: A Model

Abstract. *The salient features of this model for oncornavirus assembly are that uncleaved precursor molecules to the internal virus polypeptides possess specific recognition sites both for viral envelope constituents already inserted in the cell membrane and for the viral RNA. After orderly alignment of these components at the budding site, virus maturation proceeds through specific proteolytic cleavage of the precursor components and association of the resultant molecules into the characteristic type C virion substructures revealed by electron microscopy.*

Analysis of the composition and organization of virion structural proteins has often been useful for constructing a preliminary model for virus assembly (*1*). On the basis of the fine structure of avian and murine type C oncornaviruses, the molecular arrangement of the virion structural components in the particle, as well as the available data concerning the biosynthesis of these components, a model for the assembly of the virus can be proposed. We suggest a rela-

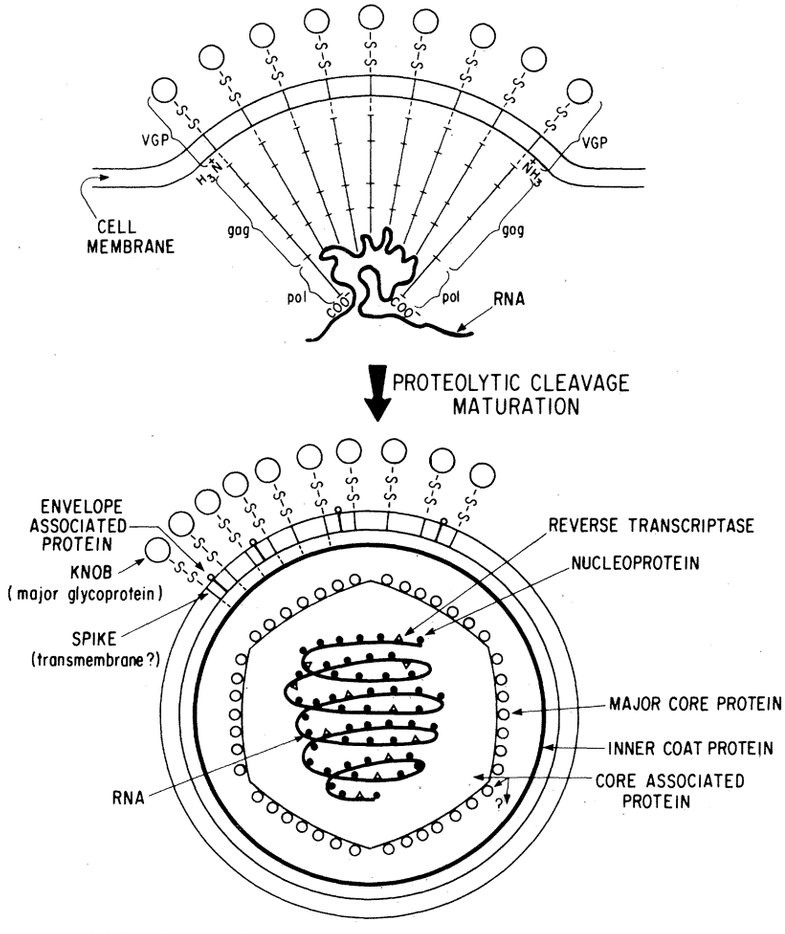

Fig. 1. A model for the assembly of type C oncornaviruses. Table 1 should be consulted for a more detailed designation of the individual murine and avian polypeptides which are indicated schematically here.

0036-8075/78/0113-0183$00.75/0