12. Y. Nakamura, G. Latham, D. Lammlein, M. Ewing, F. Dunnebier, J. Dorman, *Geophys. Res. Lett.* **1**, 137 (1974).
13. B. Goldstein, R. S. Phillips, C. T. Russell, *ibid.* **3**, 289 (1976).
14. W. T. Blackshear and J. P. Gapcynski, *J. Geophys. Res.* **82**, 1690 (1977).
15. S. K. Runcorn, *Geochim. Cosmochim. Acta* **3** (Suppl. 6), 2943 (1975).
16. D. Gubbins, *Geophys. J. R. Astron. Soc.* **47**, 19 (1976).
17. G. E. Backus, *Proc. Natl. Acad. Sci. U.S.A.* **72**, 1555 (1975).
18. J. M. Hewitt, D. P. McKenzie, N. O. Weiss, *J. Fluid Mech.* **68**, 721 (1975).
19. R. Brett, *Geochim. Cosmochim. Acta* **37**, 165 (1973).
20. S. K. Runcorn, L. M. Libby, W. F. Libby, *Nature (London)* **270**, 676 (1977).
21. R. V. Gentry, *Science* **169**, 670 (1970).
22. ——, T. A. Cahill, N. R. Fletcher, H. C. Kaufmann, L. R. Medsker, J. W. Nelson, R. G. Flocchini, *Phys. Rev. Lett.* **37**, 11 (1976); C. J. Sparks, Jr., S. Raman, H. L. Yakel, R. V. Gentry, M. O. Krause, *ibid.* **38**, 205 (1977).
23. U. von Wimmersperg and J. P. F. Sellschop, *ibid.* **38**, 886 (1977).
24. G. N. Flerov, G. M. Ter-Akopjan, A. G. Popeko, B. V. Fefilov, V. G. Subbotin, *Sov. J. Phys.* **26**, 449 (1977); I. Zvora, G. N. Flerov, B. L. Zhujkov, T. Reetz, M. P. Shalaevskj, N. K. Skobelev, *ibid.*, p. 455.
25. T. Lee, D. A. Papanastassiou, G. J. Wasserburg, *Geophys. Res. Lett.* **3**, 109 (1976).
26. S. K. Runcorn, *Geochim. Cosmochim. Acta* (Suppl. 8), **1**, 463 (1977).
27. W. M. Kaula and A. Harris, *Icarus* **24**, 516 (1975).
28. H. Mitzutani, T. Matsui, H. Takeuchi, *Moon* **4**, 476 (1972).

20 July 1977; revised 19 October 1977

Isostasy in Australia and the Evolution of the Compensation Mechanism

Abstract. *A linear transfer function analysis has been applied to gravity and topographic data from Australia to calculate the isostatic response function of Dorman and Lewis. The Australian response function is considerably different from that calculated for the United States. The differences can be explained on the basis of an apparent evolution of the isostatic compensation mechanism in which viscoelastic creep occurs in the lithosphere and relaxes the initial long-wavelength elastic stresses.*

It has been known for over a century that the measured gravitational field over mountainous regions is less than one would predict if the elevated masses simply rest upon a laterally uniform earth. Pratt (*1*) and Airy (*2*) independently proposed that low-density material buoying up the topography was responsible for the reduced attraction, and this idea is still accepted today. The adjustment of density at depth corresponding to surface elevation is called isostasy. Dorman and Lewis (*3*) undertook a systematic investigation of isostatic compensation at long length scales by calculating the linear transfer function relating the measured Bouguer anomaly to land elevation. They assumed that

$$\Delta g_B(\mathbf{r}_0) = \int_S q(|\mathbf{r}_0 - \mathbf{r}|)\, h(\mathbf{r})\, ds + n \qquad (1)$$
$$= q * h + n$$

Here $\mathbf{r}_0$ and $\mathbf{r}$ are position vectors in a standard equipotential surface (sea level), Δg_B is the Bouguer anomaly (the residual gravitational field after removal of the main field and the attraction of the elevated masses), $h(\mathbf{r})$ is the land height above sea level at $\mathbf{r}$, and q is an unknown function; n represents gravity anomalies not caused by isostatic compensation. The form of Eq. 1 is based upon the plausible assumption that the isostatic compensation of a point load would cause symmetrical density anomalies beneath it. If the isostatic gravity anomalies, $q * h$, are uncorrelated with n, we may recover the function q from measurements of Δg_B and h. This is best accomplished in the wave-number domain because, if the earth's curvature is neglected (*4*), Eq. 1 can be Fourier-transformed to give

$$\Delta G_B(\mathbf{k}) = Q(|\mathbf{k}|)\, H(\mathbf{k}) + N \qquad (2)$$

In Eq. 2 uppercase variables denote two-dimensional Fourier transforms of lowercase variables, $\mathbf{k}$ is the horizontal wave number, and Q is called the isostatic response function. Dorman and Lewis analyzed gravity and topographic data from the continental United States. They showed that the linear model is satisfactory and that nonlinear terms are not required.

We report here the results of our application of the linear transfer function analysis to measurements covering Australia. We chose Australia because the crust there is, on the average, considerably older geologically than that in the United States. We hoped to see evidence in Q that the cool thick lithosphere of the more mature Australian continent is more rigid than that of the younger United States; this difference was suggested by Molnar and Tapponnier (*5*) to explain the comparative lack of deformation of India as it pushes into Asia. The Australian Bureau of Mineral Resources gave us access to over 200,000 gravity and land elevation measurements extending over the entire Australian continent. We removed from the gravity data a background field computed from the satellite-determined (*6*) spherical harmonic representation of the earth's gravity field up to the 16th degree (Goddard Earth model 7). The masses causing this field are assumed to be too deep to be involved in isostasy. We computed the terrain correction by subtracting out the attraction of a slab with a density of 2670 kg m^{-3} and a thickness equal to the station elevation. Fraser *et al.* (*7*) showed that the errors from this approximation are quite small because of the rather subdued topography in Australia.

Figure 1 shows the response function we obtained for Australia and that of Dorman and Lewis for the United States. The uncertainty in the estimates is caused by gravity anomalies uncorrelated with topography. The two isostatic response functions evidently agree at the longest and shortest wavelengths, but in the roll-off region where wavelength (λ) = 500 km, the Australian response is consistently lower.

To understand what this difference signifies, we turn to a model of isostatic compensation. Dorman and Lewis (*8*) interpreted their response function in terms of a local linear mechanism: here a density anomaly occurs only directly beneath the elevated region with which it is associated, and the amplitude of the density anomaly is linearly proportional to the elevation. Banks *et al.* (*9*) considered this model to be untenable because density increases as well as decreases are required to fit Q for the United States. They suggested that the positive density anomalies are artifacts of the assumption of local compensation and that another model in which the density anomalies are distributed horizontally as well as vertically is more plausible. In this model, the lithosphere is represented by a thin elastic slab with internal density gradients, resting on a homogeneous fluid mantle. When a topographic load is applied, buoyancy forces from the fluid support it, but the elastic slab distributes the deflection over a wide area; this is called a regional compensation model. Applied to the Q function for the United States, this model yields values for D, the flexural rigidity of the slab, in the range 10^{21} to 10^{22} newton-m. There is a discrepancy between Walcott's (*10*) values, 3×10^{22} to 6×10^{23} newton-m, and those of Banks *et al.* (*9*) derived from an analysis of the same data. The difference is due to the use of the slab approximation in Walcott's calculation of the gravitational attraction from the deformed sheet; at all wavelengths of interest, this approximation results in a serious overestimate of D.

0036-8075/78/0217-0773$00.50/0

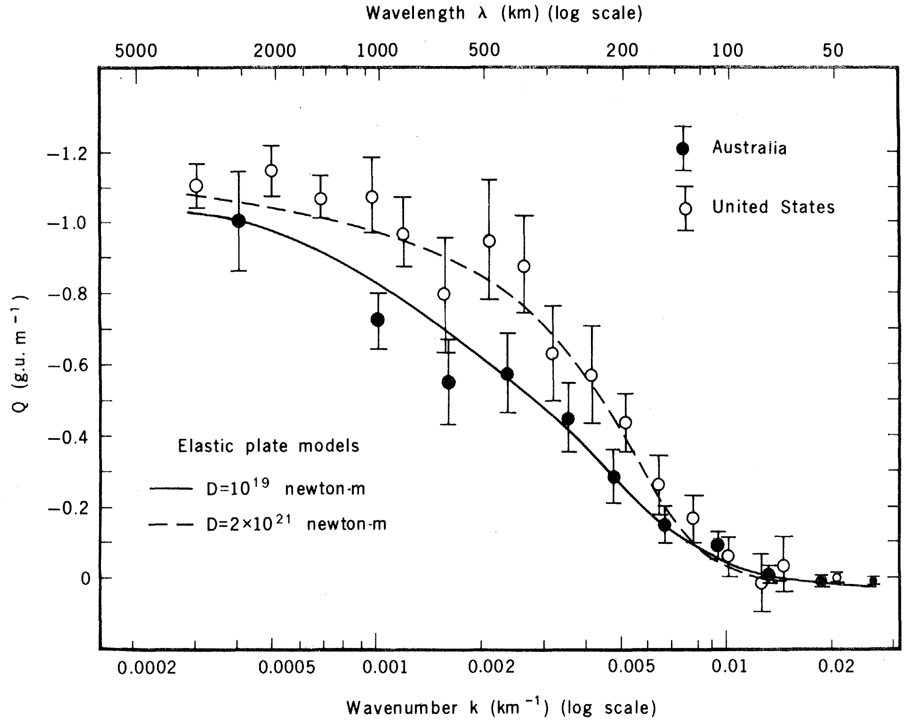

Fig. 1. A comparison of the estimated Australian and United States isostatic response functions. The function gives the isostatic Bouguer gravity anomaly arising in response to a periodic load of amplitude 1 m and wave number k. One gravity unit ($g.u.$) equals 1 μm sec^{-2} or 0.1 mgal. The two curves correspond to response functions for elastic plate models. Error bars correspond to 1 standard deviation.

Following the procedures of Banks *et al.*, we applied the regional model to the Australian data; the value of D and the density profile in the slab are treated as unknowns, but the density gradient is constrained to be positive, thus ensuring only negative density anomalies in response to topographic loads. For values of D between zero and 5×10^{20} newton-m, adequate agreement with the observed Q can be obtained (Fig. 2). The corresponding (*11*) density profiles exhibit a uniform Moho layer with a jump at 42 km; this is in fact just below the Australian Moho (*12*), so that our model automatically gives rise to a crustal thickening mechanism (similar behavior was noted by Banks *et al.* in their analysis). The fact that D may be zero and Q can still be fitted shows that the Australian data do not call for any elastic stresses at all; in this limit ($D = 0$) the model becomes one of local compensation. Although D values as large as 5×10^{21} newton-m cannot be ruled out on the basis of model misfit alone, the density profiles for $D > 5 \times 10^{20}$ newton-m are unrealistic, with the entire density gradient concentrated far below the Moho. Thus for Australia we rule out a value of D as large as that required for the United States lithosphere.

These results apparently completely contradict our expectation that older, cooler lithosphere is stronger than younger, hotter lithosphere. An explanation for this paradox is that on the long time scales considered here the lithosphere behaves viscoelastically and slowly creeps to relieve the elastic stresses. In the United States most of the topographic signature comes from the Rocky Mountains, whose age is generally put at around 50 million years (*13*). This is sufficiently recent that the initial elastic response still remains in large part. The Australian orogenies almost all occurred in the Paleozoic or earlier (*14*), and therefore sufficient time must have elapsed to allow the long-wavelength elastic stresses to disappear.

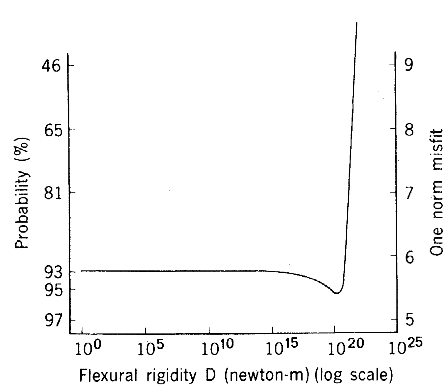

Fig. 2. Misfit of the regional compensation model as a function of flexural rigidity for the Australian isostatic response function. The scale at the left shows the probability of exceeding the indicated misfit, given a normal distribution of errors.

Suppose a load is suddenly applied to a viscoelastic sheet floating on a fluid. Initially the deflection is that of a purely elastic sheet (regional compensation as used by Banks *et al.*), but, as time goes on, the deflection becomes localized to the points immediately under the load (local compensation). Nadai (*15*) has given the solutions to the equations describing this problem; from his expressions we may derive an approximate flexural response giving the deflection at time t of the viscoelastic system in response to a periodic load of unit height with wave number k

$$\phi(k,t) = \frac{\rho}{\Delta\rho g} \times \left\{1 - \frac{4\pi^4\ell^4k^4}{1 + 4\pi^4\ell^4k^4} \exp\left[\frac{-t}{(1 + 4\pi^4\ell^4k^4)\tau}\right]\right\} \quad (3)$$

where ρ is the density of the load material, $\Delta\rho$ is the density contrast between the fluid and the load, g is the acceleration of gravity, and ℓ is equal to $(4D/\Delta\rho g)^{1/4}$, where D is the instantaneous flexural rigidity of the sheet and τ is its viscoelastic time constant. If we compare this expression with that for an elastic sheet, we can obtain an effective flexural rigidity at time τ and wave number k of

$$D_e = D \exp[-t/(1 + 4\pi^2\ell^4k^4)\tau]/\left(1 + 4\pi^4\ell^4k^4 \times \{1 - \exp[-t/(1 + 4\pi^4\ell^4k^4)\tau]\}\right) \quad (4)$$

Thus we see that, as time increases, the apparent flexural rigidity of the system at a given wave number decreases exponentially. Looking at the wavelength of maximum difference (500 km or so), we find from Eq. 4 that our hypothesis is consistent with the result of Watts and Cochran (*16*), who found a value for τ greater than 10^6 years. We definitely favor this number over Walcott's (*17*) value of 10^5 years, which is so small that it precludes any observable difference in the two response functions. To make a rough estimate of the value of τ, we take a very simple model for the most recent orogenies in the United States and Australia. We assume that, after a major episode of mountain building, the elevations of the ranges are maintained by subsequent minor rejuvenating pulses. In the United States the major event is the Eocene Laramide orogeny (*13*); in Australia it is the Tasman (*14*), which occurred in the late Permian. Thus we calculate the expected responses on the basis of approximately constant loads. Using values for D best fitting the responses of the United States and Australia in the roll-off region, we estimate that $\tau = 4.5 \times 10^7$ years, although a value as high as 10^8 years is also consistent with the range of acceptable D values. Because our data do not preclude $D = 0$ for the Australian response, we cannot produce a lower bound on the time constant.

To sharpen the estimate of τ, it is necessary to obtain more accurate response functions and to calculate them for rugged regions more homogeneous in geological age; this last requirement runs counter to the one that a relatively large area be used to gain reliable estimates at the long wavelengths. However, we plan to do this for the North American data set, separating off the Appalachian Mountains and including the Canadian Rocky Mountains. Subdivision of the Australia data set seems less promising, owing to the relatively poor signal-to-noise ratio. It is unlikely that very precise estimates of τ will be possible with this approach because the effects of orogenic history and subsequent erosion make the behavior of the topographic load a very complex function of time and space.

MARCIA K. MCNUTT
ROBERT L. PARKER
Institute of Geophysics and Planetary Physics, Scripps Institution of Oceanography, La Jolla, California 92093

References and Notes

1. J. H. Pratt, *Philos. Trans. R. Soc. London* **145**, 53 (1855).
2. G. B. Airy, *ibid*., p. 101.
3. L. M. Dorman and B. T. R. Lewis, *J. Geophys. Res.* **75**, 3357 (1970).
4. Dorman and Lewis (*3*) gave an equation in spherical harmonics that accounts for the earth's curvature. We have found that the errors in neglecting curvature are small in comparison to the noise in the estimates of Q.
5. P. Molnar and P. Tapponnier, *Science* **189**, 419 (1975).
6. C. A. Wagner, F. J. Lerch, J. E. Brownd, J. A. Richardson, *J. Geophys. Res.* **82**, 901 (1977).
7. A. R. Fraser, F. J. Moss, A. Turpie, *Geophysics* **41**, 1337 (1976).
8. B. T. R. Lewis and L. M. Dorman, *J. Geophys. Res.* **75**, 3367 (1970); L. M. Dorman and B. T. R. Lewis, *ibid.* **77**, 3068 (1972).
9. R. J. Banks, R. L. Parker, S. P. Huestis, *Geophys. J. R. Astron. Soc.* **51**, 431 (1977).
10. R. I. Walcott, *The Geophysics of the Pacific Ocean Basin and Its Margin* (American Geophysical Union, Washington, D.C., 1976), pp. 431–438.
11. Density variations below 50 km were not permitted since it is assumed that the mantle is relatively uniform in density as compared with the crust.
12. J. C. Dooley, *Bur. Miner. Resour. J. Aust. Geol. Geophys.* **1**, 291 (1976).
13. J. Gilluly, *Q. J. Geol. Soc. London* **119**, 133 (1963).
14. R. W. R. Rutland, in *Implications of Continental Drift to the Earth Sciences*, D. H. Tarling and S. K. Runcorn, Eds. (Academic Press, London, 1973), vol. 2, pp. 1011–1033.
15. A. Nadai, *Theory of Flow and Fracture of Solids* (McGraw-Hill, New York, 1963), vol. 2, pp. 283–348.
16. A. B. Watts and J. R. Cochran, *Geophys. J. R. Astron. Soc.* **38**, 119 (1974).
17. R. I. Walcott, *J. Geophys. Res.* **75**, 3941 (1970).
18. We thank the Australian Bureau of Mineral Resources; the Geology Survey of New South Wales; the Department of Mines, South Australia; the University of Tasmania; and the West Australian Petroleum Pty. Ltd. for providing the data used in this report. This work was supported under NSF grant EAR76-12588.

5 July 1977; revised 26 September 1977

L-Dopa Methyl Ester: Prolongation of Survival of Neuroblastoma-Bearing Mice After Treatment

Abstract. *L-Dopa has been shown to demonstrate enhanced toxicity toward melanoma cells in vitro. Since melanocytes arise from the neural crest embryologically, the effect of L-dopa methyl ester, a soluble analog, on the murine C1300 neuroblastoma was studied. There was significant antitumor activity against the neuroblastoma, which was enhanced by combination with a dopa decarboxylase inhibitor, Ro4-4602. In vitro studies suggested inhibition of DNA synthesis as the principal site of action. A mechanism involving sulfhydryl compound scavenging is postulated.*

L-Dopa has been shown to possess enhanced toxicity toward melanoma cells both in vitro and in vivo (*1*). Since melanocytes arise embryologically from the neural crest (*2*) and share many attributes with neural tissue, it was of interest to examine the antitumor activity against the mouse C1300 neuroblastoma model. Finkelstein *et al.* (*3*) proposed the use of this system for the evaluation of potential chemotherapeutic agents for human disease. Since the cytotoxic concentration determined from the previous study (*1*) was approximately 6.0 m*M*, we elected to study the far more soluble derivative, L-dopa methyl ester.

Table 1 shows the results of treatment of tumor-bearing mice with L-dopa methyl ester. At 600 mg/kg, the maximum tolerated dose, there was a significant therapeutic effect ($P < .01$) with a 30 percent increase in median survival. Pretreatment with the dopa decarboxylase inhibitor Ro4-4602 [N^1-(DL-seryl)-N^2-(2,3,4-trihydroxybenzylhydrazine) (*4*, *5*) resulted in an increase in the maximum tolerated dose to 1000 mg/kg and a concomitant enhancement of the therapeutic response. L-Dopa itself did not demonstrate antitumor activity, although because of its insolubility equivalent doses could not be administered to mice.

Table 2 describes the effects of L-dopa and L-dopa methyl ester on macromolecule biosynthesis in the N2A clone of neuroblastoma in vitro. A marked inhibition of thymidine incorporation was observed, with somewhat lesser effects on

Table 1. Effect of L-dopa methyl ester on survival of C1300 neuroblastoma–bearing mice. L-Dopa and Ro4-4602 were gifts from Hoffmann–LaRoche & Co., Nutley, New Jersey; L-Dopa methyl ester was obtained from Sigma Chemical Co., St. Louis, Missouri; C1300 neuroblastoma was obtained from the Jackson Laboratory, Bar Harbor, Maine. Single cell suspensions of tumor cells were prepared in saline by repeated mincing, and 1×10^6 trypan blue–excluding cells were injected intraperitoneally into male A/J mice 6 to 8 weeks of age (ten animals per group). The assay procedures are identical to standard National Cancer Institute protocols (*11*), with treatment beginning on the first day after tumor inoculation and continuing daily for 12 days. Agents were given intraperitoneally in saline. Ro4-4602 was given 1 hour before treatment.

Treatment	Dose (mg/kg)	Survival time (days)*		ILS† (%)
		Range	Median	
Control		15–18	16.5	
L-Dopa methyl ester	500	4–20	19.0	15
	600	4–29	21.5	30‡
Ro4-4602	200	14–19	15.5	−6
L-Dopa methyl ester + Ro4-4602	800+ 200	9–36	24.0	45§
	1000+ 200	12–36	33.0	100§

*Measured from the day after tumor implantation. †Increase in life-span (ILS) was calculated as $100(t/c - 1)$, where t is the median survival time of the treatment group and c is the median survival time of the control group. ‡Significant at $P < .01$. §Significant at $P < .001$.

Table 2. Effect of L-dopa methyl ester on macromolecule biosynthesis in C1300 neuroblastoma in vitro. The C1300 neuroblastoma cells were a gift from L. Green, Harvard Medical School, and are designated clone N2A. The cells were grown in McCoy's 5A medium supplemented with 15 percent fetal calf serum, penicillin (100 U/ml), and streptomycin (100 μg/ml). Cells were plated in Linbro multiwell tissue culture trays. Exponentially growing cultures were aspirated and washed, and 1 ml of serum-free medium containing 2 μCi/ml of either [^{3}H]thymidine (specific activity, 2 Ci/mmole), [5-^{3}H]uridine (specific activity, 25 Ci/mmole), or [^{3}H]leucine (specific activity, 41 Ci/mmole) (New England Nuclear Co.) and drugs was added. After 60 minutes at 37°C the medium was removed, cells were washed once with saline, and 1 ml of 10 percent trichloroacetic acid was added. The precipitate was washed three times with saline and 0.5 ml of 1*N* KOH was added. After digestion at 37°C for 4 hours, a portion was added to scintillation fluid and counted. Values are expressed as percentage inhibition compared to controls and represent means ± standard errors of the means for triplicate samples.

Concentration (m*M*)	Inhibition (%)		
	Thymidine	Uridine	Leucine
	L-Dopa		
0.5	17 ± 3	11 ± 3	9 ± 5
1.5	51 ± 5	26 ± 5	26 ± 4
3.0	79 ± 5	36 ± 7	39 ± 3
	L-Dopa methyl ester		
0.5	9 ± 5	9 ± 5	5 ± 3
1.5	88 ± 4	36 ± 6	5 ± 1
3.0	98 ± 3	37 ± 8	4 ± 1

0036-8075/78/0217-0775$00.50/0