Reprinted from
4 July 1975, Volume 189, pp. 18-21

SCIENCE

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Pathologic and experimental data suggest a model based on differential growth within the cerebral cortex.

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For centuries the convolutions (*1*) of the human brain have evoked both scientific and general interest. Biologists have extensively investigated the cerebral cortex, but remarkably little is known about the intrauterine events responsible for its convoluted form. This article is based on our observations (*2–4*) of two human congenital cerebral malformations, microgyria and lissencephaly, which manifest opposite extremes of abnormal convolutional development. Biomechanical analysis of brain development in these two conditions has led us to propose a general model of the ontogenesis of cerebral convolutions.

Normal Convolutional Development

Cerebral convolutions (*5*) appear in man in the fifth fetal month and continue their development into the first postnatal year (*6*). This period coincides with the time of maximal increase in volume of the cerebral cortex (*7*). Since cellular migration to the cortex is essentially complete by the end of the fifth fetal month (*6, 8*), this growth is the consequence of several other factors, including glial cell proliferation, growth and differentiation of individual neurons, and the influx of afferent fibers (*9*).

The first convolutions to appear, the primary ones (such as the central and calcarine fissures) and secondary ones (such as the parieto-occipital sulcus and the frontal and temporal gyri), are relatively constant in their location, configuration, and relationship to cortical architectonic fields (*10*). The tertiary convolutions, by far the most numerous, begin to develop late in the third trimester and become fully demarcated only months after birth (*6*). They appear random in their form and anatomical relationships (*11, 12*).

The earliest students of convolutional development observed that the ratio of the volume of the entire cerebral hemisphere to the surface area of the cortex changes very little throughout development; this is the so-called law of Baillarger and Dareste (*13*). Cortical folding was considered a process that served to maintain the constant ratio. This view, however, provides little insight into the origin and distribution of the physical stresses which actually cause cortical folding. Subsequent investigators (*14*) suggested that, within this framework, the location of individual convolutions depends on local changes in cortical structure, with sulci occurring in relation to boundaries between cortical architectonic fields.

Clark (*12*) presented the first analytical theory of convolutional development. He pictured the expanding cerebral hemisphere as constrained by nondeformable neighboring structures—the base of the skull and the basal ganglia below and the corpus callosum above. He suggested, accordingly, that compressive stresses are set up in the hemisphere during its expansion, and these stresses cause buckles or sulci which run parallel to the noncompressible limiting structures.

Other early investigators (*15*) proposed, however, that convolutional development is a purely intracortical process. They suggested that certain segments of the cortical surface undergo increased growth, with the resultant local bulges eventually becoming gyri. Again the analysis was entirely morphologic, and mechanical factors were not considered.

Barron (*16*), in the only experimental examination of the mechanics of cortical folding that we know of, suggested that convolutional development is, in fact, dependent wholly on events and constraints within the cortex itself. The developing cerebral cortex of sheep was surgically isolated in utero from subcortical structures at a time before the appearance of convolutions but after the completion of cellular migration. In one group of animals the "nondeformable" corpus callosum, basal ganglia, and thalamus were ablated. In another group much of the central hemisphere, including central white matter, was destroyed, markedly altering the ratio of volume to surface area. Despite these extensive ablations all animals, at term, had gyri and sulci of essentially normal size and configuration. These experiments clearly focus the analysis on intracortical events as the primary determinants of cortical folding during development.

Pathological Convolutional Development

Human brains with the malformations of convolutional development microgyria and lissencephaly (*2–4*) are remarkably abnormal in their intracortical structure. Microgyric brains (Fig. 1A) have a cortex that is markedly buckled, resulting in an increase in number and decrease in size of the gyri and sulci. Lissencephalic brains (Fig. 1B), in contrast, have a smooth surface lacking the usual secondary and tertiary gyri. Beneath the lissencephalic cortex, whose relative thickness is diminished (*4*), is a broad collection of neurons lying within the white matter of the hemispheric wall, presumably arrested there during cellular migration to the cortex.

The cellular patterns of the cortex in these two developmental malformations differ from the six-layered architecture of normal brains (Fig. 2). In microgyria most of the cells of cortical layer V (and occasionally portions of adjoining layers IV and VI) are absent (*2, 3*). In the cortex of lissencephalic brains the cells of layers II and IV are either markedly reduced in number or completely missing (*2, 4*).

The observed architectonic differences are corroborated by measurements of the total surface area, in the tangential plane, of each of the cortical layers in normal and microgyric cortex (Table 1). In normal cortex the surface area increases progressively from the innermost to the outermost cellular layer (*17*). The relative increase in area in the more superficial layers is greater than would be expected for a series

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of concentric spherical layers (*18*). Thus, in normal cortex the outer cellular layers appear to grow at a slightly faster rate than the inner layers. In microgyric cortex the surface areas of the outer cellular layers (II and III) are slightly greater than in normal cortex, implying at least normal growth of these layers. In contrast, the surface areas of the inner cellular layers (IV and V) are less than half of those in normal cortex. This reduction in surface area, and also in thickness, implies a severe retardation in the growth of the inner portion of the cortex. Thus, in both normal and microgyric cortex there appears to have been a differential in growth between the outer and inner cortical layers, which is more marked in the microgyric cortex. Qualitative observations of lissencephalic cortex suggest, on the other hand, that the growth of all cortical layers, especially II and IV, is markedly reduced without any significant differential between the inner and outer layers. These abnormalities in the intracortieal structure in both microgyria and lissencephaly—malformations which might be considered the two limiting cases of convolution formation—provide the basis for a mechanical model of normal and pathological convolutional development based on intracortical factors.

Model of Cortical Buckling

The cerebral cortex may be divided into two strata, stratum 1 consisting of the outer architectonic layers I, II, and III, and stratum 2 consisting of the inner layers IV, V, and VI. The implications of differential growth of these strata in normal, microgyric, and lisseneephalic cortex are brought out by the following model of the developing postmigratory cerebral hemisphere. Consider a sphere of radius R with two outer layers, stratum 1 and stratum 2 with thicknesses t_1 and t_2, bonded to each other and to the inner core (Fig. 3A). Differential growth leads to stresses σ_1 and σ_2 in the strata, and these are taken to be positive in compression. The greater the growth of stratum 1 relative to stratum 2, the greater is σ_1 compared to σ_2, and conversely. If the growth of each stratum is sufficiently great compared to that of the core, compressive stresses will develop in strata 1 and 2; that is, $\sigma_1 > 0$, $\sigma_2 > 0$. If the growth of each cortical stratum is less than that of the core, the stresses in the strata will be tensile; that is, $\sigma_1 < 0$, $\sigma_2 < 0$. The elastic stiffness of the strata (their resistance to incremental deformation) in the stressed state is characterized by Young's moduli E_1 and E_2 and the stiffness of the inner core by E_{core}

Table 1. Total (tangential) surface area of the cortical cellular layers in each cerebral hemisphere of a 27-week fetus with microgyria limited to one hemisphere (*24*).

Layer	Surface area (cm²)	
	Normal hemisphere	Microgyric hemisphere
I	75.8	61.8
II	77.9	86.1
III	77.6	80.2
IV	72.2	29.4
V	70.3	35.8
VI	67.5	67.8

Calculations of σ_1, σ_2, E_1, E_2, and E_{core} would require detailed knowledge of the growth process and the stress-strain properties of human fetal cerebral material, which is not available (*19*). However, by considering the likely range of the characterizing properties just defined, we have undertaken a mechanical parameter study of elastic buckling in the two-layered model. The development of the surfaee geography of the cortex is undoubtedly complicated by additional mechanieal and anatomical factors, such as the time-dependent behavior of the material, surface undulations that are present at the start of the convoluting process, and local differences in geometry and material properties within the strata. Nevertheless, the elastic model should reveal the tendency of the cortical layers to convolute or remain smooth as a consequence of the proposed differential growth delineated above.

Results of Analysis of the Model

For the normal fetal cortex shortly after completion of cellular migration we use the following estimates (*7*, figure 12): $t_1 = t_2 = 0.5$ mm and $R = 25$ mm. For stiffnesses satisfying $E_1 \approx E_2$ and the ratio E_{core}/E_1 not less than about 1/100, the buckling wavelengths are very short and the effect of the curvature of the spherical model can be neglected. With these assumptions the system can be considered as two flat plates, the cortical layers, bonded to an infinitely deep elastic foundation, the core.

A mechanical analysis (*20*) of the elastic behavior of this model under differential growth of the layers reveals that the surface will buckle if sufficient stresses σ_1 and σ_2 develop. For each set of initial parameters, there will be an entire family of possible buckling patterns. However, all such solutions will be sinusoidal in their form, similar to the surface illustrated in Fig. 3B.

If we consider a set of coordinates, x and y, on the surface, the buckling analysis produces a general expression for the incipient displacement of the surface in the radial direetion in the functional form

$$f(x,y) = \sin(2\pi x/l_x)\sin(2\pi y/l_y)$$

where l_x and l_y are the wavelengths of buckling (*21*) in the x and y directions. For each set of initial parameters, the family of possible solutions consists of the surfaces of this form for which l_x and l_y satisfy

$$\frac{1}{l_x^2} + \frac{1}{l_y^2} = \frac{1}{l^2}$$

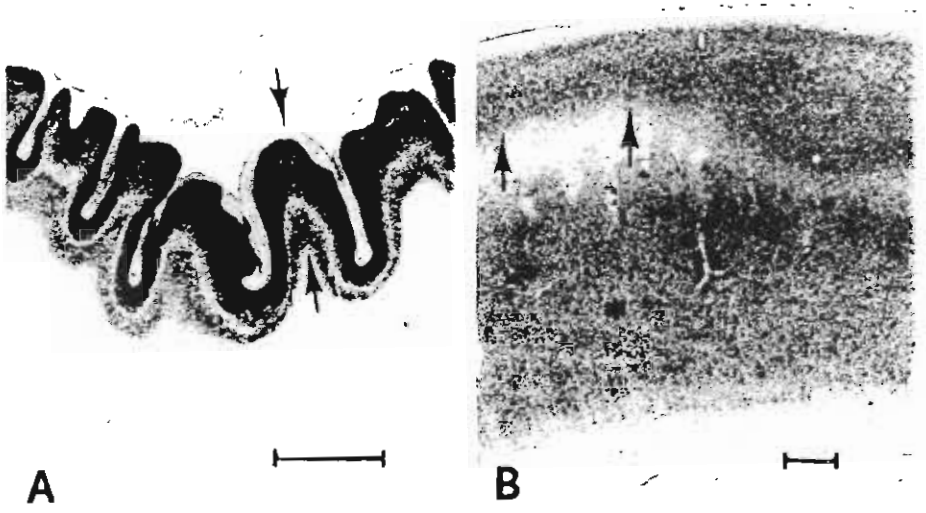

Fig. 1. (A) Microgyric cerebral cortex of a 27-week fetus. Note the markedly convoluted cortex with the intergyral wavelength approximately equal to the cortical thickness (arrows). Cresyl violet stain. Scale line, 1 mm. (B) Lissencephalic cerebral cortex in a 2-year-old child. Note the smooth cortical surface and the diminished cortical thickness (arrows). The cellular region (asterisk) deep to the cortex and involving most of the hemispheric wall is the zone of neuronal heterotopia. Cresyl violet stain. Scale line, 1 mm.

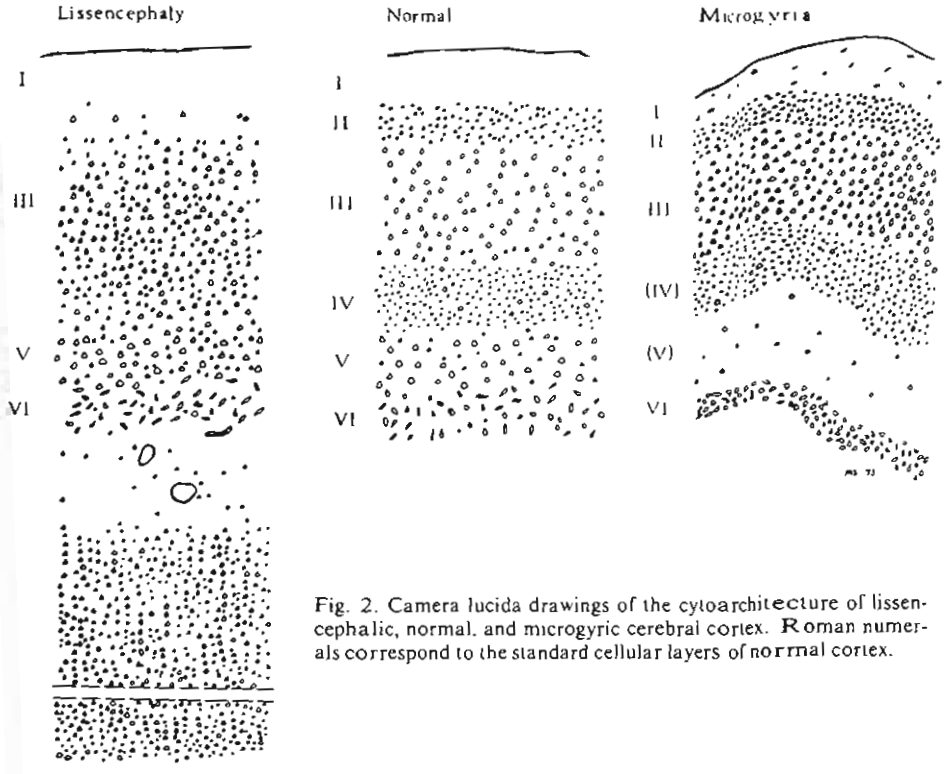

Fig. 2. Camera lucida drawings of the cytoarchitecture of lissencephalic, normal, and microgyric cerebral cortex. Roman numerals correspond to the standard cellular layers of normal cortex.

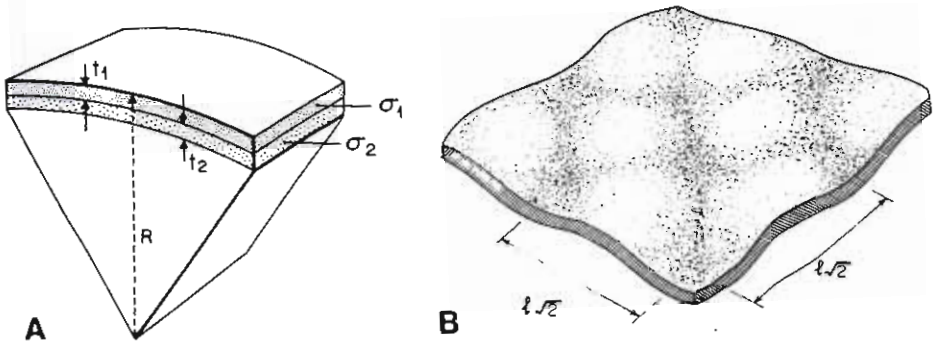

Fig. 3. (A) Proposed two-layered spherical model in the initial state before buckling. (Symbols are defined in the text.) (B) Illustration of a segment of the buckled surface predicted by the mechanical analysis of the model in (A). The surface shown here, with the wavelength of buckling ($l\sqrt{2}$) equal in both the x- and y-directions, is only one of an entire set of possible solutions.

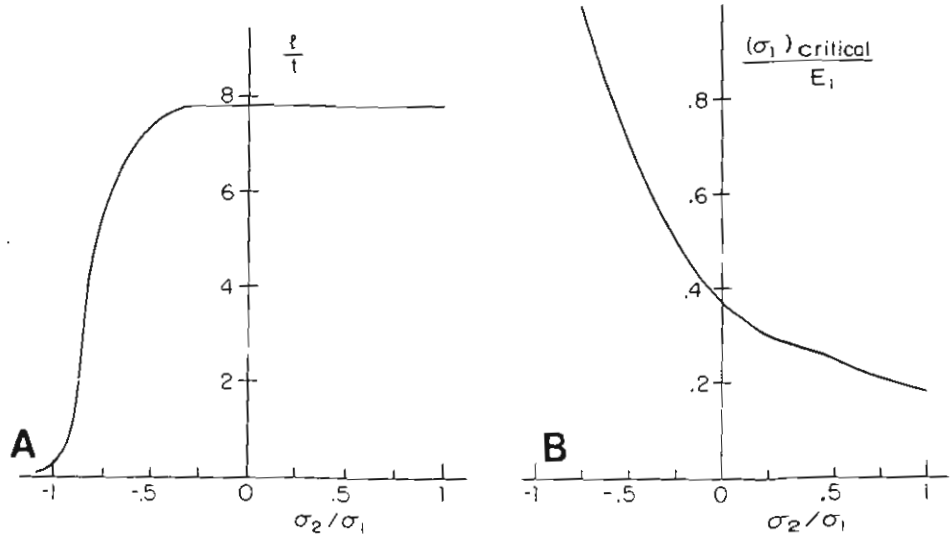

Fig. 4. (A) Plot of l/t as a function of σ_2/σ_1, for the choices $E_1 = E_2$ and $E_{core}/E_1 = 1/10$ (symbols are defined in the text). Note that for $\sigma_2/\sigma_1 > 0$, $l/t = 8$. Also as σ_2/σ_1 becomes progressively more negative, l/t diminishes markedly. (B) The critical stress in stratum 1 required for buckling, normalized by E_1, is plotted as a function of the stress ratio σ_2/σ_1.

where l can be computed for any set of mechanical parameters: E_1, E_2, E_{core}, σ_1, σ_2, and t, where $t \equiv t_1 + t_2$. The symmetrical solution—that is, the one for which the wavelength in the x-direction is equal to the wavelength in the y-direction ($l_x = l_y = l\sqrt{2}$)—is shown in Fig. 3B. We may view l as the minimum possible wavelength for any set of initial parameters. Figure 4A shows the computed values of l, expressed as l/t, as a function of the stress ratio σ_2/σ_1, for the choices $E_1 = E_2$ and $E_{core}/E_1 = 1/10$. Note than l/t is constant over a wide range of values of σ_2/σ_1. The material was taken to be elastically incompressible, an assumption which has little effect on the prediction. Decreasing the ratio E_{core}/E_1 by a factor of 10 was found to increase l by only a factor of approximately 2.

A number of observations may be made from these results of the mechanical analysis of the model. The anatomical findings discussed above suggest that during normal development stratum 1 grows somewhat more than stratum 2 and the growth of both strata is held back by the slower growth of the core. In this situation, $\sigma_1 > \sigma_2 > 0$. Thus (from Fig. 4A) for $E_{core}/E_1 = 1/10$, $l/t \approx 8$. In the normal fetus during convolutional development, $t \approx 1.0$ mm, and hence $l \approx 8t \approx 8$ mm. This predicted value of l is in reasonable agreement with measurements of the normal "incipient" intersulcal distance at the end of the seventh gestational month: 8.5 mm in the normal hemisphere of our 27-week specimen and 7.5 mm in a specimen illustrated in Sidman and Rakic (*6*, figure 10C).

In the microgyric brain the thickness of the abnormal inner cortical stratum, t_2, is less than t_1. Provided other factors remain unchanged, if the inner stratum were absent altogether, the wavelengths would be reduced by one-half (*22*). If the growth of stratum 2, relative to stratum 1, is sufficiently reduced to result in the development of a tensile stress in stratum 2—that is, $\sigma_2 < 0$ and $\sigma_2/\sigma_1 < 0$—then, as can be seen in Fig. 4A, the wavelengths will be further reduced. At a sufficiently negative value of σ_2/σ_1, $l/t \approx 1$. Hence, the model predicts that the wavelengths in microgyria may be reduced to a value approximately equal to the cortical thickness, t (*23*), a finding in agreement with histologic observation in our case (see Fig. 1A).

In the lissencephalic brain a large number of the cellular elements normally destined for the cortex have been arrested within the core. Since they grow and differentiate in their heterotopic location, we assume that the relative growth of the cortex is less than normal while the relative growth of the core is greater than normal. Hence the compressive stresses σ_1 and σ_2 are probably less than in normal brains. As can be seen from Fig. 4B, in order for buckling (at any wavelength) to occur, the compressive stress σ_1 in the outer layer must exceed a critical value. It is likely that stress sufficient to exceed the critical value never develops in the abnormal lisseneephalic cortex, and consequently its surface remains smooth.

Implications of the Model

The mechanical model presented above, which is based on the differential growth between the outer and inner portions of the cerebral cortex, yields theoretical results that are in reasonable agreement with the actual wavelengths of the incipient gyri and sulci in normal, microgyric, and lissencephalic fetuses. The major prediction is that, for a wide range of possible growth ratios, the intergyral wavelength will be eight times the cortical thickness. If, however, the growth of the inner cortical layers is interrupted, the wavelength may fall markedly. Also, if the growth of the cortex is sufficiently reduced relative to that of the entire hemisphere, no buckling will occur. The agreement of these predictions with anatomical and pathological observations implies that differential growth within the cortex itself can reasonably be considered a major determinant of convolution formation.

The model predicts that lines of buckling may occur anywhere on the cortical surface, a result in accord with the apparently random pattern of distribution of the numerous tertiary gyri. However, in this analysis we have not considered the factors that result in the relatively constant configuration and position of the primary and secondary convolutions. Perhaps stresses on the enlarging cerebrum from external constraints (*12*) or those focused at the boundaries between architectonic fields (*14*) are more significant in the development of these convolutions than the random stresses considered in the model.

Future measurements of cortical thickness, incipient buckling wavelength, and the relative values of the Young's moduli for the cortex and central white matter in normal and pathological fetal material should provide better tests of the validity of the model. Experimental studies involving, for example, the effect of intrauterine destruction of precise portions of the developing hemisphere on convolution formation will also be of interest. Such additional data, while making it possible to evaluate the present model, may provide new insights into the development of brain convolutions and, perhaps, into the more general question of the role of mechanical factors in the ontogenesis of biological form.

Summary

Our observations of the pathology of human cerebral malformations are consistent with previous experimental findings, which suggest that the forces responsible for cerebral convolutional development are predominantly intracortical. The morphological features of the cortex of the overly convoluted microgyric brain and the poorly convoluted lissencephalic brain suggest various degrees of abnormal growth of the inner and outer cortical layers in these two malformations. These observations provide the basis for a general mechanical model of convolutional development. The model is an elastic sphere consisting of two superficial layers bonded to an inner core. A mechanical parameter study of various growth behaviors of the two superficial (cortical) layers predicts sinusoidal buckling of the surface in the normal and microgyric cases but the absence of buckling in lissencephaly. The predicted minimum incipient buckling wavelengths (intergyral distances)—eight times the cortical thickness in normal brains and equal to the cortical thickness in microgyric brains—are in reasonable agreement with those observed in fetal brains.

References and Notes

1. These undulations, referred to as convolutions, consist of outward bulges called gyri and infoldings called sulci. Convolutions are present in the brains of other large mammals as well
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7. A 400-fold increase in the volume of the "neopallium" from 13½ weeks to term is observed by G. B. Jenkins [*Contrib. Embryol.* 13 (No. 59), 41 (1921)].
8. See figure 3 in R. L. Sidman and P. Rakic, *Brain Res* 62, 1 (1973); P. Rakic, *Science* **183**, 425 (1974).
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10. Architectonic fields are segments of the cortex with a more or less distinctive and homogeneous cellular arrangement.
11. G. E. Smith, *J. Anat.* **41**, 237 (1907).
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17. This is true only for layers II to VI. The surface area of layer I in normal, but particularly in microgyric cortex is less than expected. Histologic study suggests that this is due to the apposition, and perhaps fusion, of the pial surfaces of adjacent segments of layer I within the depths of sulci.
18. For a sphere, the area of the surface is $A = 4\pi r^2$, where r is the radius. The predicted ratio of A_0, the area of the outer cellular layer (layer II), to A_i, the area of the inner cellular layer (layer VI), for perfectly spherical layers, with cortical thickness t, is

$$\frac{A_o}{A_i} = \frac{4\pi R^2}{4\pi(R-t)^2} \cong \frac{R}{R-2t}$$

since $t \ll R$. The radius of curvature R of the normal hemisphere in this 27-week fetus is 84 mm, and the cortical thickness, t, is approximately 1.7 mm. The predicted ratio is therefore

$$\frac{A_o}{A_i} \approx \frac{R}{R-2t} = \frac{84\text{ mm}}{80.6\text{ mm}} = 1.04$$

The measured ratio A_o/A_i in our specimen is 77.9 mm/67.5 mm = 1.16. Hence the observed ratio is greater than that predicted for concentric spheres.
19. Although data related to the biomechanical properties of human fetal brain are unavailable, it is likely that E_{core} is small compared to E_1 and E_2. Our own observations of fresh autopsy material suggest that the subcortical region (core) has less stiffness than the cortex (strata). Histological studies demonstrate that the core is made up of unmyelinated fibers. The strata, in contrast, are composed predominantly of cell bodies, which are likely more elastic. The viscoelastic properties of the adult brain have been studied by G. T. Fallenstein, V. D. Hulce, and J. W. Melvin [*ASME (Am. Soc. Mech. Eng.) Pap. No. 69-BHF-6* (1969)]; J. E. Gaiford and J. H. McElhaney [*ibid., No. 69-BHF-7* (1969)]; L. Z. Shuck, R. R. Haynes, and J. L. Fogle [*ibid., No. 70-BHF-12* (1970)]; and A. Schettini and E. K. Walsh [*Am. J. Physiol.* **225**, 513 (1973)]. S. M. Estes and J. H. McElhaney [*ASME (Am. Soc. Mech. Eng.) Pap. No. 70-BHF-13* (1970)] did measure the stress-strain relationships in myelinated white matter in the brains of elderly human adults. Estimates of Young's modulus from their data range from 2 to 7 pounds per square inch, with loads of 1 to 10 pounds per square inch. However, the material studied was fully myelinated and the range of loads at which testing was carried out is orders of magnitude greater than the stresses proposed in the present investigation.
20. J. W. Hutchinson, unpublished data.
21. Wavelength here is equivalent to the intersulcal or intergyral distance.
22. By definition $t \equiv t_1 + t_2$. In the normal brain we are assuming $t_1 = t_2$. If in the microgyric brain t_2 were to become 0, then t would be reduced by one-half. Since $l = 8t$, l would also be reduced by one-half.
23. If $l/t = 1$, then $l = t$.
24. The distribution of the microgyria has been previously reported (*3*). The normal hemisphere is indistinguishable from that of an age-matched control. The surface area of each layer was obtained by measuring its length in horizontal histological sections with a Dietzgen map measure and integrating these values over the axis perpendicular to the plane of sectioning. The specimen was available in 1080 serial sections, and the lengths of the layers were measured in 25 representative sections.
25. The authors are grateful to P. Rakic, N. Geschwind, T. McMahon, and R. Sidman for helpful suggestions and criticism.