The data of the table indicate that as the percentage of agar in the gelatine is increased the mixture swells more in distilled water and less in acid or alkali, thus approaching the behavior of pure agar. Concerning the relative effects of acid and alkali, assured conclusions are not now possible but the data suggest that acid tends to increase imbibition at the ends of the series, that is as pure agar and pure gelatine are approached, while alkali tends to increase it in the middle mixtures containing the two colloids in more nearly equal proportions. D. T. MacDougal

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THE THEORY OF AUTONOMOUS FOLDING IN EMBRYOGENESIS[1]

The experiments of Roux,[2] carried out on the embryonic chick, prove conclusively that the folding of a neural plate into a neural tube is not dependent, as His[3] had supposed, on the mechanical effect of one tissue upon another, but is autonomous. Self-differentiation in this instance is identical with self-folding. The question therefore arises: How can the neural plate fold itself?

Our reply must necessarily bear on all cases of autonomous folding, and reciprocally any one of them might serve as the basis for this analysis. The nervous system, however, is by far the largest, most easily studied, and, in addition, the most familiar of all the embryonic tissues in which self-folding occurs. Moreover, in its simpler forms, it indicates so clearly the direction in which an explanation of its autonomous transformations is to be sought, that for the present it seems best to limit the discussion to what may be justified as a type case.

For our immediate purposes, the neural plate of *Cryptobranchus allegheniensis* is especially suitable. Not only is it unusually large, as neural plates go, but wherever cell-boundaries are distinct, it is, without question, unicellular in thickness. The first problem to be solved is the rôle of cell-multiplication.

In a neural plate in which the cells are irregular in position and dovetailed into one another as they are in crowded columnar epithelia, inequalities in the rate of division and protoplasmic synthesis at or near the two surfaces might lead to folding, but in the *Cryptobranchus* embryo, in which the plate is partly syncytial and in which the visible cell-walls are continuous from one surface to the other, and remain so during the entire period of folding, it is difficult to conceive how cell-multiplication could result in anything except uniform enlargement. The exclusion of this factor from participation in the process of involution, however, does not depend on mere argumentation, for comparison of the number of nuclei in comparable regions of the flat, half-folded, and completely folded plate, shows that the number of cells per section actually does not increase[4] (Table I.). Indeed in less simple material, such as the neural plate of the mammal, in which the number of cells does increase during folding, the restriction of the mitoses to the concave surface must, if effective at all, exert a force opposed to the forces that bring about the curvature. In this instance,

TABLE I

Number of Nuclei in Comparable Sections

Stage I, Flat	Stage II, Half-folded	Stage III, Folded
63	56	55
53	64	60
58	50	73
69	56	47
72	50	69
58	82	59
59	70	64
58	74	51
58	58	52
68	51	55
Ave. 62	61	59

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[1] Read at the joint meeting of the American Society of Zoologists and Section F of the American Association for the Advancement of Science, in Columbus, December, 1915.

[2] "Die Entwicklungsmechanik," W. Engelmann, Heft 1, Leipzig, 1905.

[3] "Unsere Körperform, und das Physiologische Problem Ihrer Entstehung," F. C. W. Vogel, Leipzig, 1874.

[4] For the validity of these comparisons see Glaser, *Anatomical Record,* Vol. 8, pp. 528–530.

therefore, a neural plate folds *in spite of* an increase in the number of its constituent cells.

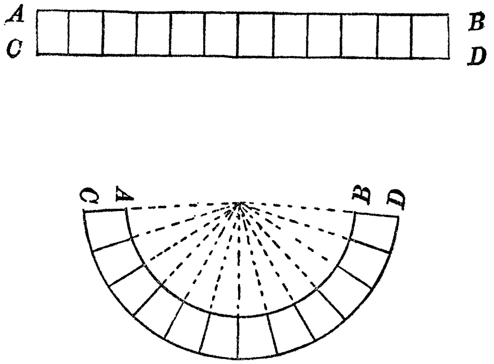

FIG. 1. Diagrammatic representation of a neural plate *A B C D*, conceived of, for the sake of simplicity, as entirely flat and made up of one layer of rectangular cells. The lower half of the figure shows the same plate symmetrically folded, its upper and under sides having become the outlines of two concentric circles. With the cells constant in number and position, the line *A B* is now necessarily shorter than the line *C D*.

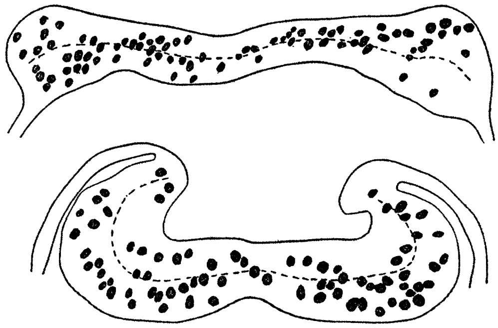

FIG. 2. Two sections through the embryonic nervous system of *Cryptobranchus allegheniensis*, showing the nuclear distribution in Stages I. and II. The sections are from the same series and regions as those dealt with in the tables but contain for Stage I., six, and for Stage II., one nucleus more than the maximal number recorded in Table I. In the unfolded plate there are in the present case, 78 nuclei, of which 47 are in the upper half above the dotted line, and 31 in the lower; in the half-folded plate, there are 75 nuclei, 21 in the upper zone, and 54 in the lower. Nuclei which happen to fall on the line separating the two zones are ascribed to the one into which the greater portion of their mass projects.

The only remaining way in which a neural plate can fold itself is by a rearrangement of materials present at the beginning. In this connection the most patent fact, emphasized long ago by Rhumbler[5] and Conklin[6] in their studies of invaginate gastrulation, is a change in the shape of the cells whose sectional outlines alter from the rectangular form to that of a trapezium (Fig. 1). This geometrical transformation, which might be forced upon the cells from without, necessarily has the same result when autonomously produced, for it involves lengthening of one surface, shortening of the other, and a redistribution of the cell-contents. The extent of the latter, as indicated by the migration of nuclei from the side becoming concave to that becoming convex, is clearly shown for two sections in Fig. 2, and for a series, in Table II.

TABLE II

Distribution of Nuclei in Upper and Lower and Inner and Outer Zones

Stage I, Flat		Stage II, Half-folded		Stage III, Folded	
Upper	Lower	Upper	Lower	Inner	Outer
32	31	31	25	15	40
32	21	22	42	15	45
34	24	16	34	21	52
55	14	27	29	13	34
39	33	18	32	22	47
38	20	27	55	16	43
31	28	33	37	26	38
33	25	29	45	13	38
37	21	21	37	20	32
44	24	19	32	20	35
Ave. 38	24	24	37	18	39

According to this, the distribution of the nuclei is not only completely reversed during folding, but the final relation between the number in what become the inner and outer zones, respectively, of the definitive tube, is as 2 to 1. Provided only that the nervous system is, by its structure and relations, incapable of indefinite expansion, these changes are all that are required to bring about the folding.

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[5] "Zur Mechanik des Gastrulationsvorganges," *Arch. f. Entwicklungsmech.*, Bd. 14.

[6] "Mosaic Development in Ascidian Eggs," *Jour. Exp. Zool.*, Vol. 2, p. 163.

In my attempt to gain some insight into the manner in which these changes might be effected in the absence of coercion from without, I determined, at constant magnification, the areas of comparable sections during the process of involution. The marked relative increases shown in Table III. were found.[7]

TABLE III

Relative Areas of Comparable Sections

Stage I, Flat	Stage II, Half-folded	Stage III, Folded
9.4 cm.^{2}	13.7 cm.^{2}	17.5 cm.^{2}
8.1	11.3	19.5
10.6	11.4	19.5
9.9	10.1	20.6
9.1	10.1	20.5
9.6	10.9	18.1
9.1	11.5	19.0
8.2	12.0	18.5
8.3	10.2	18.9
9.9	10.1	18.8
Ave. 9.2	11.1	19.1

This increase in area indicates growth in volume, and can be the result only of enlargement on the part of the individual cells constituting the nervous system. The immediate problem is obvious.

In Table IV. are given the water-content as well as the distribution of water in the larvæ of *Rana pipiens* and *Amblystoma punctatum,* four to five days after fertilization.

Since the period of differentiation under discussion has been completed at the stage of development considered in the table, and since this differentiation includes folding, and folding is associated with enlargement, it follows that the differential absorption of water by the nervous system probably took place during the process of involution. As the results show, the water-content rises to a point practically identical with the figure 80.5 per cent. given by Donaldson for the cord of the adult *R. pipiens.*[8]

TABLE IV

Water Content and Distribution of Water in Embryos of Rana pipiens and Amblystoma punctatum Four to Five Days after Fertilization

Material	Fresh Weight, Grams	Dry Weight, Grams	Dry Substance, Per Cent.	Water, Per Cent.
R. pipiens:				
38 larvæ	0.1278	0.0557	43.6	56.4
50 larvæ	0.1718	0.0722	42.0	58.0
39 larvæ	0.1815	0.0730	40.2	59.8
41 larvæ	0.1788	0.0733	41.0	59.0
Average			**41.7**	**58.3**
24 yolk-sacs	0.0440	0.0204	46.5	53.5
31 yolk-sacs	0.0585	0.0264	45.1	54.9
Average			**45.8**	**54.2**
24 nervous systems	0.0464	0.0098	21.1	78.9
31 nervous systems	0.0714	0.0149	20.9	79.1
50 nervous systems	0.0916	0.0185	20.2	79.8
Average			**20.7**	**79.2**
A. punctatum:				
16 larvæ	0.0955	0.0399	41.8	58.2
15 larvæ	0.0992	0.0406	40.9	59.1
Average			**41.4**	**58.6**
125 nervous systems	0.3914	0.0785	19.9	80.1
52 nervous systems	0.1756	0.0400	22.8	77.2
15 nervous systems	0.0524	0.0106	20.2	79.8
69 nervous systems	0.2039	0.0363	17.8	82.2
Average			**20.2**	**79.8**

But this absorption of water can only account for the enlargement of the nervous system, not at all for its folding.

To explain this in complete harmony with all the known facts, only one assumption is necessary. The neural plate is exposed to an external environment, whose constancy, within the limits under which normal development takes place at all, is very high. Laterally each cell of the plate is bounded by a chemical system fundamentally like itself. Disturbances of equilibrium on any one of these surfaces are relatively unlikely. However, on its under side, the plate is subjected to a constant change of conditions due to the multitude of processes going on within the rest of the embryo. To mention only one factor, there is a distinct increase in the acidity of the internal medium.

On this basis we may interpret the absorp-

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[7] For details concerning the distribution of this increase within the sections themselves, see Glaser, *loc. cit.*, pp. 530–533.

[8] Donaldson, Henry H., "Further Observations on the Nervous System of the American Leopard Frog, etc.," *Jour. Comp. Neurol.*, Vol. 20. Also earlier papers.

tion of water as the result of a change in those surfaces of the absorbent cells which are exposed to the inconstant intra-embryonic environment. If this change involves a weakening of the face of the neural plate that becomes convex, the curvature that leads to the formation of a tube would be accounted for.[9]

Accordingly then, the absorption of water is not the cause of folding, but a symptom of that cause. If this interpretation is correct, the water content of the cells at any given level in the early stages of involution can not be uniform. In fact the theory demands that the marginal cells of the neural plate, the first, it will be recalled, to undergo a change of shape, shall have a higher water-content than the cells in the middle of the plate which only assume the wedge-shape during the last stages of involution.

For the decision of this crucial question, no direct method is as yet available. However, it is possible to secure evidence indirectly which seems to me convincing.

If the eggs of the starfish are placed in hypotonic sea-water, and given an opportunity to absorb more water than they normally contain, they at once increase in volume, and their nuclei, easy to deal with on account of their spherical shape, also enlarge. The facts on which this statement is based are given in Table V.

TABLE V

Asterias Eggs in Various Concentrations of Sea-water

No. of Eggs	Conc. Sea Water	Conc. Dist. Water	Diam. Eggs	Diam. Nuclei
18	100%	0%	142μ	.68μ
	66	34	170	.82
23	100	0	138	.66
	75	25	144	.70
47	100	0	152	.66
	60	40	188	.82
49	100	0	154	.66
	60	40	170	.80

Before applying this information to the problem in hand, I had first of all to determine whether these facts held for the nervous system, and especially whether measurable differences could be demonstrated in those regions known to have contained during life, different proportions of water.[10]

TABLE VI

Relative Water Contents of Embryonic Cords and Brains

	Embryonic Cords		Embryonic Brains
Amblystoma	125	>	125 by 2.2 per cent.
Rana	139	>	135 by 1.9 per cent.
Rana	192	>	188 by 2.3 per cent.

Relative Sizes of Nuclei

Nervous System of *Cryptobranchus Embryos*

Stage I			Stage II			Stage III		
Cord	Brain	Ratio	Cord	Brain	Ratio	Cord	Brain	Ratio
109	109	1:1.2	126	114	1:1.1	125	113	1:1.3
119	114	1:1.2	107	108	1:1.1	143	123	1:1.2
120	125	1:1.1	127	129	1:1.2	133	113	1:1.3
121	119	1:1.1				115	131	1:1.3

Control 36-hour Chick

End of Cord	Forebrain	Ratio
110	124	1:1.4

Relative Sizes of Nuclei in Center and at Edges of Neural Plate in Cryptobranchus during Folding

Number and Positions of Nuclei

Central	Lateral	Ratio
110	115	1:1.2
112	120	1:1.2
112	111	1:1.1
135	122	1:1.2

In both *Amblystoma punctatum* and *Rana pipiens* (Table VI.), a comparison of the anterior and posterior ends of the embryonic nervous systems, indicates a higher water-content in the larval brain than in the cord. Since these results are consistent, and, in sense, agree with corresponding differences found by Donaldson (*loc. cit.*) for the adult nervous system of *Rana pipiens,* I feel fairly certain of the essential correctness of my values, and

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[9] For the relation between this view and the Rhumbler Surface-Tension Hypothesis, as well as for a criticism of the latter, see Glaser, *loc. cit.*, pp. 536–548.

[10] That the embryonic brain has a higher water content than the cord is indicated by the figures which I published in Science, N. S., Vol. XXXIX., pp. 730–731, in 1914. The evidence there presented was meager and, unfortunately, I overlooked some arithmetical errors. Recalculation has made no essential difference in the results, however, and further evidence now shows them to have been essentially correct.

infer, therefore, that the embryonic brain, like that of the adult, also has a water-content higher than that of the cord at the same age.

If this is indeed correct, and, moreover, if nuclear volume varies with the water-content of the cell, and, furthermore, if fixation does not destroy or completely reverse the volumetric relations, one would expect the nuclei in the anterior end of an embryonic nervous system to be larger than those in the posterior.

In *Cryptobranchus* embryos such comparisons are easily made. The nuclei are large so that errors, inevitably committed in determining their volumes, are relatively small. Certain precautions however are essential. Thus nuclei in various stages of mitosis must obviously be excluded. Also, since the resting nucleus is ovoid in shape, it is necessary to consider only those similarly oriented with reference to the plane of section. Absolute volumes are, of course, not practicable, nor are they requisite. All that the theory demands is that the average size of the nuclear sections in the regions which had the higher water-content shall be greater than those in the regions in which the water-content was lower. Tracings of some 2,800 nuclei whose outlines on paper were cut out with scissors and weighed under uniform conditions of atmospheric moisture, give results remarkable for their uniformity.

The absolute regularity of the ratios based on *Cryptobranchus,* and on the control observation on the thirty-six hour chick, convinced me that nuclear size, even in preserved materials, can be utilized as an index of original water-content. If now, the absorption of water is itself an index to the surface alteration to which I attribute the change in shape undergone by the cells during involution, then the nuclei of the lateral curling edges in any given section should on the average be larger than those in the, as yet, unfolded center. This, as indicated in the last division of Table VI., is true for *Cryptobranchus.*

Since this expectation has been fulfilled, I feel that the problems involved in the autonomous folding of the nervous system, and by implication, also involved in such other autonomous foldings as that of the entodermal plate in typical invaginate gastrulation, have begun to merge with the physical-chemistry of the tissues concerned, and the conditions to which their constituent cells are subjected at various periods of development.

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SOCIETIES AND ACADEMIES

THE AMERICAN MATHEMATICAL SOCIETY

THE twenty-third summer meeting and eighth colloquium of the society were held at Harvard University during the week September 4–8, 1916. Monday and Tuesday were devoted to the summer meeting proper, two sessions being held on each day for the presentation and discussion of papers. The colloquium opened on Wednesday morning and extended to Friday afternoon. Courses of lectures were given by Professor G. C. Evans, of Rice Institute, on ''Topics from the theory and applications of functionals, including integral equations,'' and Professor Oswald Veblen, of Princeton University, on ''Analysis situs.''

Ninety-nine were in attendance. President E. W. Brown occupied the chair, being relieved by Vice-presidents E. R. Hedrick and Virgil Snyder. The council announced the election of the following persons to membership in the society: Mr. Herman Betz, Cornell University; Mr. J. A. Bigbee, High School, Little Rock, Ark.; Mr. Hillel Halperin, Vanderbilt University; Dr. J. R. Kline, University of Pennsylvania; Professor J. J. Luck, University of Virginia; Dr. F. J. McMackin, Dartmouth College. Seven applications for membership in the society were received.

Through the generosity of Harvard University the freshman dormitories and dining room were thrown open for the use of the society during the meeting. On Monday noon the members were shown the collection of mathematical models belonging to the university. On Wednesday afternoon a visit was paid to the university library, and on Wednesday evening to the observatory. Resolutions were adopted at the meeting expressing the thanks of the society for the hospitality of the university and its officers.

Fraternal greetings were exchanged by cable with the Scandinavian mathematicians assembled at Stockholm. A vote of congratulation was tendered to the secretary on his twenty-first year of service in that capacity.