ON THE MECHANISM OF MORPHOLOGICAL DIFFERENTIATION IN THE NERVOUS SYSTEM

II. THE RELATION BETWEEN COMPRESSION AND THE DEVELOPMENT OF A SERIES OF VESICLES.

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EIGHT TEXT FIGURES AND THREE PLATES

I. INTRODUCTION

The simple neural tube mentioned so frequently in embryological literature is really no more than a convenient fiction. Practically it cannot be found at any stage of development. The mere differences in the amounts of tissue in the anterior and posterior ends of the neural plate alone preclude this possibility, but in addition, long before the separation of the plate from its extra-neural ectoderm is complete, the developing 'tube' prefigures a serial differentiation that culminates in a succession of vesicles, within limits, highly constant for the vertebrate nervous system, and, as one of its basic attributes, calling for explanation.

The stages in embryogenesis upon which a study of this problem must be based, are necessarily as commonplace as those dealt with in my first paper[1] yet despite their familiarity with this period of development, embryologists do not tell us why the nervous system differentiates a series of vesicles, and particularly why there are five such fundamental divisions in its anterior end. Many do not even ask the necessary questions although His, over forty years ago, considered the subject as legitimately within the province of the student of development.

[1] On the Mechanism of Morphological Differentiation in the Nervous System. 1. The Transformation of a Neural Plate into a Neural Tube. Anat. Rec., vol. 8, pp. 525–551, 1914.

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In fact His[2] himself attempted to explain serial differentiation. The analysis, in Unsere Körperform, begins with the 'closed neural tube,' whose anterior end, as indicated in figure 1, is larger than its posterior, and is characterized by three enlargements—the precursors of the five secondary brain vesicles.

In a later stage, figure 2, His illustrates the relative positions of the five secondary vesicles in the flexed state. The curve, typical of cranial flexure, is divided into a 'Brückenkrümmung,' involving the fifth and fourth vesicles; a 'Mittelwölbung,' involving the mid brain; and the 'Hackenkrümmung,' involving the second and first. At the extreme anterior point of the first vesicle is the 'Trichterfortsatz' Tr.

His then attempts to show how this form can be derived from that given in figure 1. The brain, according to the argument, begins as a tube whose comparatively large lumen is enclosed by moderately elastic walls. These conditions are identical with those given in a piece of rubber tubing.

If the edge of a rubber tube is made fast by threads in the manner indicated in figure 3 longitudinal compression will pro-

Fig. 1 After His. Chick embryo of the second day. *H*, brain, with three vesicles indicated; *Ag*, optic vesicle; *W*, Wolffian ridge; *Uw*, somites; *Ump*, unsegmented mesodermal bands; *Am1*, head fold of the Amnion; *Am2*, lateral folds of the Amnion; *Mp*, open portion of the neural tube. The heart is indicated by means of dotted lines. Enlarged 20 ×.

Fig. 2 After His. Brain of chick embryo of the third day. *Ag*, optic vesicle; *Vh*, forebrain; *Tr*, 'Trichterfortsatz;' *Zh*, interbrain; *Mh*, midbrain; *Hh*, hindbrain; *R*, location of fourth ventricle; *Br*, 'Brückenkrümmung;' *Nh*, afterbrain; *Gh*, auditory vesicle. Enlarged 30 ×.

Fig. 3 After His. Rubber tube whose upper end has been drawn backwards by means of a thread.

Fig. 4 After His. For explanation of legends see figure 2. The dotted line indicates the anterior limits of the foregut.

Fig. 5 Sagittal section through chick-head about 38 hours old, showing the relations of foregut, floor of the second brain vesicle, and the anterior end of the notochord.

Fig. 6 After His. Upper figure, head of embryonic pike; middle, of trout, and lower, dorsal view of same. Legends as in figure 2. *Rg*, olfactory pit.

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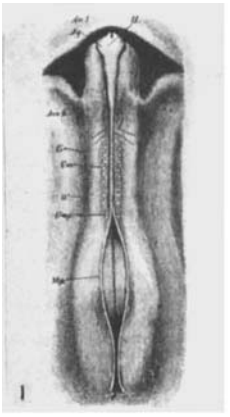
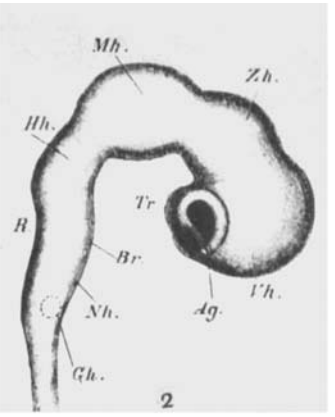
[2] Wilhelm His: Unsere Körperform und das Physiologische Problem ihrer Entstehung. F. C. W. Vogel, Leipzig, 1874. Achter Brief, pp. 93–104.

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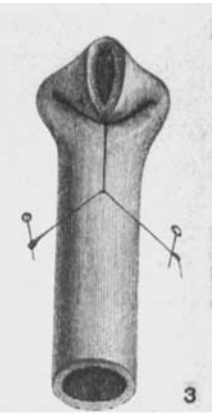
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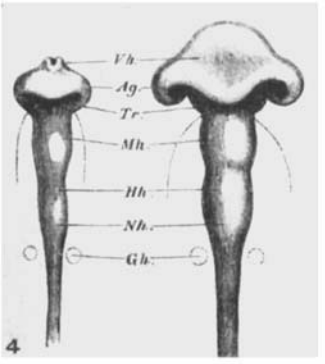
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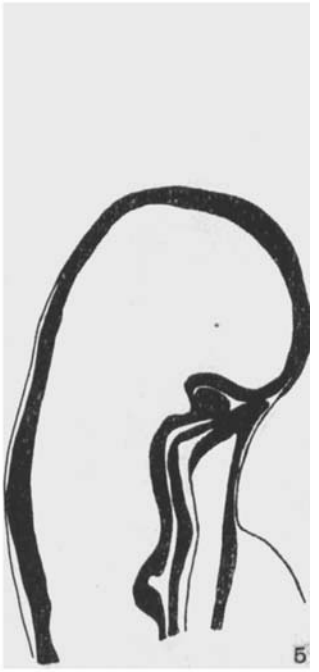
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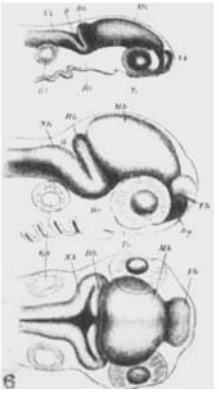
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duce an abrupt bend just behind the level of fixation, and there will appear in this region a pair of lateral swellings, whereas on one side—either the upper or the lower, as the case may be,—a sharp groove, deepest in the median line, shallower toward the edges of the sidewise expansions, will cross the tube in a transverse curve with concave face forward.

His points out how exactly this form duplicates the ventral surface of the second vesicle in the stage of development depicted in figure 1.

The suggestion that identity of form in the two sets of cases is the result of identity in the mechanical conditions under which they were produced is very much strengthened, as His emphasized, by the union "welche durch den Axenstrang und später durch die aus ihm entstandene chorda dorsalis zwischen der Medullarplatte und dem Darmdrüsenblatte, längs der Mittellinie unterhalten wird."[3]

This union later undergoes the following modifications: first the entoderm separates from the chord,

> und, viel später, diese vom Medullarrohre . . . . Am innigsten ist die Verbindung durch zwischengelagerte Masse zwischen dem Ursprünglich vordersten Rande der Medullarplatte und vom vorderen Ende des Vorderdarmes. Die Verbindung ist hier eine so innige, dass, wenn in sehr später Zeit der Vorderdarm vom Gehirn sich trennt, die Trennung nicht im Verbindungsstücke geschieht, sondern in der Continuität des Vorderdarmes selbst. Ein kleines stück von diesem bleibt als Vorderer Lappen der Hypophysis in dauernder Verbindung mit dem Gehirn.[4]

His continues,

> Es wächst aber das Medullarrohr, und speciell das Gehirn rascher in die länge als der Vorderdarm; da es nicht zu einer Trennung beider Theile kommt, so muss der längere Theil sich Krümmen, und müssen ferner die unmittelbaren Folgen der Zerrung in den mit einander verbundenen Strecken des Vorderdarms sowohl, als des Medullarrohres zu Tage treten. Beides trifft in sehr prägnanter Weise ein, nicht allein erhebt sich das Medullarrohr über dem Vorderdarm in waschendem Bogen, sondern es ziehen sich an beiden Theilen die Verbundenen Enden trichterförmig aus, wir bekommen auf die Weise am

[3] Loc cit., p. 99.
[4] Loc. cit., p. 100.

Gehirn den oben betrachteten Trichterfortsatz (fig. 2), am Vordarm die . . . . bekannte sog. Rathke'sche Tasche.[5]

The union of the 'trichterfortsatz' with Rathke's pouch is, under the conditions of growth, mechanically the exact equivalent of the piece of string in figure 3. The striking similarity of the forms produced in the two cases scarcely requires comment and may almost be considered proof of the correctness of the assumptions. One factor, not emphasized by His, however, is the notochord. Given the fusion between 'Trichterfortsatz' and Rathke's pouch, flexure resulting from the faster growth of the nervous system would be accentuated by the notochord whose anterior end would play the rôle of a fulcrum about which the curvature would take place.

But His' account is not free from anachronisms, nor will it bear a too close scrutiny from the standpoint of comparative anatomy and embryology. The final conclusion which he wishes drawn, "von der Abhängigkeit . . . . in welcher die Gehirngliederung von den auftretenden Longitudinalbiegungen des Organs steht,"[6] does not follow. If this were correct, sharpness in the demarcation of the vesicles from one another should vary directly with the degree of cranial flexure in individual as well as comparative ontogeny. This, for the first case is not strictly true, and, for the second, scarcely at all, since the vesicles are distinct before cranial flexure, and forms exhibiting a high degree of flexure have their vesicles no more sharply delimited than those in which the bending of the embryonic head is never very marked. I have no reason to doubt that His was correct with respect to the origin of both the flexure, and the lateral expansions, or optic lobes, but the differentiation of the vesicles themselves cannot be explained as the result of flexure.

II. ON THE EFFECTS OF DIFFERENTIAL GROWTH

It is clear that His considered differential growth the cause of flexure, and flexure the cause of vesiculation. Since, however, only the first vesicle with its ventral groove and lateral expan-

[5] Loc. cit., p. 100.
[6] Loc. cit., p. 104.

sions can be accounted for by flexure, the case for this factor is hardly made out.

From his manipulation of rubber models, forced in various ways to simulate special regions of the nervous system, as well as from the general tenor of the argument, it is likely that His would not have denied that differential growth, in the early stages of flexure, results in some sort of compression in the longitudinal axis. Be this as it may, it is certain that he attributed to this factor not only flexure, but also the changes in relative position which the vesicles undergo during later stages of development. Concerning the head of the embryonic pike, figure 6, he writes: "Durch die wachsende Zusammenschiebung der Theile ist der hintere Hirnabschnitt, oder das Nachhirn unter die davor liegende Anlage des Kleinhirns, und diese unter diejenige des Mittelhirns geschoben worden."[7]

III. HIS' DEMONSTRATION OF DIFFERENTIAL GROWTH

His attempted to demonstrate the differential growth of the nervous system on chick embryos ranging roughly from the twenty-fourth to the ninety-sixth hour of incubation.[8] The method consisted in comparing at four levels, those of the eye, the 'Gehirnblase,' and the first pair of somites, the areas in transverse section of the 'neural tube'—thought of as spread out flat, and the ectoderm, measured from the median axis to the point of fusion with the lateral muscle plate. On this basis, he was able to convince himself that the nervous system actually grows at a faster rate than the tissues with which it was compared.

Although this method may be capable of demonstrating the point, it is certainly not able to show that differential growth in width is accompanied by differential growth in length. The

[7] Loc. cit., p. 103.

[8] According to his own statements, the youngest stage used was of the second day, but his figure with its nine pairs of somites hardly bears this out. See figure 1 of the present paper.

association of the two is of course very probable, but by no means necessary.

Differential growth in length can be determined directly only by measurements in the long axis, and if the values so secured have a certain sense and magnitude, they may be made the basis for inferences concerning compression in that axis.

IV. METHOD OF DETERMINING COMPRESSION IN THE LONG AXIS

In order to discover the presence or absence of compression in the long axis it is necessary to find at least one measurable relation which differential growth either changes or brings about. This relation must be longitudinally effective, widely applicable, in magnitude independent of absolute measurements, and finally, capable of exact expression.

Many attempts were made to satisfy these conditions before it was found that the necessary data, accuracy, and reliability were obtainable in a very simple way.

With the camera lucida, optical sections of embryonic chick heads, at convenient magnification and a focus giving maximal outlines, were carefully traced. About these outlines I then erected the system of lines indicated in figure 7.

The base of this system is a line tangential to the anterior face of the first pair of somites. Upon this base perpendiculars, themselves tangential to the sides of the head at its widest level, were erected, and finally, parallel with the somitic base line, a tangent to the anterior edge of the head. In this way the entire cephalic region is included within the area of a rectangle.

The purpose of these preliminaries is to get a measure of the length of the head. Without the rectangle it would be easy enough to find an anterior point of reference, but it is never possible to tell exactly where the posterior limit of the head is. In fact in the early stages this grades so insensibly into the body that any posterior limit permitting comparison between various embryos and different stages, of necessity has to be chosen arbitrarily. If then an arbitrary point is imposed by the conditions of the case, it is best to choose one whose relations to the rest

of the embryo are not only significant, but also likely to present the greatest relative constancy. The somites possess these qualifications more than any other structures, and so I took the longer sides of the cephalic rectangle which rests upon the first pair, not as *the*, but as *a* measure of head length.[9] Since we desire a measure of differences in the rate of linear growth be-

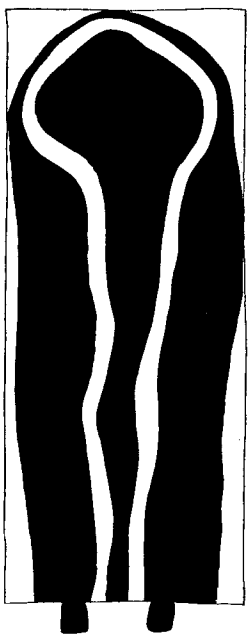


Fig. 7 Diagram to illustrate the cephalic rectangle. The line tangential to the anterior face of the first pair of somites, which are indicated in solid black, is the somitic base line. The perpendiculars erected upon this line are tangential to the head at its widest points. The head-length was arbitrarily determined along these perpendiculars as the distance between the somitic base line and the parallel tangent to the anterior surface of the head.

[9] To carry out these and the subsequent measurements on live embryos presents, for the present, insuperable difficulties. Fixed material, no doubt, differs in absolute values from the living, and it is possible that the relations between measurements which I shall discuss, are also not the same. However, absolute values need not concern us at all in the present connection, and if the relative values upon which my argument rests were seriously changed, I should hardly expect the constancy in sense which they exhibit.

tween the neural mass and the head, the simplest method is to compare the length of the head with the length of the nervous system, in various stages of development, measured from the somitic tangent as a base. Provided the head of the embryo exhibits no serious irregularities, its length may be determined arbitrarily in the manner indicated above, but, on account of the vesicles, the length of the 'brain' cannot be given by the cephalic rectangle.

Several methods involving the volume of the brain were tried but discarded in favor of one which in addition to simplicity, is capable of giving exactly and directly the very information that is wanted. All that is necessary is to determine by means of a map-measurer the perimeter of the nervous system beginning at its intersection with the somitic tangent on one side and ending at the corresponding point on the other. The length of the nervous system will be half this perimeter.[10]

V. THE NEURO-CEPHALIC QUOTIENT

With the aid of these measurements it is possible to express in the form of a fraction the relation in each stage between the length of the head and that of the nervous system. The fraction chosen is derived by dividing half the neural perimeter into the head length and tells us how many units of head length, within the limits of the cephalic rectangle, are available for every unit of length in the nervous system. This fraction I shall call the Neuro-Cephalic Quotient.

Very few embryos approach the ideals of rectitude and symmetry depicted in text-books and wall-charts. Out of the entire collection with which I have worked I have been able to find only eight justly to be characterized as diagrammatic. The outlines of these are reproduced in plate 1, figures A, B, C, D, E, F, G, and H, whereas the number of somites, and the corresponding neuro-cephalic quotients are given in table 1.

[10] Since this method is applicable to the nervous system it might be asked why I did not apply it also to the head instead of relying on the long sides of the cephalic rectangle. The answer is, because the perimeter of the head in early stages is distinct only in the anterior region.

On account of the small number of cases the scientific value of this particular table is negligible. Nevertheless it suggests certain problems and questions which must be dealt with before we can arrive at a just estimate of the significance of the quotient.

The values, taken for the time being as they stand, seem to indicate that when diagrammatic embryos are arranged in series according to somites—or, in other words, according to age and degree of development, the size of the quotient will be found to vary inversely with the number of somitic units. This, if correct, means that as development goes on the amount of head length into which a given length of nervous system must fit, decreases progressively.

TABLE 1

EMBRYO	NUMBER OF SOMITES	QUOTIENT
A	2	1.485
B	8	0.902
C	9	0.877
D	9	0.837
E	10	0.820
F	10	0.820
G	10	0.846
H	11	0.772

Given this condition, differentiations of some sort, spreading, collapse, telescoping, or vesiculation, are to be expected. Leaving aside, for the moment, the question why vesiculation prevails, let me explain why I choose to consider first these rare diagrammatic forms. The reason is very simple: because in these, the presence of a high degree of symmetry indicates that the developmental processes in general have been in nearly perfect balance, and have given a result relatively or quite free from complications calling for special explanations. Briefly, these forms are the simplest available.

Granted the advantage of simplicity—we must ask why a well balanced development gives rise to the obvious discrepancies which the table exhibits and furthermore why it is itself so rare.

The effect of error introduced by the various technical methods employed in preparing the embryos for study cannot be denied,

nor can I claim for my measurements a maximal degree of accuracy. Nevertheless I see no reason for suspecting greater errors than inhere in embryological and biometric work in general. For reasons which I shall attempt to make clear, I believe that the major discrepancies inhere in the material itself.

Referring to the table, the general sense of the values is very obvious. There is, however, no absolute proportionality between somitic increase and the shrinking quotient. Furthermore, embryos like C and D, each with nine somites, have quotients separated by a wider margin than C and G. A series arranged according to somites, even in diagrammatic forms, does not coincide absolutely with a series based on quotients. That there is a general coincidence, however, will hardly be denied.

It was the desire to find embryos in which just this sort of discrepancy could be expected to assert itself in minimal degree that lead me to select the most diagrammatic forms for separate treatment. But even in these complete elimination of discords is impossible. If now the lack of harmony between theory and practice is to be sought in the embryo itself rather than in the methods by which it was handled, we must analyze our material in an attempt to get at the real explanation.

Such explanation will be found, I think, when we realize the true nature of the developmental process itself. To be alive is to solve a constellation of interlocking problems in equilibration. In the adult, departures from balance occur within comparatively restricted compass, and, being for the most part quickly reversed, result in few or relatively unimportant morphogenetic changes;[11] in the embryo, on the contrary, the excursions are often very wide. Indeed it is hardly too much to say that a developing organism 'blunders' from one crisis to another, until gradually, by the narrowing of its 'horizon,' it reaches that state of relative stability which is characteristic of the adult. Nothing that happens in the fully developed organism can be compared with the multiplicity and complexity of the immediate and remote adjustments consequent upon the differentiation of

[11] See Glaser, The Basis of Individuality in Organisms. Science, vol. 44, pp. 219–224.

the germ layers From the dynamic standpoint, development might be defined as the symptom of an organic instability in which departures from exact balance occur within limits so wide as to escape fatality by only a narrow margin.

This granted, it follows that the sum of opportunities within the developing system is exceedingly great. Although unquestionably exact and theoretically predictable in all its details, embryogenesis, within the boundaries of what is 'normal,' nevertheless, varies tremendously. It need occasion no surprise then if we find differences in the several tissue-maneouvres, or in the exact time of onset of this, that, or the other process. Of several embryos which might be expected to exhibit identical conditions in all respects, one may lead or lag in the morphogenetics of its nervous system, a second in that of its somites, and another in its circulatory equipment. In fact the early discrepancies or temporary misfits of development may at any instant simulate disorganization. By this it is not intended to suggest that 'normal' embryogenesis is strictly a matter of chance, but only that its 'administration' appears relatively loose. To us this looseness is emphasized subjectively because we remain ignorant of so large a share of the elements underlying the process. We may be sure, however, that the minor errors of development sooner or later receive adequate correction for the end results of embryogenesis are precise and give an organism which actually describes the genetic constitution of its ancestors.[12]

Taking development as it is, our quotient, to have significance, must be applicable to a wide range of cases, which, no matter how they may deviate from the diagrammatic, nevertheless cannot be considered otherwise than normal. Within this range, if our preliminary test is to be trusted, we should find the same general relations exhibited by the ideal embryos. However, since the measurements upon which the quotient rests, themselves bear no obviously immediate relation to the factors upon which the production of somites depends, we should not expect absolute correspondence between somitic increase and a falling

[12] See Note 11.

quotient. All that we are entitled to expect is that the quotient in general will vary inversely with the number of somites.

If the quotient is a true indicator of compression in the longitudinal axis, and if compression is related causally to serial differentiation, we are also entitled to expect some relation between this differentiation and the quotient. Here again, we should not set our minds on absolute correspondence, for quite apart from the difficulty of exact determinations in this connection, the amount of differentiation which a given degree of compression calls forth depends on many things. Age is one; what differentiations had taken place before a particular degree of compression was reached, is a second; the thickness and mechanical properties of the nervous system are a third; the rate at which the differentiations are produced is a fourth; the exact axis of maximal compression is a fifth; and no doubt there are many others. There is, however, no accurate way, particularly in the more complicated cases, of expressing the degree of differentiation. Furthermore the attempt to do so would necessitate also the consideration of that portion of the system which lies posterior to the somitic base line of the cephalic rectangle. Nevertheless, little serial differentiation should be associated with a large, and the reverse with a small quotient.

Correspondences between quotient and somites on the one hand, and quotients and differentiation on the other, do not complete the list of what we may expect. A third matter—that of aberrancies—must receive consideration.

From our present standpoint, the aberrancies theoretically to be considered are those in which the nervous system is either underdifferentiated or has erred or has been forced to err seriously in the opposite direction. In the first case we should expect relatively high, in the second, relatively low, quotients. As a matter of fact, I have not found enough cases of undifferentiation to feel warranted in giving them special prominence, but overdifferentiation is common. In fact, in one of its varieties, it is too common to leave much doubt that the resulting forms must be classified as normal. This type, characterized by the partial telescoping of the first and second vesicles exceeds in

frequency the known percentage of faulty hatchings or total failures by so large a margin as to suggest very strikingly indeed the likelihood that many nervous systems during some stage of their development exhibit temporarily, at least, too much differentiation. Cases in point are illustrated on plate 2, embryos I, J, K, L, M, N, O.

To what extent now, our several expectations are fulfilled can be seen by comparing the figures of the forms illustrated in plates 1 and 2, with the corresponding values given in table 2 in which the embryos are arranged in a series beginning with the highest and ending with the lowest quotient.

The omission from this table of 12 and 14 somite embryos is due to the fact that only one of each kind was available. The only other grounds of elimination were asymmetry or a degree of aberrancy which could have but one interpretation. Such embryos with somites and quotients indicated are referred to in table 3 and illustrated in plate 3.

If we accept table 2 as indicative of the norm for the various stages dealt with, the quotients in table 3 become significant. As can be seen by reference to plate 3, the embryos now under consideration fall into two groups—in one of these, including U, W, and X, the embryo is asymmetrical, in the other, T, V, Y, and Z, the embryos are overdifferentiated. With respect to Z, nothing definite can be said, since table 2 does not contain the quotient normal for the 27 somite stage. Embryos T, V, and Y, however, all have quotients too low for their respective ages. In other words the compression to which the nervous system is subjected is higher than normal and has resulted in too much differentiation.

The asymmetrical forms, U, W, and X, suggest that if a certain degree of compression fails to set in, or is not properly directed, the aberrant condition will be reflected in an asymmetrical distribution of the neural mass.

CONCLUSION

A comparative study of the illustrations in the plates and the values given in tables 1, 2, and 3 may, I think, be justly summarized by saying that our expectations in general have been

TABLE 2

Normal embryos

QUOTIENT	SOMITES	REMARKS
1.890	3	
1.672	2	
1.485	2	
1.313	4	
1.132	3	
1.0475	5	
1.017	5	
1.012	4	
1.0095	5	
0.968	6	
0.952	6	
0.949	6	
0.925	8	
0.920	7	
0.911	10	
0.903	7	
0.902	8	
0.9009	9	
0.887	9	
0.877	9	
0.871	10	
0.863	9	
0.851	10	
0.849	10	
0.847	10	
0.846	10	
0.842	10	
0.842	10	
0.837	9	
0.820	10	
0.820	10	
0.818	11	
0.812	11	
0.811	10	
0.800	11	
0.772	11	
0.737	13	Telescoped forms Plate 2 I
0.664	13	Telescoped forms Plate 2 J
0.649	15	Telescoped forms Plate 2 K
0.605	16	Telescoped forms Plate 2 L
0.592	15	Telescoped forms Plate 2 M
0.577	16	Telescoped forms Plate 2 N
0.573	17	Telescoped forms Plate 2 O
0.572	17	
0.572	16	

TABLE 3

QUOTIENT	EMBRYO	SOMITES	REMARKS	QUOTIENT
0.817	T	9	Asymmetrical	Too low
0.790	U	13	Asymmetrical	Too high
0.789	V	10	Overdifferentiated	Too low
0.787	W	13	Asymmetrical	Too high
0.768	X	13	Asymmetrical	Too high
0.541	Y	14	Overdifferentiated	Too low
0.522	Z	27	Overdifferentiated	

fulfilled. The relations postulated in advance between the neurocephalic quotients, on the one hand, and aberrancies, degrees of normal differentiation, and somitic increase on the other, are capable of being verified. The relation which at this time I wish to especially emphasize, is the association of a falling quotient with the multiplication of somites.

The quotient correctly understood is a measure of longitudinal compression. The somites are recognized as a measure of development. It follows, therefore, that the movements of the quotient are related in time and sense to the serial differentiation to the nervous system precisely in the manner in which they should be related, if compression in the longitudinal axis is a condition upon which the vesiculation of the nervous system

TABLE 4

SOMITES	CASES	QUOTIENT
2	2	1.579
3	2	1.511
4	2	1.163
5	3	1.025
6	3	0.956
7	2	0.912
8	2	0.914
9	5	0.873
10	11	0.845
11	4	0.801
13	2	0.701
15	2	0.621
16	3	0.585
17	2	0.573

depends. The assumption of a 'causal' connection between compression and the formation of the brain vesicles is therefore warranted.

The justice of this assumption appears still greater when we average the results for each stage of development dealt with in table 2. This was done and the outcome is given in table 4.

If now, with the aid of table 4 we construct a curve in which quotients are plotted along the ordinate and the number of somites along the abscissa, the relation between a falling quo-

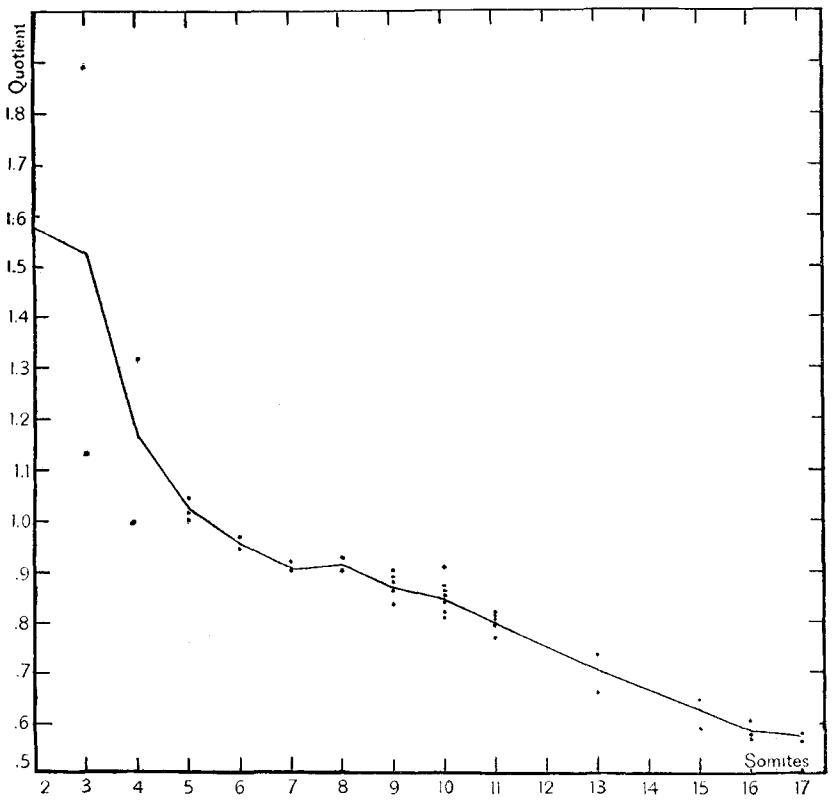


Fig. 8 Showing the relation between a falling neuro-cephalic quotient and somitic increase. The curve is constructed by joining the loci of the averages given in table 4. The dots indicate the loci of the individual quotients given in table 2.

tient and somitic increase exhibits itself in the most striking manner.

On the basis of this curve, figure 8, I infer that during the period of development considered, a rising state of longitudinal compression is one of the conditions determining the differentiation of a series of vesicles in the brain.

SUMMARY

1. Cranial flexure, although capable of explaining the lateral and ventral differentiations of the prospective second brain vesicle, is nevertheless not related to the general process of vesiculation in the manner in which it should be if the formation of vesicles were dependent upon flexure, as His maintained.

2. According to His, flexure depends on differential growth.

3. According to the results presented in the present paper, vesiculation also depends upon differential growth and precedes flexure.

4. Differential growth, to play a rôle in this connection, must be longitudinally effective. Such effectiveness is undemonstrable by the method of His.

5. Effectiveness in the long axis can be demonstrated by comparing the length of the embryonic head with that of the nervous system. The relation between these two measurements, within the arbitrary limits set by the cephalic rectangle, has been expressed in the form of a fraction.

6. This fraction, the Neuro-Cephalic Quotient, is derived by dividing half the perimeter of the nervous system into the head-length. It tells how many units of head-length are available for every unit of length in the nervous system.

7. The quotient is largest in the earliest stages, and decreases with the progress of development. It is inversely proportional to the number of somites, and, so far as can be determined in the absence of accurate modes of expression, with the degrees of differentiation exhibited by the nervous system. Telescoped forms, and those abnormally over-differentiated, have expectedly low quotients.

8. Despite the variability which inheres in developmental processes by their very nature, the relations between quotient on the one hand, and somites, or differentiation of the nervous system, on the other, are such as to warrant the conclusion that a rising state of compression in the longitudinal axis is one of the important conditions under which the vesiculation of the embryonic brain takes place.

PLATE 1

EXPLANATION OF FIGURES

Outlines of heads of diagrammatic 2 to 11 somite chick embryos referred to in table 1. The posterior line through the nervous system is the somitic base line. In embryo A the nervous system did not extend backward as far as the somitic tangent. In this case two base levels are indicated, one used to measure head-length, the other to determine the neural perimeter.

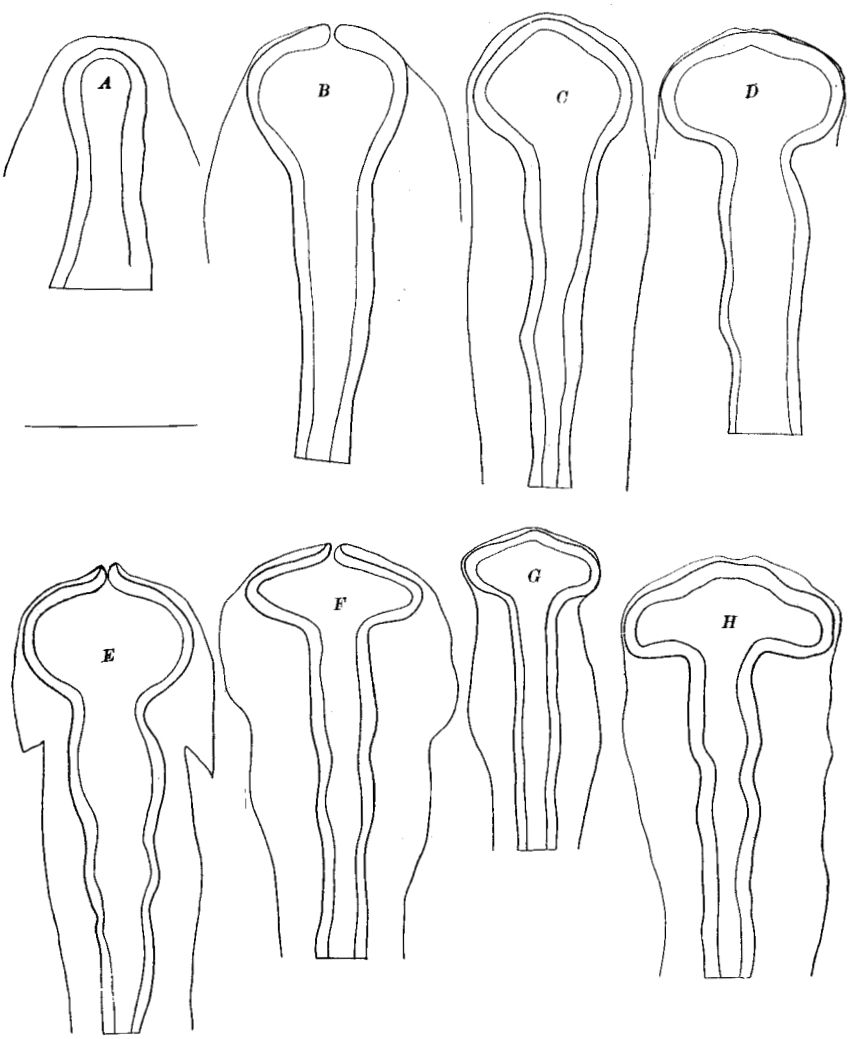

A
B
C
D
E
F
G
H

PLATE 2

EXPLANATION OF FIGURES

Telescoped forms with 13 to 17 somites and low quotients. Referred to in table 2.

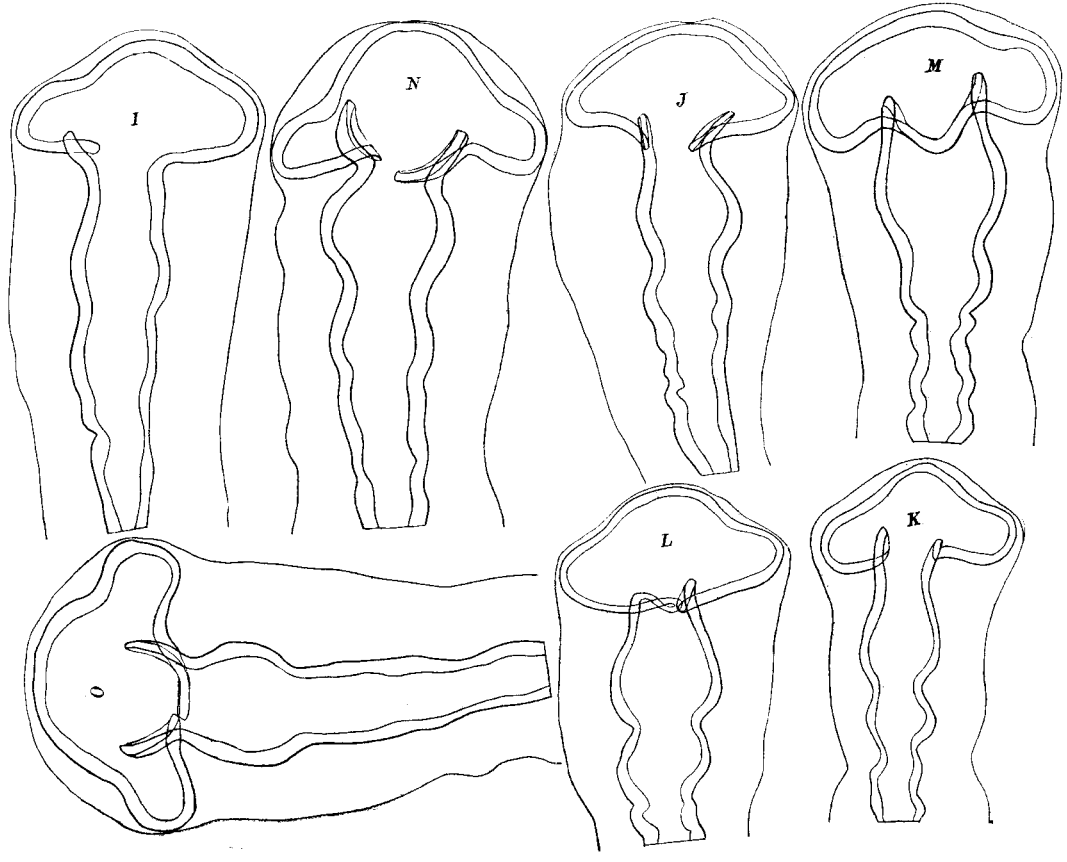
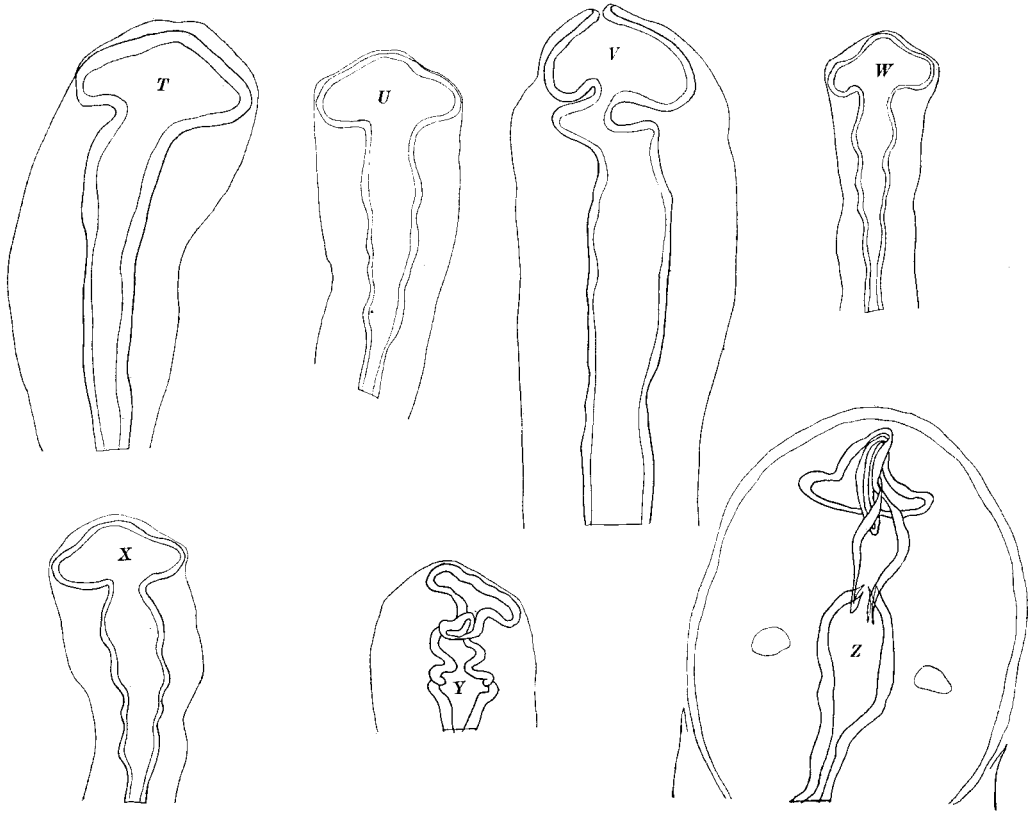

I
N
J
M
L
K
O

PLATE 3

EXPLANATION OF FIGURES

Aberrant forms. Embryos T, V, Y, and Z are over-differentiated. As shown in tables 2 and 3, T, V, and Y have quotients too low for their respective ages. The quotient normal for the 27 somite stages has not been determined; therefore no statement can be made regarding embryo Z.

Embryos U, W, and X, have quotients too high for their respective ages, and suggest that compression must reach a certain magnitude and moreover be properly directed in order that the neural mass may distribute itself symmetrically.


T
U
V
W
X
Y
Z