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Estudios sobre la dinámica de la morfogénesis y la herencia en la reproducción experimental. X. Frecuencia de la cabeza de *Planaria dorotocephala* en relación con la edad, nutrición y actividad motriz.

El autor ha descrito en trabajos anteriores el hecho de que el nuevo extremo anterior producido durante el desarrollo regulador de trozos aislados de *Planaria dorotocephala* varía desde el estado de cabeza normal, pasando por varios grados de inhibición en el desarrollo de dicho órgano, hasta producir una acefalia completa. Por razones descriptivas ha distinguido cinco tipos diferentes de extremo anterior: normal, teratofálmico, teratomórfico, anoftálmico y acéfalo. La palabra "frecuencia de la cabeza" significa la frecuencia con que aparecen estos diferentes tipos en un lote de trozos del animal, bajo condiciones determinadas. La frecuencia de la cabeza es menor en los trozos de animales fisiológicamente mas jóvenes (mas pequeños) que en los de animales fisiológicamente mas viejos (mayores). Lo mismo sucede en los trozos procedentes de animales mal alimentados. Es por el contrario mayor en los trozos estimulados frecuentemente en el sentido locomotor, durante varias horas después de seccionados, que en los trozos que no se estimulan. La misma serie de formas del extremo anterior aparecen bajo condiciones fisiológicas diferentes y bajo condiciones externas físicas y químicas diferentes, consistiendo los cambios producidos experimentalmente en cambios de la frecuencia de las diferentes formas. Este efecto no específico de los factores fisiológicos y externos indica que la acción de ambos grupos de factores es esencialmente cuantitativa. La interpretación cuantitativa de los cambios en la frecuencia de la cabeza, mencionados previamente, es aplicable a los hechos expuestos en el presente trabajo.

STUDIES ON THE DYNAMICS OF MORPHOGENESIS AND INHERITANCE IN EXPERIMENTAL REPRODUCTION

X. HEAD-FREQUENCY IN PLANARIA DOROTOCEPHALA IN RELATION TO AGE NUTRITION AND MOTOR ACTIVITY

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THREE FIGURES

Analytic investigation of reconstitution or regeneration in isolated pieces of *Planaria dorotocephala* has shown that the process is by no means uniform in different pieces, even in those from the same animal. The structures produced at the anterior ends of pieces present the most interesting conditions as regards variation, for they constitute a graded series ranging from normal heads at one extreme, through various degrees of incomplete head development, to a completely headless condition in which the wound at the anterior end merely heals and nothing further occurs. In spite of the fact that they actually constitute a graded series, it has been found convenient for purposes of analysis to divide the different types of anterior end into several groups representing different degrees of departure from the normal and approach toward the headless condition. These different groups have been named, defined, and figured in earlier papers (Child, '11 a, '15 b, p. 106, '16). Investigation has shown further that the character of the anterior end developing in an isolated piece varies in a definite way with the length of the piece or the fraction of body length represented by it and with region of body from which it is taken (Child, '11 b, d). Moreover, it has been found possible to control and alter experimentally to a very high degree the character of anterior end produced. The results of experiments with KNC (Child, '16) and temperature (Behre, '18)

have already been published in full, the results of various other experiments including some of those recorded in the present paper have appeared in brief preliminary form (Child, '11 a), and further experiments on the action of various anesthetics are in progress. These experiments have demonstrated that the various types of anterior end produced by the action of external chemical and physical agents are the same as those which arise in relation to length of piece, region of body, and other physiological conditions.

In most of the work along this line five types or categories of anterior end have been distinguished (Child, '11 a, '16): normal, a head with two distinct eye-spots, lateral cephalic lobes, and pointed tip, as in nature; teratophthalmic, a head of normal shape, but with eye spots more or less approximated, to the median line, often unequal in size, or more or less completely fused in consequence of failure of the median region of the cephalic ganglion to develop completely (Child and McKie, '11); teratomorphic, a more extreme degree of inhibition of the median region, showing a single or completely fused eye spots in the median line and cephalic lobes more or less approximated at the front of the head, in consequence of incomplete development of the median region of the tip; anophthalmic, with a distinct outgrowth with rudimentary ganglion, but without eye spots; acephalic or headless, with mere healing of the wound and no outgrowth. The term 'head-frequency' has been used to indicate the frequency with which these different types of anterior end occur in a given lot of pieces.

The present paper is concerned with the influence of certain physiological conditions upon head-frequency. The methods of experimental procedure are essentially similar to those described in earlier papers. Each lot of animals used consists of individuals of the same length from a single laboratory stock kept under known conditions of nutrition, temperature, etc., for at least several weeks before the experiment. Each lot of pieces isolated from such animals represents as nearly as possible a given fraction of length and a given region of the body. In all series tabulated except one, the experimental lots consist of fifty pieces each and

all tabulated data are in percentages. It may be pointed out once more that in these head-frequency data only differences greater than 10 per cent are to be regarded as significant. The sources of error are such that it is not safe to attribute definite significance to differences less than this.

HEAD-FREQUENCY IN RELATION TO SIZE OR PHYSIOLOGICAL AGE

It has been shown that susceptibility to lack of oxygen (Child, '19 c), rate of CO₂ production (Child, '19 a), and oxygen consumption (Hyman, '19 a, b, c) all decrease with increasing size in *P. dorocephala*, and Allen ('19 a) has recently recorded a similar decrease in oxygen consumption with increasing size in two other species. As regards the question whether size may be regarded as a criterion of physiological age, attention may be called to several points: First, animals sexually produced are approximately equal in size at the time of hatching, therefore the size of such an animal at any given time represents the amount of growth it has undergone, and if physiological senescence is associated with growth and progressive development, the animal must grow old as it becomes larger. In cases where comparison has been possible, animals asexually produced have been found to show approximately the same physiological condition in all respects as sexually produced animals of the same size. Second, the physiological changes which normally accompany growth and progressive development have been prevented, at least so far as could be determined, in *Planaria velata* by giving only sufficient food to maintain a given size (Child, '14 c). Third, animals of the same size and living under similar conditions are much more alike physiologically than animals of different size. Fourth, sexual maturity occurs only at a relatively advanced physiological stage when a certain size and metabolic condition are attained, and can be prevented from occurring by insufficient feeding or by frequent regeneration. Fifth, the physiological changes with increasing size in *Planaria* are similar to those usually regarded as characteristic of physiological senescence in the higher animals and man. In short, certain progressive physiological changes

occur with increase in size in *Planaria* as in other animals generally, and size therefore serves as a criterion of physiological condition so far as it concerns these changes. Whether we call these changes physiological senescence or something else is purely a matter of definition. They certainly consist in a decrease in rate of the fundamental activities of life, and if they go far enough either death or a break-up of the individual with reorganization and regressive changes occurs. For the present there seems to be ample justification for designating as physiological senescence

the progressive changes in condition associated with increase of size in *Planaria* and so for using size as a criterion of physiological age.

Table 1 shows the effect of this factor of size or physiological age upon head-frequency. Each pair of lots, Ia, IIa, etc., gives the percentages of the different types of head in corresponding pieces from animals of two different sizes. In every case the head-frequency is distinctly greater, usually much greater in the pieces from the larger (older) animals. The experiment has been performed many times with various sizes of animals and

pieces, being often used as a class experiment, and always with the same result, a higher head-frequency in the pieces from larger animals.

It may appear at first glance that these differences in head-frequency are due simply to the fact that in the longer older animals and the pieces of larger size there is more available

TABLE 1
Head-frequency in relation to physiological age (size)

	PIECE	NORMAL	TERATOPH- THALMIC	TERATO- MORPHIC	ANOPHTHAL- MIC	ACEPHALIC	DEAD
Series 339, 368. Pieces A, B, C (fig. 1), 50 each, from well fed animals: I, 7 mm. II, 20 mm.	IA	54	42			4	
	IIA	86	14				
	IB		2			96	2
	IIB	32	28	6	28	6	
	IC	4	12		2	76	6
	IIC	34	14		26	26	
Series 321. Pieces B, C (fig. 1), 50 each, from well fed ani- mals: I, 10-11 mm. II, 16-18 mm.	IB	6	12	6	26	50	
	IIB	20	36	10	24	8	
	IC		6		8	86	
	IIC	4	14	2	16	62	
Series 201, 277. Pieces A, B, C, D (fig. 2), 10 each, from well fed animals: I, 5-6 mm. II, 16 mm.	IA	60	40				
	IIA	90	10				
	IB		20			80	
	IIB	60	40				
	IC	10	40	10		30	10
	IIC	90	10				
	ID	60	30				
	IID	100					

nutritive material for the development of a new head, but there are various reasons for believing that this is not the case: first, head-frequency is lowest in pieces from levels near the mouth where the amount of nutritive material in the pieces is greatest; second, it has been shown elsewhere that head-frequency may be altered experimentally in both directions without altering the amount of nutritive material (Child, '16; Behre,

'18), and further data bearing on this point are presented below; third, normal heads and often biaxial heads may develop on pieces so short that the whole substance is used up in the development of the head or heads. Taking all the facts into account, it is evident that while the amount of nutritive material may play some part in determining head-frequency, it is not the primary factor in determining the differences between large and small animals.

HEAD-FREQUENCY IN RELATION TO NUTRITIVE CONDITION

It has been shown that starvation in *P. dorotocephala* is accompanied by various changes in physiological condition. The susceptibility of body wall and ectoderm (probably also of parenchyma) increases from the beginning of starvation, that of the alimentary tract in the later stages (Child, '15 a, chap. VII, '19 c). Carbon dioxide production and oxygen consumption decrease in the early stages of starvation, undoubtedly because of the decrease in activity of the alimentary tract in the absence of food, but later increase (Child, '19 a; Hyman, '19 a, and in advanced stages of starvation the animal may have a much higher rate of respiration than at the beginning of starvation, and this rate is still further increased by renewed feeding. As regards rate of respiration and susceptibility, the starving animal apparently becomes physiologically younger, and with renewed feeding may again begin growth and progressive development from a stage physiologically earlier than that at the beginning of starvation. It is of interest, in the light of these facts, to determine the effect of starvation upon head-frequency, and data along this line are given in table 2.

Table 2 shows in all cases that the head-frequency in pieces from starved animals is less than in fed animals, even when of the same size.

Certain points in the various series demand brief notice. So far as actual difference in percentage is concerned, it will be observed that the effect of starvation is in general most conspicuous in the most anterior pieces (A) and in series 327 in the long pieces (X). The differences in these cases are entirely or almost en-

tirely between normal and teratophthalmic, and it has been found that very slight changes in physiological condition will determine the development of teratophthalmic instead of normal heads or vice versa. It is probable, therefore, that the large differences

TABLE 2
Head-frequency in relation to nutritive condition

	PIECE	NORMAL	TERATOPHTHALMIC	TERATO-MORPHIC	ANOPHTHALMIC	ACEPHALIC	DEAD
Series 368. Pieces A, B, C (fig. 1), 50 each	IA	10	90				
I, from animals 7-8 mm., starved 17 days	IIA	54	42			4	
	IB				2	96	2
II, from animals 7-8 mm., well fed	IIB		2			96	2
	IC		6			88	6
	IIC	4	12		2	76	6
Series 327. Pieces A, B, C, X (fig. 1), 50 each	IA	20	72	2		2	4
I, from animals 6-7 mm., starved 19 days	IIA	38	58			4	
	IIIA	30	66				4
	IB		6	6	4	82	2
II, from animals 6-7 mm., starved 18 days, fed once	IIB			2	2	94	2
	IIIB	6	30	4	14	42	
	IC					92	8
III, from animals 6-7 mm., heavily fed	IIC					100	
	IIIC			4		96	
	IX	30	70				
	IIIX	30	70				
	IIIX	70	18				12
Series 320. Pieces B, C (fig. 1), 50 each	IB			2	10	64	24
I, from animals 14-16 mm., starved 40 days	IIB	4	46	6	30	14	
	IC			2	4	86	8
II, from animals 14-16 mm., well fed	IIC	2	6	2	22	68	
Series 638. Pieces A, B, C (fig. 1), 50 each	IA	22	70	2	2	2	2
I, from animals starved 93 days, reduced from 25 mm. to 7-8 mm.	IIA	88	8				4
	IB		30	12	10	32	16
	IIB	2	60	8	12	18	
	IC		4	4	10	82	
II from animals 20 mm., well fed	IIC		10	2	16	72	

in percentage in normal and teratophthalmic in the anterior pieces have no greater significance physiologically than smaller differences in percentages between headless and anophthalmic for example.

In series 368, 327, and 320 starved and fed animals and pieces are of equal size, but in series 638, well-fed large animals are compared with animals originally of still larger size, but reduced by starvation to a small fraction of the original size.

In all cases the comparative results are the same, the head-frequency being lower in the starved lot. In series 327 the animals of lot II are fed once after eighteen days of starvation and are compared with animals starved nineteen days (I) and heavily fed animals of the same size (III). Here the single feeding of lot II apparently increases head-frequency in *A*, but not elsewhere. The head-frequencies are low, even in the fed animals (III) of this series, except in the long pieces (*X*), because of the small size of the animals, but the difference between starved (I) and fed (III) is very great in *B* and *X*. That lack of available nutritive material is not the primary factor in determining the decrease in head-frequency in starvation is indicated by various facts: for example, the slight effect of the single feeding in series 327 II upon head-frequency indicates that some other factor than nutritive material is chiefly concerned. These pieces were well filled with food, at least during at least the earlier stages of regeneration. Moreover, all the series show that starvation and feeding do not alter essentially the relation between head-frequency and body-level, although there can be no doubt that in starvation nutritive reserves are exhausted first and resorption of the alimentary tract proceeds most rapidly in the anterior body regions. In other words, these regions are most starved, but still show a much higher head-frequency than the less starved regions near the mouth, and even after heavy feeding there is less surplus nutritive substance in the anterior body region, because of the alimentary tract is less extensively developed there than in regions about the mouth, yet anterior pieces show the highest head-frequency. In short, it is evident from these data on head-frequency in relation to starvation as well as from those on size

in the preceding section that amount of available nutritive material is not the primary factor in determining head-frequency. Further discussion is postponed to the final section of the paper.

HEAD-FREQUENCY IN RELATION TO MOTOR ACTIVITY OF PIECES

These experiments consist essentially in determination of head-frequency in pieces which are repeatedly stimulated to motor activity during a longer or shorter time beginning immediately after section (II) as compared with that of smaller pieces which are left undisturbed (I). The results for two series are given in table 3. In both cases the pieces *B* and *C* (fig. 1) are used because such pieces have neither an extremely high nor an extremely low head-frequency and change in both directions is readily possible. In *A* pieces and in pieces from the posterior zooids the head-frequency is usually so high that only decrease appears clearly in experiment. The methods of stimulation were various: currents of water were used to loosen the pieces from the glass, some motor activity usually following; individual pieces were loosened and turned over with the aid of a camel's-hair brush and usually attempted sooner or later to turn back again. Gentle stroking or slight pressure with a camel's-hair brush was also found to be effective. In series 302 such stimulation was repeated at least every hour for some eight hours after section, after which the pieces were left undisturbed overnight. On each day following until the new heads and eyes were distinctly visible the pieces were stimulated at least once an hour from 8.30 a.m. to 6 p.m. and at least twice between 8 and 11 p.m. In order to equalize oxygen supply as far as possible the water on the unstimulated lots (I) was stirred gently at the times when the other lots were stimulated, the stirring being usually not sufficient to induce motor activity.

In series 498 the stimulation of II was repeated every five to ten minutes during the first two hours after section, once an hour during the second two hours, and again every five to ten minutes during the third two hours. After this the pieces remained undisturbed. It was known at the time of this experiment that the continuation of the stimulation during several days as in

series 302 was wholly unnecessary, since under ordinary conditions it is determined within five or six hours after section whether a piece shall give rise to a head or not (Child, '14 d).

In table 3 the column 'teratophthalmic' is divided into two columns, *a* and *b*, which represent two different degrees of teratophthalmia. Column *a* includes the cases in which the two pigment spots of the eyes are distinct, but differ in size or are

TABLE 3
Head-frequency in relation to motor activity of pieces

	PIECE	NORMAL	TERATOPHTHALMIC		TERATOMORPHIC	ANOPTHALMIC	ACEPHALIC	DEAD
			a	b				
Series 302. Pieces B, C (fig. 1), from animals 16-18 mm., starved 8 days I, undisturbed, water occasionally stirred II, stimulated to motor activity as often as possible during 6 days after section	IB			8	8	26	58	
	IIB		10	14	12	32	32	
	IC			4	4	12	80	
	IIC	4	2	8	2	18	64	2
Series 498. Pieces V, C (fig. 1), from well-fed animals 16-18 mm. I, undisturbed II, stimulated to motor activity frequently during 6 hours after section	IB	4	38	44	6	8		
	IIB	20	48	32				
	IC		22	34	4	20	22	
	IIC	8	36	32		14	10	

somewhat asymmetrical in position. Column *b* includes those cases in which the two pigment spots are more or less approximated to each other and united by a band of pigment or partly fused. The forms of column *a* are somewhat nearer normal than those of column *b*.

The head-frequency data for these two series in table 3 show that in every case the stimulated lots (II) have a distinctly higher head-frequency, or more specifically, approach more closely to normality. The difference appears as clearly in columns *a* and

b under the head 'teratophthalmic' as in the other columns. In series 498 with well-fed animals the level of head-frequency is higher in all pieces than in series 302 with animals starved eight days and only moderately fed for several weeks previously, but the differences between I and II are distinct in every case. Moreover, the short period of stimulation in series 498 is apparently about as effective in increasing head-frequency as the long period in series 302. According to the evidence from head determination (Child, '14 d), this is to be expected, but it is of interest to find the data confirming expectation.

DISCUSSION

Extensive investigation of the conditions determining and affecting head formation in isolated pieces of *Planaria* has led to

Figure 3

certain conclusions concerning the physiological relations of the new head to other parts of the piece.

It is a well-known fact that regulatory development at the anterior end of a piece begins with the formation of a head, whatever the level from which the piece is taken, and that the parts which normally lie between the head and the level represented by the piece are formed later by reorganization of regions posterior to the new head and never develop unless at least a rudimentary head is formed first (Child, '11 c). In short, the head seems to arise as something more or less independent physiologically of other parts of the piece, while the further reorganization of the anterior regions of the piece occurs only under the influence of the new developing head.

Moreover, it has been shown that the relation between the cells from which the new head develops (fig. 3, *x*) and the rest of

the piece (fig. 3, y) is in a sense antagonistic, in that conditions which stimulate or accelerate the physiological activity of x in relation to y , or conversely, decrease the activity of y in relation to x increase head-frequency, while conditions which increase the activity of y in relation to x or decrease the activity of x in relation to y decrease head-frequency (Child, '14 d, '16). These relations have been expressed in the formula head-frequency $= \frac{\text{rate } x}{\text{rate } y}$. This formula is merely a brief expression of relations indicated by the experimental data. The physiological situation is apparently as follows: In an isolated piece certain cells (x) along the cut surface are isolated by the cut from all the correlative factors that formerly reached them from parts anterior to the cut and are also stimulated by the wound. These correlative factors represented a large part of the factors which determined the differentiation and behavior of these cells as a part of the body, and in their absence the cells tend to lose this differentiation and to become physiologically younger. But the relation of the cells x to the regions posterior to them (y) have not been altered by the cut, and any correlative factors which reach x from y must tend to prevent or retard its dedifferentiation and independent development. Consequently, the result in any particular piece will vary as one or the other of these factors has the ascendancy. For the present we may express this relation in terms of the activity of the regions x and y . If the activity (and probably the energy-liberating activity is primarily concerned) of x is sufficiently intense as compared with that of y , the cells of x will be in large measure independent of y and will dedifferentiate and develop anew in spite of y , and the product of this development will be a normal head; i.e., the primary developmental reaction of planarian protoplasm will occur (Child, '11 c, '15 b, pp. 96-102). If on the other hand, the activity of y in relation to that of x is sufficiently intense to inhibit or retard these processes to some extent, the development of the head will be retarded and its structure will range from a slight degree of teratophthalmia to extreme anophthalmia, or in the extreme case the development of a head is completely inhibited and the piece remains acephalic.

With this brief statement of the general conception of head-formation in pieces, we may turn to the interpretation of the data recorded above. As regards the relation between head-frequency and size, it was pointed out above that the rate of oxidation is unquestionably higher in the small than in the large animals. In isolated pieces of a smaller animal the tissue throughout is physiologically younger and more active, consequently the region x in its reaction to the absence of the parts in front and to the wound does not undergo so great an increase in rate in relation to y as in a piece of a larger older animal, and is therefore less independent of y in its development; i.e., shows a lower head-frequency than in the pieces from larger, older animals. From this point of view the lower head-frequency in the younger animals is essentially a consequence of their higher rate of metabolism or oxidation.

As regards the starved animals, it has been pointed out that lack of available nutritive material cannot be the primary factor in determining the lower head-frequency. The facts noted above concerning changes in susceptibility, CO_2 production and oxygen consumption during starvation indicate that the decrease in CO_2 production and oxygen consumption in the earlier stages are merely the result of the decrease in activity of the alimentary tract in the absence of food and that the rate of oxidation in ectoderm and body wall—probably also in the parenchyma—increases from the beginning of starvation. These are the regions chiefly concerned in the determination of head-frequency in pieces, and if the conclusions concerning rate of oxidation are correct, it is evident that the lower head-frequency in starving as compared with fed animals is due to difference in the relation $\frac{\text{rate } x}{\text{rate } y}$ of the same sort as in young animals as compared with old. In other words, the rate of energy-liberating metabolism being higher in the piece as a whole (fig. 3, y), the changes in the region x do not increase its rate over that of y so far as in well-fed or old animals. Consequently, in starving animals dedifferentiation and new development of x is less independent of correlative factors in y than in fed animals, and head-frequency is therefore lower.

In the pieces stimulated to motor activity, head-frequency is increased as compared with those at rest. The interpretation suggested for this fact is that the cells at the anterior end which are concerned in head-formation (fig. 3, *x*), are stimulated to a greater degree than the rest of the piece by the forward movement and that their independence of the correlative factors in *y* is therefore greater than in the pieces at rest. In other words, rate *x* undergoes increase in relation to rate *y* in this case and the result is increase in head-frequency.

It is clear, then, first, that the three physiological factors, age as indicated by size, nutrition, and motor activity, influence head-frequency; second, that this influence consists in increasing or decreasing the relative number of pieces in a lot which produce either heads or heads of a particular degree of development. As regards the various degrees of head-development, it is a fact of considerable interest that the different forms of head produced remain the same as regards their structure, whether such factors as size and region of piece (Child, '11 b, '14 b, '14 d), physiological age, nutrition, and motor activity or an external chemical agent such as KNC (Child, '16) or a physical agent such as temperature (Behre, '18) are concerned. It is impossible to escape the conclusion that the characteristics of the series of head forms from normal to acephalic are determined by the specific constitution of the protoplasm and that the effects of the various physiological conditions in altering head-frequency are essentially quantitative and non-specific. In the light of all these and various other facts, the quantitative interpretation presented above has gradually taken form and thus far no facts have been observed which are in conflict with it.

In conclusion, it may be pointed out that the tabulated data confirm earlier work on head-frequency in relation to length of piece and region of body (Child, '11 b, '16). In table 1 the pieces of series 201 and 277 are longer in relation to total length of body than the pieces of other series of the same table and the head-frequency is higher in these longer pieces. Similarly, the *X* pieces of series 327 in table 2, being longer than the *A* pieces of the same series, show a higher head-frequency than these, al-

though the anterior ends of both are at the same level of the body. The tables also show, as do the earlier data, that in pieces of equal length head-frequency decreases with increasing distance from the head of the animal, back to the level of the posterior zooid (Child, '11 d). Series 201 and 277 of table 1, the only series of this paper in which the posterior zooid is included, show an increase in head-frequency in the region of the posterior zooid. These relations between head-frequency and relative length of piece and region of body have been discussed and interpreted in the same terms as the relations between head-frequency and physiological condition considered in this paper (Child, '11 b, '14 b, '14 d) and recent work on carbon-dioxide production in pieces (Robbins and Child, '20) has added further evidence in support of the conclusions drawn from the earlier investigations.

SUMMARY

1. Head-frequency in the regeneration of pieces is lower in physiologically younger (smaller) than in physiologically older (larger) animals.

2. Head-frequency is lower in pieces from starved than in pieces from well-fed animals, even when the two are of the same size.

3. Head-frequency is higher in pieces which are frequently stimulated to motor activity during at least several hours after section than in pieces remaining undisturbed.

4. The range of head forms is the same in relation both to physiological conditions and to external chemical and physical agents, and the changes produced are changes in the frequency of the different forms. This non-specific effect of both physiological and external factors indicates that the action of these factors is essentially quantitative. It is shown that the quantitative interpretation of changes in head-frequency previously advanced serves for the facts presented in this paper.

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