

Entwicklung der meisten Organe. Wachstum und Entwicklung sind an sich mit einander verknüpft. Man kann die Zellteilung einmal rein von physikalischen Gesichtspunkten aus als ein Massenproblem ansehen: Die einzelne Zelle nimmt an Masse zu. Ein Miszverhältnis von Oberfläche zu Zellinhalt zwingt zur Zellteilung, die in diesem Falle lediglich der Möglichkeit einer Massenzunahme eines Organismus dient. Wenn (z.B. durch Unterdrückung der Glykolyse) die Massenzunahme der einzelnen Zelle gehemmt ist, wird seltener der Zwang zur Zellteilung bestehen und damit die Möglichkeit der differenten Potenzverteilung auf verschiedene Zellkomplexe. In diesem Falle würde die Verhinderung des Massenwachstums, die sich in einer verminderten Gewichtszunahme des Körpers zeigen würde, durch Verminderung der Zellteilungen zu einer Hemmung der Gesamtentwicklung führen.

Auf diese Weise liesze sich — unter bewusster Vernachlässigung anderer Regulationsmechanismen, die sicher in dem ganzen Komplex mitspielen — erklären, warum Organe nach Erreichung bestimmter Größen ihr Wachstum einstellen. Ist durch Entwicklung eines genügenden Gefäßsystems für ausreichende Sauerstoffzufuhr gesorgt oder ist der Atmungsapparat der einzelnen Zelle für die betreffende Zellart weit genug entwickelt, so hört das Wachstum auf. Das gleiche gilt im Gegensatz zum Tumorgewebe für das Granulationsgewebe. Bei ihm liegt eine äusserlich bedingte Atemschädigung durch Zerstörung des Gefäßsystems vor. Sobald diese durch Gefäßbildung beseitigt ist, hört das Wachstum auf. Die Narbe organisiert sich. Bei der Tumorzelle ist die Energiestoffwechselabweichung in der Zelle selbst begründet. Sie lässt sich nach den bisher gemachten Erfahrungen nicht durch erhöhte Sauerstoffzufuhr beseitigen. Unter erhöhten Sauerstoffpartialdruck gebrachte Mäusecarzinomzellen *in vitro* behalten ihre Malignität (geprüft an der Weiterverimpfbarkeit) und ihren abwegigen Stoffwechseltypus oder sie gehen zu Grunde. (Eigene unveröffentlichte Versuche.) Erhöhte Sauerstoffzufuhr kann nur bei Zellen mit intakter Atmung, aber nicht bei der Tumorzelle zu einer verstärkten Atmung, zur Unterdrückung der Glykolyse, des Wachstums, zur Tendenz, sich zu differenzieren, sich dem Bauplan des Gesamtorganismus einzuordnen führen, wohl aber — wie sich gezeigt hat — schneller zum Tod der Tumorzelle als der gesunden Zellen. Bei gesunden wachsenden Zellen kann die Differenzierung im Gegensatz zum Wachstum durch Sauerstoffüberangebot mindestens *relativ* gefördert werden.

Zusammenfassung.

Durch Aufzucht in Sauerstoff-reicher Atmosphäre wird das Wachstum von Hühnerembryonen gehemmt, die Differenzierung aber relativ und z.T. auch absolut gefördert.

Anatomy. — *Cephalization and the boundary values of the brain- and body sizes in mammals.* By S. T. BOK. (Communicated by Prof. M. W. WOERDEMAN.)

(Communicated at the meeting of May 20, 1939.)

The researches by VAN ERP TAALMAN KIP showed that in a series of rodents of progressive body sizes the total number of nerve cells in the cerebral cortex as well as the number of dendrites per nerve cell increase according to fixed rules: the number of nerve cells in proportion to the 5/6th power of the body surface and the total length of the dendrites per neuron to the square root of the linear body measures. This increase in length of the dendrites per neuron takes place in two ways: from mouse to rat by a *congruent enlargement of the tree of dendrites*, consequently with increasing radius but e.g. with the same number of dendrite endings, from rat to cavia on the contrary by *increased ramification of the dendrites*, where the radius remains the same but e.g. the number of dendrite endings increases. (From cavia to rabbit a congruent enlargement was observed again.)

These two ways of increase of dendrites may without constraint be compared to *growth* and *division*, two processes which also during increase in size of various other parts of the body occur alternately. Logically there would be, by the side of this growth and division of the dendrites, yet a third way, viz. a *division of the neurons*, where the division, which in the second case is restricted to the dendrites, would penetrate through the cell body and the neurite (here is not meant a division of already differentiated neurons, but a more potential process, which would take place before the ultimate histological differentiation and would result in a double number of neurons). Indeed, such divisions of neurons must occur in the mammals, considering the fact that according to the same investigation by VAN ERP TAALMAN KIP the number of neurons in the human cerebral cortex is considerably larger (about $34 \times$) than it would be if the cortical structure of man would differ from that of the rodents only in such a way as, according to the above-mentioned rules, corresponds with the proportion in body size. Between these rodents and man, consequently, 5 such general neuron divisions would have taken place ($2^5 = 32$).

Such a general neuron division would influence the brain weight much more strongly than the first two ways: these two merely enlarge the size of the dendrite trees and the tissue components belonging to them, by neuron division also the spaces (white substance!) occupied by the cell bodies and by the mostly long neurites would be doubled.

This consequence is in agreement with the researches of DUBOIS, who from comparison of body weight and forebrain weight (weight of the part of the brain in front of the medulla oblongata) concluded that the brain weight of the mammals increases in two ways: in the first place with the body size (viz. in proportion to the 5/9th power of the body weight) and secondly by bounds, each being a doubling of the forebrain weight. The first way corresponds with the increase in number, demonstrated by VAN ERP TAALMAN KIP, of the cortical neurons in proportion to the 5/9th power of the body weight and the second with the neuron division advocated here ¹⁾.

DUBOIS also ascribed the duplications of the brain weight to general neuron divisions (likewise conceived in a developmental stage before the differentiation of the neurons). However, he considered these divisions independent of the body size: they would be the manifestation of a higher degree of neural organization, for which reason he called them cephalization steps. Indeed, animal species with more cephalization steps (with a higher degree of cephalization) are usually also placed higher in the system of the mammals by the systematists. According to the view I suggested, however, the neuron divisions would be one of three ways by which the nervous system follows an increasing body size, so that indeed they would be connected with the body size. As the result of their action they would place the neural organization on a higher level, so that the fact of correlation between cephalization and degree of organization remains unaltered.

That by the side of this there is also a correlation between body size and degree of cephalization, as is required by the conception given here, is apparent from fig. 1, where the cephalization exponent ²⁾ of a number of mammals has been plotted against the logarithm of the body weight. The smallest mammals have the lowest cephalization exponents (the points farthest to the left are at the same time the lowest); with increasing body size (more to the right in the graph) the minimal as well as the maximal

¹⁾ This agreement is not so easily interpreted as it might appear, since the changes in the space occupied by one neuron are not taken into account and besides DUBOIS weighed a large part of the brain whereas VAN ERP TAALMAN KIP only studied the cerebral cortex, so that the results may not yet be compared in detail, although upon the whole the similarity is striking. Moreover, DUBOIS likewise found 5 duplications between mouse and man.

²⁾ As cephalization exponent has been used here the exponent c from the formula $E = 2^c \cdot k \cdot P^{5/9}$. E representing the forebrain weight, P the body weight and k a proportional factor equal for all mammals. For closely related species, where E is proportional to $P^{5/9}$, c is consequently the same; if k is well chosen, c would always be an integer, provided all cephalization steps were pure duplications.

For the graphs the data concerning forebrain- and body weights have been used, contained in the table on p. 9 of the dissertation by BRUMMELKAMP, who obtained these data from DUBOIS, KOHLBRUGGE, LAPICQUE, LAWSON-LAWRY, OWEN and WEBER. To these data I added those of *Balaenoptera Sibbaldi*, recorded by DUBOIS.

and the average cephalization exponents grow regularly larger. That both magnitudes are correlated is also apparent from the correlation index, calculated for these points at 0.50.

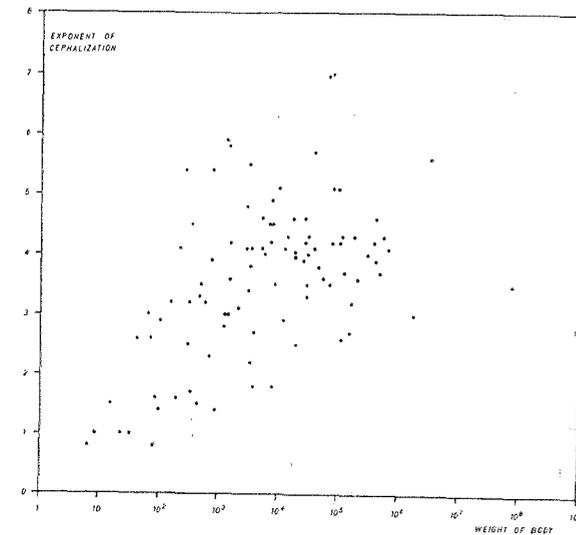


Fig. 1.

Consequently, given a connection between body size and cephalization, the question may be raised whether conditions may exist, in which the other ways of increase of dendrites have to give way to a cephalization step. This question may be illustrated by an example: to which general rule is it due that no rodents of human size are found but that with the increase in body size rather a number of neuron segmentations and consequently cephalization steps disturbed the continuous adaptation of the cerebral cortex to the increasing body size?

In fig. 2 the forebrain and body weights of the above-mentioned table have been logarithmically plotted against each other.

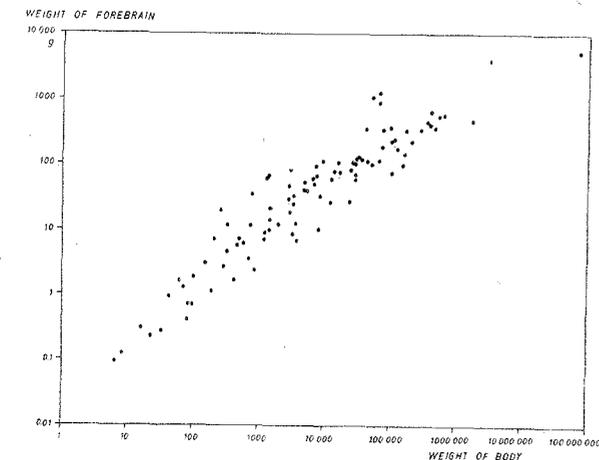


Fig. 2.

If the cephalization steps of DUBOIS would be clearly apparent from these numbers, the points in this graph would all be situated on (and not between) a set of parallel lines, which with the horizontal axis form an angle with a tangent $= 5/9$ and whose mutual vertical distance is $= \log 2$. These lines have been drawn in figure 3: the points do not lie clearly upon them, many lie in between. That this is the case might partly be the result of the fact that the exact steps were found best by DUBOIS if fairly closely related species were compared. The larger groups linked to each other in this way by steps of 2 might have shifted somewhat irregularly, so that in this larger material they are no longer conspicuous. BRUMMELKAMP on the other hand thought that the steps in principle are twice as small as DUBOIS assumed and consequently amount to $\sqrt{2}$. Between every two successive lines in fig. 3 yet another line parallel to the preceding ones would have to be drawn and the smallness of these steps would promote the above-

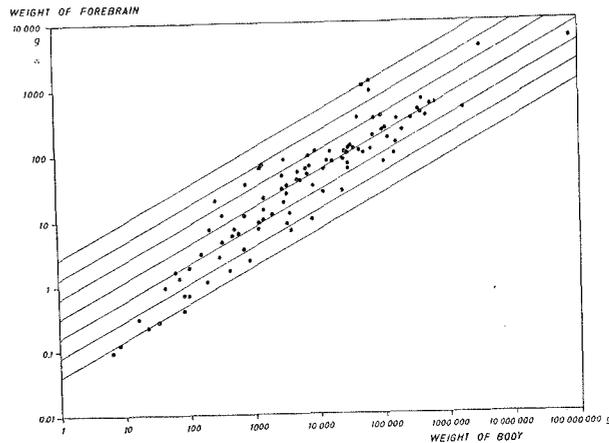


Fig. 3.

mentioned indistinctness. The question whether the cephalization steps amount to $2 \times$ or to $\sqrt{2} \times$ need not greatly influence the above-mentioned conception of the neuron divisions, since it is as yet unknown whether such a neuron division would immediately result in two neurons, each equally large as the neuron before division or first a certain percentage (e.g. $\sqrt{2}$ times) smaller, after which only in following species the original size would be reached by growth.

The relation points in fig. 2 form a connected field which has an exceedingly sharp boundary and a simple form. Unprejudiced consideration might lead to the conclusion that the relation between forebrain weight and body weight is a simple one, which is given by the straight axis of this field of points, and that among the various species represented here only relatively small and arbitrarily distributed deviations from this central relation occur. This relation itself would practically be a direct proportion between forebrain weight and body weight, the above-mentioned axis in this logarithmic graph forming an angle of nearly 45° (so with a tangent of nearly 1) with the horizontal axis.

If in this graph points, belonging to closely related animal species, are connected by lines, as has been done in fig. 4 for 1. a number of *Muridae*,

2. a number of *Siuridae*, 3. a number of *Canidae* and 4. a number of *Anthropoidae*, it appears that these lines indicating the "relation of the

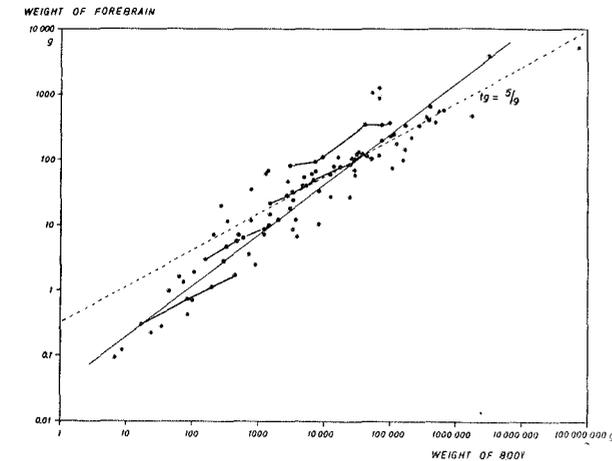


Fig. 4

species" by no means run parallel to the above-mentioned axis: on an average they lie in the direction of a line, the angle of which with the horizontal axis has a tangent $= 5/9$, i.e. they demonstrate, as was to be expected, the connection found by DUBOIS between forebrain- and body weight of closely related species. Seen in the whole of the field of points, they start on the left (so with the animal species with the smallest body weight) on the left boundary of the field of points and run obliquely through the field until at the lower boundary they must of necessity end. If we should arrange the mammals 1^0 according to the species and 2^0 according to body size, we should not, without passing the boundaries of this field, be able to come gradually without steps from mouse to man. At least at the lower boundary of the field we should have to shift to a higher line of species and on this higher line we should not "start" before the left upper boundary of that field. These two boundaries consequently show in some way or other conditions which restrict the growth and division of the dendrites and where nothing but a neuron division (cephalization step) must occur (which of course by no means excludes that such a step may occur also in the middle of the field of points).

These boundaries of the field are exceedingly sharply drawn and therefore it is the more surprising that there has never been paid attention to them. Fig. 5 shows that these boundaries form straight lines. Moreover, the directions of these straight lines point to simple relations between forebrain weight and body weight: the tangent of the gradient of the lower boundary line is $2/3$, that of the upper one $4/3$, i.e. along the lower boundary lie animal species, the forebrain weight of which is proportional to the $2/3$ power of the body weight, along the upper boundary they are proportional to the $4/3$ power. Leaving out of consideration the in-

respect relatively small differences in detail in the forms of these animal species, we may for a proportion with the $2/3$ power of the body weight

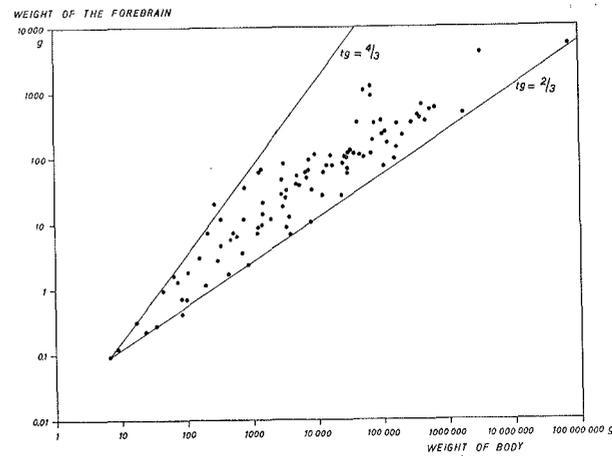


Fig. 5.

read a proportion with the body surface, so that the lower boundary is given by species, the forebrain weight of which is proportional to the body surface, and the upper boundary by species of which the forebrain weight is proportional to the square of the body surface. That means that the ratio *brain weight: body surface* is not lowered below a certain figure and that the ratio *brain weight: square of the body surface* does not rise above a certain figure. (These figures are those of the smallest animal, the *vesperugo pipistrella*.)

On the ground of these data the graphic representation may be more clearly arranged by plotting vertically not the brain weight itself but this ratio *forebrain weight: body surface*. In reality in fig. 6 the ratio *forebrain weight: $2/3$ power of the body weight* was plotted vertically, not the body surfaces but the body weights being measured. Since it is further known that the forebrain weights, apart from a few exceptions, are proportional to the surface of the neocortex, after composing the field of points the zero of the vertical axis has been shifted in such a way that the figures placed there correspond to the ratio *neocortical surface: body surface* or to the neocortical surface per unit of body surface. For the same reason not the body weight but the body surface was plotted horizontally ¹⁾.

Owing to this transformation the field of points appears to have assumed a surprisingly simple form, viz. that of an isosceles trapezium, the basal angles of which are 45° and the lower side is three times longer than the upper one.

¹⁾ Vertically, therefore, has been plotted $\log eE : pP^{2/3}$, in which E represents the forebrain weight, P the body weight and e and p are proportional factors, so that eE represents the exact neocortical surface for man and $pP^{2/3}$ his body surface. Horizontally $\log pP^{2/3}$ has been plotted.

In the lower side we recognize the lower boundary of the field in the figures 2 and 5. The fact that this lower boundary had to be horizontal here follows from the previously known peculiarity that of all species of mammals represented here the neocortical surface per unit of body surface is the same, viz. equal to the minimum value. The new figure (6) shows

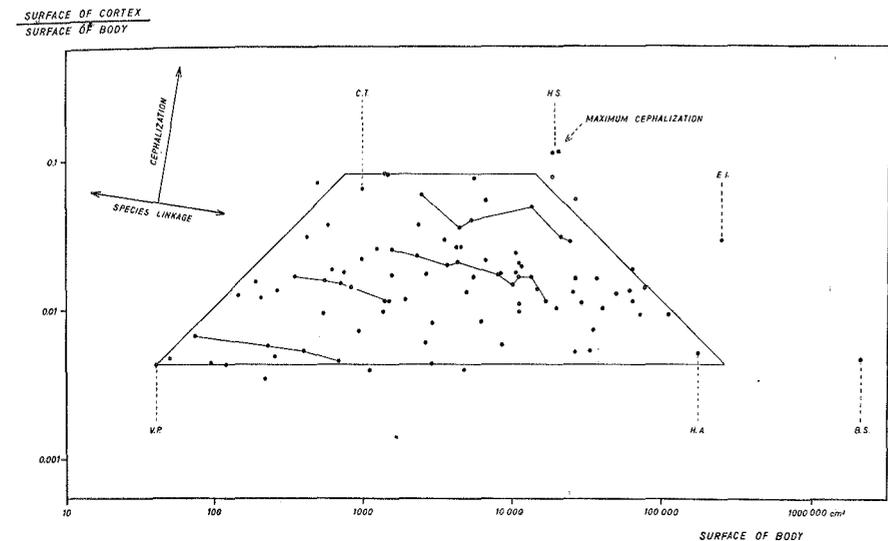


Fig. 6: The relation between neocortical surface and body surface of a number of mammals, compared with the body surface.

- V.P. : *Vesperugo pipistrella*
- C.T. : *Cercopithecus talapoin*
- H.S. : *Homo sapiens*
- H.A. : *Hippopotamus amphibius*
- E.I. : *Elephas indicus*
- B.S. : *Balaenoptera sieboldii*

how accurately this minimum value has been maintained. At the same time it is striking that with so many animal species this minimum value occurs (apart from small differences, to which we can attach no value, owing to the relatively great uncertainty in the determinations of the body weight). In fig. 6 the lower boundary has been drawn through the relation point of the smallest of the represented species (*vesperugo pipistrella*, indicated by the characters V. P.). There the relation between the brain weight and the $2/3$ power of the body weight is 0.01×2.8 . The latter factor is in man 72 (over 25 times as large). In 14 of the 95 represented species this factor is at most only 20 % larger, and to these species belong animals with very different body sizes, as is apparent from the table of page 522.

Opposite this lower boundary lies a likewise horizontal upper boundary. Consequently, along this boundary too the neocortical surface per unit of body surface has a constant value and this means a maximum value (only man is represented above this maximum value; *pithecanthropus erectus*, as far as this may be determined, lies just within it). The maximum value

Species	Data obtained from	Body weight (in grammes)	Forebrain weight (in grammes)	Forebrain weight divided by the 2/3 power of the body weight ($\times 100$)
Balaenoptera Sibbaldi (Balaenoptera sieboldii GRAY)	DUBOIS	7400000	5243	3.0
Hippopotamus amphibius (Hippopotamus amphibius L.)	WEBER	1755000	479	3.3
Sus scropha domesticus (Sus scropha domesticus L.)	LAWSON-LAWRY	104539	73.9	3.3
Manis Javanica (Manis Javanica L.)	KOHLBRUGGE	8000	10.0	2.5
Lagostomus trichodactylus (Lagostomus trichodactylus BENN.)	OWEN	3854	6.69	2.7
Erinaceus europaeus (Erinaceus europaeus L.)	WEBER	885	2.36	2.6
Mus norvegicus (Rattus norvegicus (ERXL.))	WEBER	448	1.69	2.9
Mus rattus (Rattus rattus (ERXL.))	DUBOIS	200	1.137	3.3
Scotophilus gigus (Scotophilus gigus DOBSON)	WEBER	101	0.666	3.1
Crocidura schweizeri (Crocidura schweizeri PETERS)	WEBER	82	0.409	2.2
Vespertilio murinus (Vespertilio murinus L.)	DUBOIS	33.3	0.283	2.7
Rinolophus ferrumequinum (Rhinolophus ferrum-equinum SCHREB.)	DUBOIS	23.5	0.230	2.8
Crocidura araneus (Crocidura araneus BLAS.)	LAPICQUE	8.8	0.128	3.0
Vesperugo pipistrella (Pipistrellus pipistrellus SCHREB.)	DUBOIS	6.5	0.096	2.8

appears to be $19 \times$ the minimum value. *With the mammals the neocortical surface per unit of body surface is consequently limited between a minimum and a 19 times larger maximum value.* This limitation is not such that with one species the highest and with another the smallest value occurs, but a conspicuously large number of species of very different body sizes lie exactly on these boundary values.

The right side of the trapezium points to a maximum in the absolute size of the neocortical surface: to all points of this line, namely, belongs the same neocortical surface (and the same brain weight). This follows from the consideration that along this line (owing to its gradient of -45°) with an increase of the horizontally plotted magnitude ($\log S$ or \log surface of the body) the vertically plotted magnitude ($\log N/S$) decreases by the same figure, so that their sum remains the same: $\log S + \log N/S$ consequently is constant, so that $\log S + \log N - \log S$ or $\log N$ and therefore also N along this line is constant. Points on the left of this line point to a smaller neocortical surface, points on the right to a larger one. However, practically no points are found on the right of this line; only two points (the elephant and the whale) form an exception.

Consequently, with the species of mammals represented here the neocortical surface remains below a certain maximum value. This maximal value of the neocortical surface (and consequently also of the forebrain weight) is, for example, specific to *hippopotamus amphibius* (H. A. in fig. 6).

The neocortical surface (and the forebrain weight) is minimal with the species represented most to the left below, *vesperugo pipistrella*, which minimum according to the figure is 19^3 times smaller than the maximum. The neocortical surface (and the forebrain weight) consequently varies 19^3 times. This variation, therefore, is equally large as the variation of the body surface.

In the left boundary we recognize the left upper boundary of the field of points in the figures 2 and 5. Along this boundary the relation *neocortical surface: square of the body surface* (or *brain weight: body surface*²) is constant and maximal. This follows from the consideration that along this line, owing to its gradient of 45° , the vertically plotted value rises as much as the horizontally plotted one, so that their difference is constant: $\log N/S - \log S = \text{constant}$, so that $\log N - \log S - \log S$ or $\log N - 2 \log S$ or $\log N/S^2$ and consequently also N/S^2 is constant.

Consequently also the relation between the neocortical surface (or the forebrain weight) and the square of the body surface with the mammals is limited by a certain maximum value. The biological significance of this limitation is not so selfevident as that of the three above-mentioned limitations. Possibly this relation has a functional significance, in connection with the integrating function of the nervous system. The first two limitations point to an intimate relation between the size of the nervous system and

the body *surface* (by which is meant a two-dimensional body measure, which by no means need to be e.g. the surface of the skin). If now this body surface (this two-dimensional body measure) determines the number of afferent (and efferent) stimulation tracts, then a body surface twice as large would double this number of stimulation tracts and the receiving and transmitting apparatuses linked to them. At the same time, however, it must be possible to connect each of these tracts with twice that number of other tracts, so that the number of possible connections — expressed very schematically — maximally would become 2^2 times larger. It is possible that this consideration indicates the direction of the significance of this fourth boundary, which determines the maximum of the relation between neocortical surface (or forebrain weight) and the square of the body surface. The fact that this maximum is indeed determined, may with certainty be read from the many points lying along this left side of the trapezium.

The maximum variation of this relation N/S^2 is, like that of the neocortical surface and of the body surface, 19^3 times. The minimum value is situated near the lower right angle of the trapezium (the hippopotamus).

Recapitulating we may consequently state that the brain- and body measures in the present species of mammals are subject to the following four restrictions:

1. the relation *neocortical surface* : *body surface* (or the quantity of neocortical surface per unit of body surface) with the mammals does not descend below a certain minimum value (present e.g. in *vesperugo pipistrella*, see V.P. in fig. 6);
2. the same relation does not exceed a certain maximum value, which is $19 \times$ larger than the mentioned minimum value;
3. the relation *neocortical surface* : *square of the body surface* does not exceed a special value (likewise present in *vesperugo pipistrella*);
4. the neocortical surface does not exceed a certain maximum value (19^3 times the minimum value, present in *vesperugo pipistrella*).

It appears from the regularity of the trapezium that between these four restrictions there must exist a mutual relation.

To these four restrictions only very few exceptions occur. The relation points for man are found just outside the upper right angle of the trapezium, so that it is doubtful whether man forms an exception. Only the elephant and the whale (E.I. and B.S. in fig. 6) lie definitely outside. However, the great majority of the represented species lie inside and so many points just touch the described boundary lines that these boundaries undoubtedly must have an intrinsic value, as regards the structure of the nervous system as well as the restriction of the idea mammal.

Which exactly is this significance cannot yet be ascertained. It will be of great value to make the same determinations on other classes in order to find out whether other classes may be limited in a similar way and of

what nature the differences between those classes, considered in this way, will then appear to be.

Similarly it will be of great value to make a chart in this way of the extinct species of mammals, in order to see whether and how the trapezium changes with time. Possibly this will also throw light upon the few, still living, very large species which lie outside the trapezium.

It is interesting to see how the relation of the species and the cephalization are expressed in this trapezium graph.

In a simple way we can conclude that the ideal line of the relation of the species, which in fig. 5 had a gradient with a tangent $= 5/9$, here is a descending line with a tangent $= -1/6$. This is also demonstrated by the fact that the same points which are mutually connected in fig. 5 are likewise connected in fig. 6. The cephalization steps, consequently, lie here in a steep direction, which is characterized by a gradient with a tangent $= 5/6$ (see the arrows drawn on the left above). The upper angular point on the right consequently has the highest degree of cephalization. Here *pithecanthropus erectus* is found, and one cephalization step outside man (man and woman indicated separately). Along the lines of the relation of the species, so following the increasing body size with growth or division of the dendrites, the relation *neocortical surface* : *body surface* descends constantly. This is clear, owing to the fact that the brain weight and consequently the neocortical surface increase in proportion to the $5/9$ power of the body weight or in proportion to the $5/6$ power of the body surface, i.e. somewhat less rapidly than the body surface. If our starting-point lay not so high in the figure (if we had started from a not specially highly cephalized species), this descent would come to a stop when the relation *neocortical surface* : *body surface* reaches the minimum value (lower side of the trapezium). With a then consequently necessary enlargement by neuron division we may not start on the following line of species before N/S^2 has the maximum value. If our starting-point lay higher (or if we reach such a higher point after a general neuron division), then the limit of the lines of the relation of the species, and consequently the necessary indication for a neuron division, is reached when the neocortical surface reaches its maximal size.

The observed fact, that the indicated simple limits, fixed for the mammals to the relation between brain- and body size, form necessary indications for the cephalization steps (general neuron divisions) is a second confirmation of the view that the cephalization steps are connected with the increasing body sizes.