Anatomy. — *Brain-Bodyweight relation in human ontogenesis.* By J. ARIËNS KAPPERS. (Communicated by C. U. ARIËNS KAPPERS.)

(Communicated at the meeting of June 27, 1936).

Data concerning brainweight in fetal life are rare and the number of data from one author is far too small to be used for our purpose. The softness of the fetal brain makes it difficult to obtain fresh specimens, while preserved material can be used only as far as its weight is concerned with the greatest precaution.

The most reliable data, also on account of their number, are those mentioned in the series collected by JACKSON [1]). Of about 800 male and female specimens of various stages of fetal life published by WELCKER and BRANDT, LEGOU, FAUCON, ARNOVLJEVIC, ANDERSON, BOYD, LOMER, MEEH, LIMAN, THOMA, OPPENHEIMER, MÜHLMANN, COLLIN and LUCIEN, BENEKE and some by himself, JACKSON made a sharp selection, using for brainweight only 316 specimens from the second intra-uterine month to birth.

In his tables he gives the average weight percentage of various organs, calculated on the average total weight in such a way that for each individual specimen for each organ of this specimen the bodyweight percentage is calculated and from this the average of all the cases in each intra-uterine month is given. He also gives the variations, adding the minimum and maximum values. Since also the absolute bodyweights are mentioned, the average absolute weight of each organ may be easily calculated from his tables.

Evidently the average weights do not represent the condition at the beginning or at the end of a month, each average being taken over a whole month. Yet the average date of the month for which the average weight figures hold good, may be calculated with a fair degree of accuracy, the more so as the average body weights at the end of each month are calculated after the data of AHLFELD, LEGOU, FEHLING and MICHAELIS. The curve constructed by means of these averages is the ideal mean of the curves constructed after the data of each of these authors which do not run exactly parallel, especially not for the end of the prenatal period.

For the postnatal period we used VIERORDT's figures [2]) which were also critically selected by this author from data from various sources.

The number of brains whose weight was taken was 483, distributed over 25 years. A disadvantage of VIERORDT's means is that the figures used for making it, were not first calculated individually as JACKSON did. VIERORDT's figures have been partly corrected by DONALDSON [3]). Of these postnatal data only male specimens were used.

Especially the averages of these brainweights suffer from a certain lack of exactitude

---

1) JACKSON, C. M. On the Prenatal Growth of the Human Body and the relative Growth of the various Organs and Parts. The American Journal of Anatomy, Vol. IX.

2) VIERORDT, H. Daten und Tabellen für Mediziner, Jena (1906).

3) DONALDSON. The growth of the brain. London (1898).

by the relatively small number of specimens in some age periods. This as well as the fact that the postnatal data concern periods of a whole year and do not give the condition at the end of such a year also explains that — according to these figures — the brainweight does not continually increase after birth but sometimes gives a lower average for an older year. This does not agree with what may be expected in a period of growth and apparently is due to an insufficiency of reliable data. —

Since curves are more instructive than a series of figures to indicate the increase of brain- and bodyweight, we give in fig. 1 the logarithmic curves of their evolutionary increase up to the 25th year.

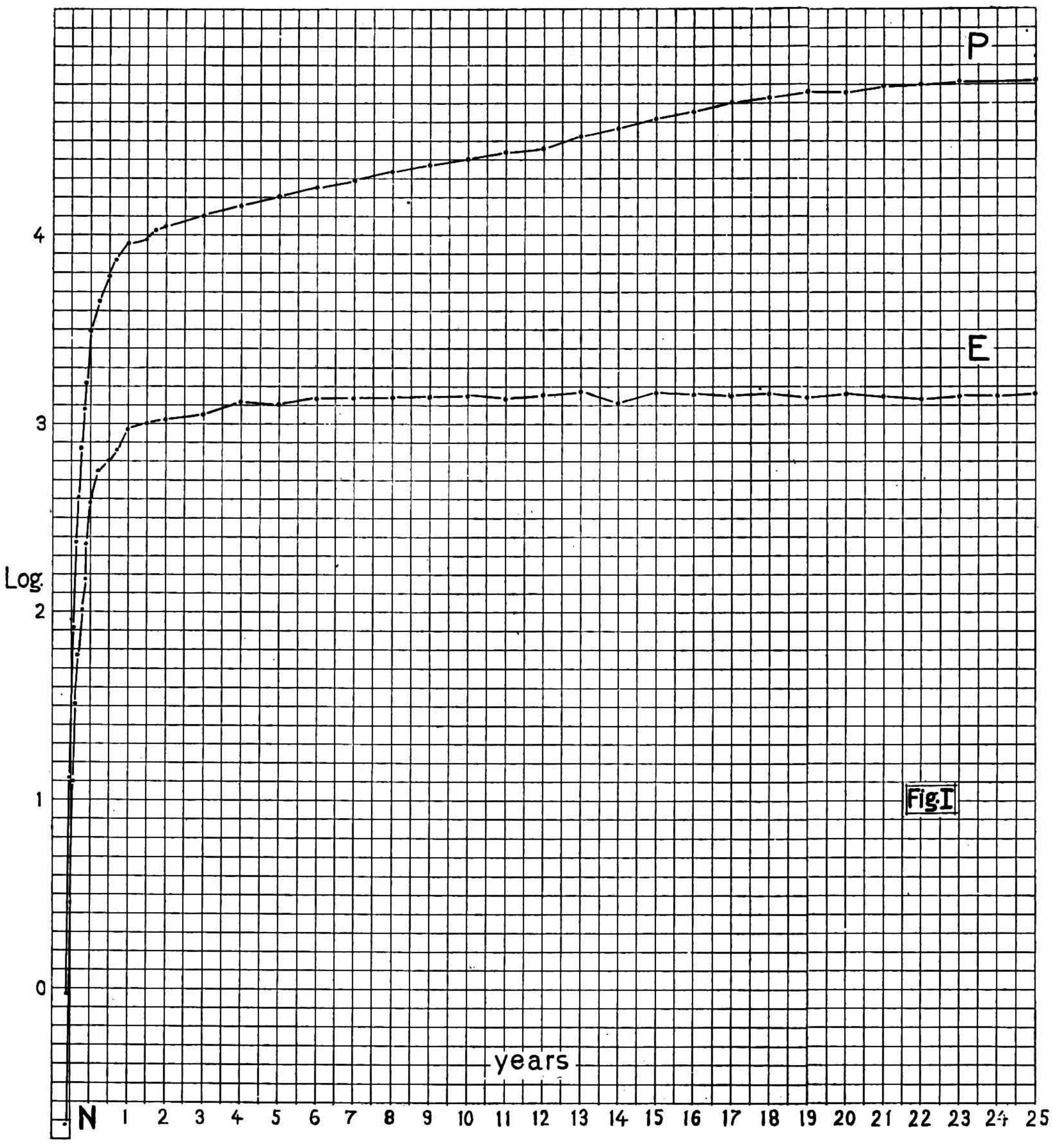

Fig. I. Graph of the logarithmic grouwth of brain- (E) and bodyweight (P) from the second intra-uterine month to the twenty-fifth year, after JACKSON's and VIERORDT's data. Time on the absciss, logarithms of the weight in grammes on the ordinate.

As is well known, growth usually is a more or less cyclic process in which the rapidity shows maxima and minima. If we draw a monocyclic growth curve by a graph in which time is put on the absciss and weight on the ordinate, this graph will be *S*-shaped. It is furthermore known (FAURÉ—FREMIET [1]), ROBERTSON [2]) a.o.) that the human organism as a whole passes through at least three of such cycles, the first of which, covering the whole fetal period, is not yet finished at birth but some time after it. The second cycle has a maximum about the 5th year, while the third, having its maximum at puberty, only finishes in the adult.

These cycles are also observed in studying JACKSON's and VIERORDT's bodyweight figures. They even are indicated more or less in fig. 1. It appears that the first cycle, which for its greater part covers the fetal period, is more important for the final weight of the body as a whole than the following cycles, the rapidity of growth, i.e. the increase of weight per time unit, relatively and logarithmically expressed, being much greater than in the postnatal cycles, the rise of the fetal curve being much steeper than in the postnatal curves. From the figures it furthermore appears that the first cycle ends between the second and third year [3]), when the second cycle begins, as is also shown in our curves by the strongly diminished rise of the growth line in the second and third year. After this year again a new but small rise occurs, obtaining its maximum at the 5th year.

This maximum is much smaller than that in the first, chiefly fetal cycle where it coincides approximately with the 9th intra-uterine month and it is also smaller than the maximum in the third cycle which lies between the 15th and 16th year.

Turning to the growth curve of the brain, we find that here also at least three cycles occur, each showing a distinct maximum. The first one, covering the fetal period, has the greatest percentual maximum of all, just as in the growth curve of the bodyweight, and, similarly as the latter, it only ends after birth about the second year. Its maximum coincides with the ninth intra-uterine month.

Owing to the lesser exactitude of the data concerning postnatal brain-weights, the following cycles cannot be well determined. Yet, a closer analysis shows that certainly two postnatal maxima occur, proving the existence of two cycles, the first postnatal maximum falling between the 3rd and 4th year, the second or last one in puberty, about the 13th year.

Contrary, however, to what was found with bodyweight, the maximum increase of brainweight of the second cycle — in the 4th year — is

---

[1]) FAURÉ-FREMIET, E. La Cinétique du développement. Paris (1925).

[2]) ROBERTSON, B. On the normal rate of growth of an individual and its biochemical significance. Archiv. für Entwickl. Mech. Bd. XXV. Idem, Further remarks. Ibidem Bd. XXVI.

[3]) According to the data used by ROBERTSON (i. l. c.) the first growth cycle finishes at the end of the first natal year.

percentually larger than the maximum increase of the third cycle, coinciding with the 13th year.

Apart from the above-mentioned maxima, another though very small maximum seems to occur in the 9th year. The figures hitherto available however, are too uncertain to consider this maximum as indicating a cycle of its own and it may be better to consider it as a preceding indication of the maximum at the onset of puberty.

Resuming our results concerning brain- and bodyweight, we find that in both processes at least three cycles occur, the maxima of which are such that those of the brainweight occur about the same time (slightly earlier) as those of bodyweight. In both processes the first cycle closes about the second year, the second runs from the second to the 7th year, when the last cycle begins, which closes with adult life. Furthermore in both processes maxima occur at the 9th intra-uterine month, about the 4th—5th year and at the onset of puberty.

Consequently there is a close parallelism in the growth of body and brain. The *S*-shape of the first cycle of brain increase is seen in fig. 2, which at the same time shows that this cycle is not an ideally symmetric one.

As ROBERTSON [1]) pointed out, a monocyclic *S*-shaped growth curve is very similar to a graph of an autocatalytic reaction. In such reactions the products resulting from it, act as a catalyser on the reaction itself. This causes the rapidity of the reaction to increase at the beginning pari passu with the increase of reaction products. This possibility, however, being limited by the consumption of the necessary material, the rapidity of reaction, after having attained a maximum, again decreases to reach the zero point, when the available material is exhausted.

This parallelism of growth curves and autocatalytic reactioncurve induced ROBERTSON — without sufficient explaining it biologically — to express these curves by the formula $Log \frac{x}{A-x} = K\ (t-t^1)$ (for the deduction of this formula see footnote [2]), for its greater reliability than that of other formulae of relation see footnote [3]). In this formula x = weight of the growing organ or organism at the time t, A = its maximum weight at the end of the growth cycle and t^1 = the time at which half of this maximum weight has been attained. K is a constant that may be calculated for a given value of x at a given time t.

HERINGA [4]) gave us various arguments to show that this relation may be

---

1) ROBERTSON, l.c.

2) ROBERTSON, l.c. Bd. XXV.

3) ROBERTSON, B. Explanatory remarks concerning the normal rate of growth of an individual and its biochemical significance. Biologisches Zentralblatt. Bd. XXX (1910).

4) HERINGA, G. C. Organische opbouw en afbraak. Vlaamsch Geneesk. Tijdschr. N⁰. 3 (1929).

understood, starting from the hypothesis that, generally speaking, the intensity of a biological process is a function of one of the products resulting from it.

From ROBERTSON's examples it appears that his formula is widely applicable in zoological as well as in botanical processes of growth. Elaborating this conception, ROBERTSON used the same formula as a point of issue for the mathematical expression of the relation between the growth of the body and one of its organs, applying the following formula:

$Log\ \frac{x^{I}}{A_{I}-x^{I}} = a\ Log\ \frac{x^{II}}{A_{II}-x^{II}} + b$, in which x^{I} and x^{II} are the weights of the organ and of the organism at the same time; A_{I} and A_{II} the respective maximum weights and a and b two constants, calculated according to the method of the least squares. Substituting VIERORDT's data in this formula, ROBERTSON finds the following relation between brain- and bodyweight:

$Log\ \frac{X^{I}}{1.5-X^{I}} = 1.723\ Log\ \frac{X^{II}}{66.3-X^{II}} + 1.675389$, in which X^{I} is the brainweight, X^{II} the bodyweight at a given age and 1,5 and 66,3 the final maximum values of brain- and bodyweight, expressed in kilogrammes [1]).

With this formula ROBERTSON calculates by substitution the brainweights going with certain bodyweights in the postnatal period. That his results are quite conform to the reality appears from the following table:

TABLE I.

Age	Bodyweight	Brainweight		Difference $\pm \frac{\text{calc.} \pm \text{observ.}}{\text{observ.}} \cdot 100\%$
		Observed	Calculated	
Neonatus	3.1 K.G.	0.381	0.311	— 18.3 %
1st year	9.0 „	0.945	0.991	+ 4.8 %
5th year	15.9 „	1.263	1.300	+ 2.9 %
10th year	25.2 „	1.408	1.430	+ 1.5 %
15th year	41.4 „	1.490	1.487	— 0.2 %
20th year	59.5 „	1.445	1.499	+ 3.7 %
25th year	66.3 „	1.431	1.500	+ 4.8 %

In this table the difference between the calculated and observed brainweights varies from 0.2—18.3 %.

1) According to two mathematicians I consulted in this matter, ROBERTSON may have committed a mistake in applying the method of the least squares (ROBERTSON l.c. Arch. Entwickl. Mech. Bnd. 25). Correcting this mistake, we get as value for the constants 1.711 and 1.663, a difference not large enough to give considerable changes in the above-mentioned table.

Applying the same formula to the fetal period, we observed that the differences were far greater, varying from 51.4 %—99.8 %, so that apparently this formula, though giving good results for the postnatal period, is not applicable to the fetal period.

This, however, is not strange. If we consider fig. 3, giving the curve of the relation between body- and brainweight unto the 10th year, we see that the shape of this curve in the fetal period is very different from that in the postnatal period, for which ROBERTSON used his formula.

Yet, it appeared to me that ROBERTSON's basis formula of relation may be applied to the fetal period. Following his method, we found another mathematical expression for the relation between brain- and bodyweight during the fetal period and the two first years after birth — thus covering what is called the first growth cycle:

This mathematical expression is as follows:

$$Log \frac{X^{I}}{1.0254 - X^{I}} = 0.8943 \; Log \frac{X^{II}}{11.0 - X^{II}} + 0.1022.$$

The adjoining table gives the results obtained with this expression:

TABLE II.

Age	Bodyweight	Brainweight		Difference
		Observed	Calculated	
1st year	9.0	0 9447	0.8503	— 9.9 %
Neonatus	3.1	0.381	0.3630	— 4.7 %
In 9th intra-ut. mth.	1.609	0.232983	0.212390	— 8.8 %
In 8th " "	1.196	0.149022	0.153836	+ 3.2 %
In 7th " "	0.784	0.102999	0.111292	+ 7.1 %
In 6th " "	0.4131	0.059073	0.066692	+ 12.8 %
In 5th " "	0.2340	0.032666	0.040595	+ 24.2 %
In 4th " "	0.08088	0.012714	0.015890	+ 24.9 %
In 3rd " "	0.01496	0.002865	0.003537	+ 23.4 %
In 2nd intra-ut. mnth.	0.000904	0.000185	0.000288	+ 55.6 %

The difference between observed and calculated brainweights, after substitution of the bodyweights according to JACKSON's data, now only varies between 3.2 % and 24.9 %, so that with the above-mentioned formula we obtained a somewhat more satisfactory mathematical expression for the body-brainweight relation in the fetal period conform to and thus confirming ROBERTSON's supposition.

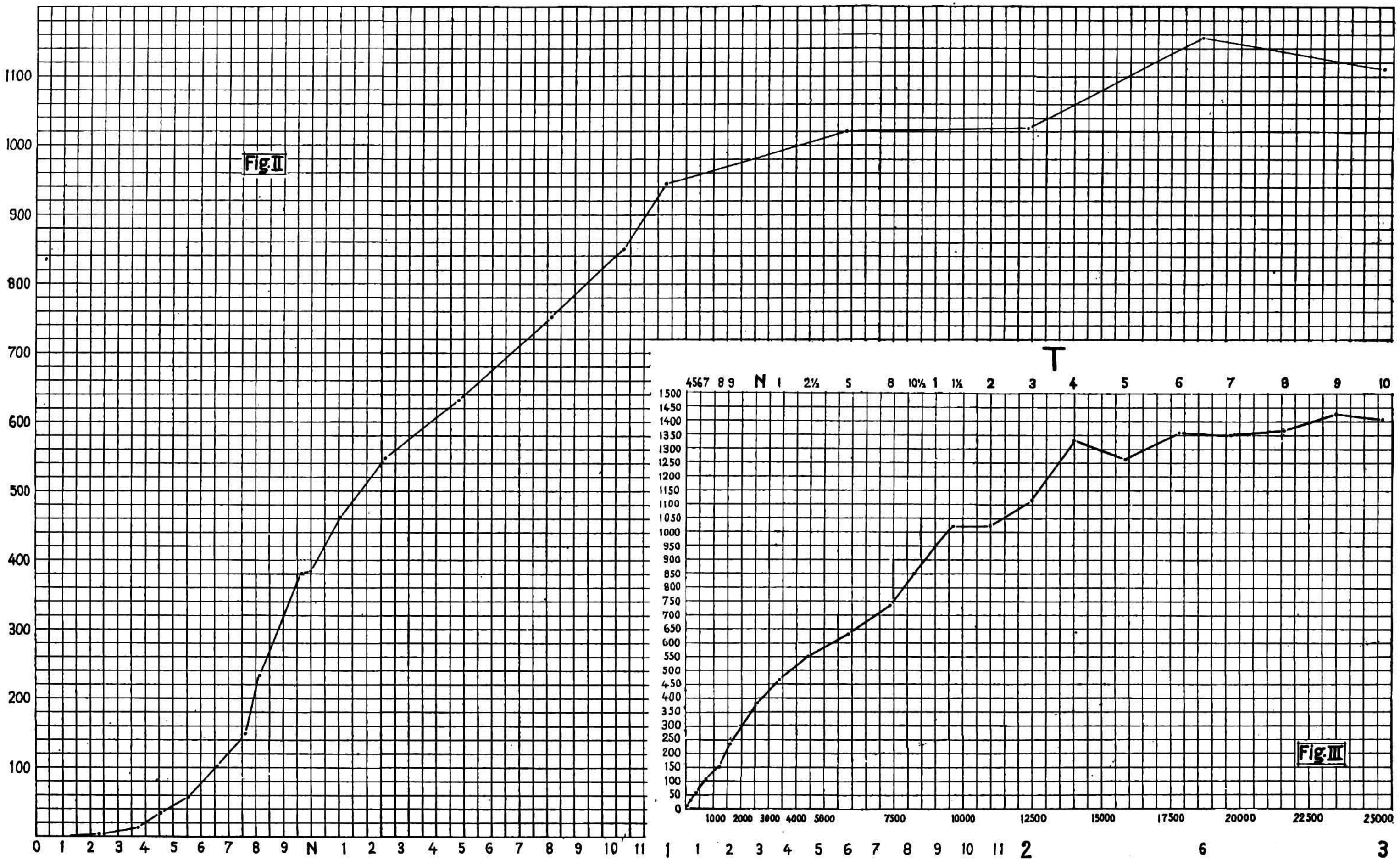

Fig. II. Graph of the absolute growth of the brain from the second intra-uterine month to the third year. Time on the absciss, weight in grammes on the ordinate; after JACKSON's and VIERORDT's data.

Fig. III. Graph of the relation curve of body- and brainweight. Bodyweight in grammes on the absciss, brainweight on the ordinate, also in grammes. Above the absciss, parallel to it, time is given; after JACKSON's and VIERORDT's data.

The discrepancies between observed and calculated values are certainly due to the quality and quantity of the material, as is most evident in the youngest intra-uterine month of which only three objects were available. Besides, these discrepancies will become less, if the upper limit of the first growth cycle will be more exactly established and with the increase of the reliability of the other data, necessary for this sort of work. This holds good specially for the first five fetal months.

This much appears that the relation between brain- and bodyweight may be expressed fairly exactly for the whole ontogenetic development by the following two mathematical formulae which, though equal in character, differ by their constants and their maximum values, at the same time showing that the relation in the first cycle differs a good deal from that in the second and third.

For the first growth cycle — including fetal life plus the first two years of natal life — the formula is:

$$Log \frac{X^{I}}{1.0254-X^{I}} = 0.8943 \, Log \frac{X^{II}}{11.0-X^{II}} + 0.1022;$$

for the rest of postnatal life, i.e. for the two cycles following the 2nd year, the formula is:

$$Log \frac{X^{I}}{1.5-X^{I}} = 1.723 \, Log \frac{X^{II}}{66.3-X^{II}} + 1{,}675389.$$

The shape of the curves expressing these formulae as far as they are real, is thus, in some degree, indicated in the continuous line of fig. 3 from the 4th intra-uterine month unto the 10th year.

A totally different way to analyse growth processes is by using growth curves of the total organism in which the percentual increase per time unit is expressed, as was done by MINOT [1]) a.o.

For this purpose a diagram is made of the number of weight percentages to be added to a body in a special time unit (period), so that the final weight would be normal at the end of that period.

This number of percentages might then be inserted graphically at the beginning of that period. One might call this potency of increase, expressed in percentages, the "growth energy".

Already MINOT pointed out that this "growth energy", with all organisms without any exception, is very large in an early ontogenetic period, decreasing gradually until it reaches the zero point [2]) in attaining the adult stage.

The developmental increase of the parts of an organism, i.e. of separate organs, shows the same. In fig. 4 we give the curves of the percentual increase of brain- (E) and bodyweight (P) to the 2nd year, calculated with

---

1) MINOT, CH. S. The problem of age, growth and death. The popular Science Monthly, Vol. LXXI (1907).

2) Also JACKSON and MÜHLMANN (quoted by JACKSON l.c.).

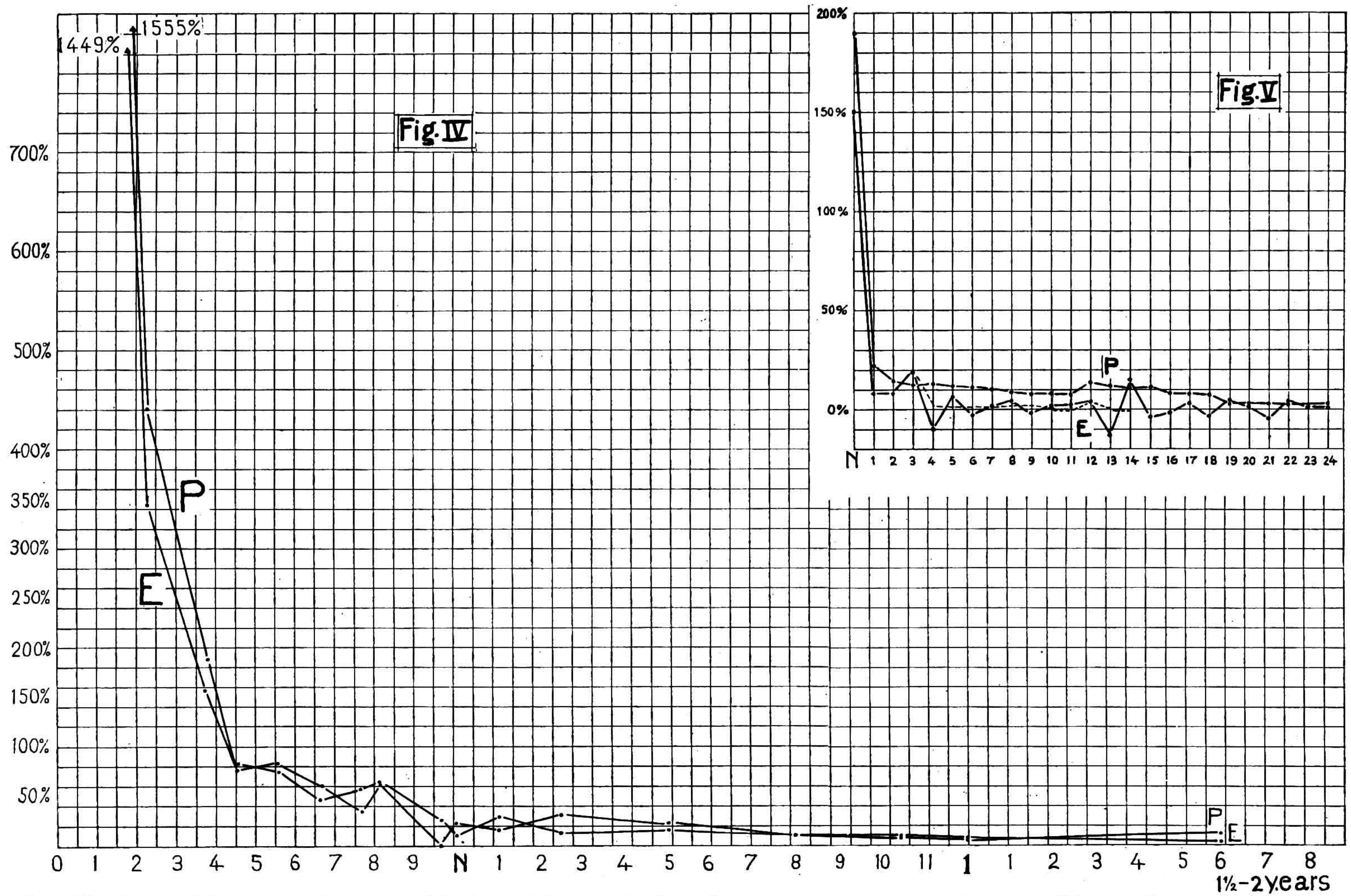

Fig. IV. Graph of the percentual increase of body- and brainweight from the second intra-uterine month to the 1½ year (see text). Time on the absciss. Percentual increase on the ordinate; after JACKSON's and VIERORDT's data.

Fig. V. Graph of the percentual annual increase of body- and brainweight from birth till the 25th year; after VIERORDT's data. Dotted line: curve of brain increase after eliminating the negative values.

JACKSON's and VIERORDT's data. In both curves the increase of the average data of each i.e. the "growth energy", is very large from the second to the third intra-uterine month, viz. 1449 % and 1555 %. The curves then descend rapidly, although the periods between which the percentages have been calculated are approximately the same. In other words there is a pronounced slowing down of the percentual weight increase per time unit, which again rises somewhat before birth about the period of the maximum weight increase of the first cycle.

In fig. 5 about the same is seen. This figure shows the percentual increase in periods of one year according to VIERORDT's data. As pointed out above (p. 872) there are no absolute periods of one year between these data. Yet also here we see small rises of the curves between the 4th and 5th year and at the onset of puberty, corresponding with the maxima of the two postnatal growth cycles.

In figs. 4 and 5 some points are striking. First of all the fact, that also here the growth curves for brain- and bodyweight run practically in the same way, the character of both curves being very similar. This was to be expected after what has been said above.

It furthermore appears that the absolute difference in percentual increase between body and brainweight — so pronounced at the beginning of ontogenetic development — very soon decreases, though even this small difference in the last part of development has to be considered as relatively important.

Finally the relation between the growth energy of body and brain in the fetal period comes very near the value 1, as shown by our calculations. This does not hold good for the postnatal period, in which this relation, though much more variable, with the exception of the first four years remains far above the value 1. — The relation between the percentual increase of body and brainweight calculated over the whole fetal period, i.e. from JACKSON's second month's data till birth, is 1.4. For the postnatal period to adult age it is 6.9.

At the beginning of ontogenetic development, when the percentual increase of both body- and brainweight per time unit is very high, the differences between the whole organism and the organ are larger than later on when this increase for body and brain and also their absolute difference is small. In the fetal period their relation, however, is about 1, whereas — as stated above — this relation in the postnatal period is much higher.

The difference in relative weight (and size) in various periods between body and brain, i.e. the smaller relative weight of the brain in the adult compared to the beginning of the postnatal period, is an expression of the relatively greater percentual increase per time unit of the total organism in the intervening period, although the difference of its absolute value compared to the "growth energy" of the brain is small.