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Norms for some structural changes in the human cerebellum from birth to old age

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Resumen por el autor, Robert S. Ellis.

Normas para algunos cambios estructurales del cerebelo humano desde el nacimiento hasta la vejez.

En el recién nacido el cerebelo humano es relativamente pequeño comparado con el cerebro, pero crece rápidamente y a la edad de unos quince meses las partes del encéfalo adquieren aproximadamente los mismos pesos relativos del adulto. El peso relativo del cerebelo no varía de un modo significativo con la estatura, sexo, raza o inteligencia. Entre el nacimiento y la edad de quince meses la capa celular de los granos externos desaparece, las células de Purkinje crecen hasta alcanzar el tamaño normal del adulto, las capas molecular y granulosa interna adquieren la misma anchura relativa de las del adulto y las vainas de mielina crecen rápidamente, especialmente al final de este periodo. Estos cambios deben relacionarse con el hecho de que próximamente en este tiempo la actividad motriz del niño aumenta progresivamente y está comenzando a andar. Con el principio de la senescencia coincide una pérdida de células de Purkinje y una pérdida resultante de fibras mielinadas. Con este cambio estructural debe relacionarse la pérdida de fuerza y coordinación muscular, tan característica de la vejez. Existen algunas pruebas de que durante la vejez el hemisferio cerebelar derecho pierde mas células que el izquierdo, a causa tal vez de los efectos del uso excesivo de la mitad derecha del cuerpo. En los casos estudiados se ha encontrado menor número de células de Purkinje en los cerebelos de las hembras que en los de los varones.

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NORMS FOR SOME STRUCTURAL CHANGES IN THE HUMAN CEREBELLUM FROM BIRTH TO OLD AGE

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EIGHT CHARTS

In a previous paper (Ellis, '19) I reported the results of a quantitative study of the Purkinje cells in normal, subnormal, and senescent human cerebella; the variations in the number of these cells in different cerebella were correlated with differences in muscular strength and in the development of motor coördination. However, the results presented for the decrease in the number of Purkinje cells with advancing age were based on such a small number of cases that it seemed desirable to extend the observations and to determine with more certainty the accuracy of some of the conclusions reached. This has been done, and the results of the further study are presented in this paper. In addition, I have reviewed the literature on the growth of the human cerebellum, have added some original observations, and have attempted to give a résumé of some important normal—not pathological—structural changes in the cerebellum from birth to death in old age. Variations from the norm have been observed, and as far as possible these structural changes have been correlated with changes in motor efficiency.

For the increase in the weight of the cerebellum during growth I have used the results of Boyd ('61), Danielbekoff ('85), and Pfister ('97–'03); on the significance of the relative weight of the cerebellum I have reviewed the work of Gall (1807), Leuret ('39), Hatai ('15), Marshall ('92), Bischoff ('80), Meynert ('67), Weisbach ('66–'67), and Spitzka ('07), and I have calculated the relative weights of 152 cerebella from data given by Mall ('09) and by Bean ('06), and to this I have added the relative weights of the cerebella of eighteen idiots and imbeciles whose brains are in The Wistar Institute Museum. On the disappearance of the layer of external granule cells I have reviewed the work of Vignal ('89), Berliner ('05), Biach ('09), Löwy ('10), Takasu ('05) and Addison ('11), and I have verified their conclusions by a study of a number of cases of human cerebella. For the relative thicknesses of the molecular, internal granular, and fiber layers, I have reviewed the work of Engel ('63), Krohn ('92), and Roncoroni ('05) and I have added some original measurements. Material for satisfactory measurements of the growth in size of the Purkinje cells has not been available, but I have made a few measurements on such cases as I could obtain. I have counted the Purkinje cells in two areas of both hemispheres of sixty-three cerebella from negroes, whites, and mulattoes of both sexes and of ages ranging from twelve to ninety-two years, and have compared these results with those already reported. On the growth and degeneration of the myelin sheath I have reviewed the work of Engel ('63), Lui ('94), de Sanctis ('98), Berliner ('05) and Löwy ('10).

Finally I have studied the degeneration of the cells of the dentate nucleus in senescence.

Many of the papers discussed are, it is true, rather old, but I have felt justified in bringing these various data together in order to get a general view of the different changes in the cerebellum during life and of the relation of these to variations to functional efficiency.

THE WEIGHT OF THE CEREBELLUM

Perfectly satisfactory weights for the human cerebellum during the early stages of growth are not available, and hospital material probably gives results which are below the average for the population at large. It is consequently not surprising that the weights recorded by different observers show more or less variation.

Boyd, in England, made extensive records of the weights of the parts of the brain, as well as of other organs, and these have been compiled and published by Sharpey ('61), and by Marshall

('92). Table 1 gives the weights of the cerebellum from birth to twenty years of age together with the percentage which the cerebellum is of the encephalon. These are in ounces in the original tables, but I have taken the liberty of converting them into grams for the sake of comparison with other results.

The body weights listed by Boyd show that the infants autopsied were much underdeveloped, and it is probable that the brain weights for the period of infancy are below normal.

A somewhat more satisfactory series of weights for the period of growth has been made by Pfister, in Berlin ('97–'03). Instead of taking all the cases that came to hand, he has been careful to reject all the brains that were underdeveloped, oedematous, anaemic, or pathological in any way that would appreciably affect the gross weight. His results are presented with Boyd's in table 1.

As the weights given by Boyd and Pfister naturally show some variation, I have attempted to determine the normal curve for the growth in weight of the cerebellum and for the encephalon as a whole during the first two years. This is shown in chart 1. The method used was as follows: The weights given by Boyd, Danielbekof (not given in table 1), and Pfister were plotted, and smooth graphs for the combined data were drawn so as to represent as nearly as possible the recorded weights. The graphs thus drawn are intended to show the normal relation between the weights of the encephalon and the cerebellum in both sexes, and from these graphs it is possible to determine the normal weights for either sex at any age less than two years. A series of values determined in this manner is given in table 2.

In both the chart and table I have made the relative weights of the cerebellum in males and females the same. It seems, however, not improbable that in females there may be some precocity and that consequently during early growth the relative weight of the female cerebellum may be somewhat higher than that of the male. The results of Pfister especially, and of Danielbekof also, would at least agree very well with this view, although they do not prove it.

TABLE 1

The increase in the weight of the cerebellum after birth

BOYD						PFISTER					
Age	Sex	Encephalon	Cerebellum	Percentage weight of cerebellum	Number of cases	Age	Sex	Encephalon	Cerebellum	Percentage weight of cerebellum	Number of cases
0 (birth)	♂	331	20	5.9	45						
	♀	284	18	6.2	45						
						2–4	♂	431	28	6.0	17
						wks.	♀	396	24	6.0	13
1–3	♂	495	30	6.1	16	2	♂	461	31	6.7	10
mos.	♀	453	26	5.6	22	mos.	♀	415	29	6.7	6
						3	♂	519	41	7.8	10
						mos.	♀	504	39	7.9	11
4–6	♂	605	49	8.1	15	4–5	♂	583	45	7.9	8
mos.	♀	561	48	8.6	25	mos.	♀	562	50	8.9	19
						6–8	♂	733	72	9.0	12
						mos.	♀	666	65	9.5	14
7–12	♂	779	78	10.0	45	9–10	♂	786	81	10.0	6
mos.	♀	730	66	9.0	45	mos.	♀	684	67	10.0	8
						11–12	♂	851	85	10.0	5
						mos.	♀	727	69	10.8	2
						13–18	♂	944[1]	100	10.6	11
						mos.	♀	873[1]	96	11.0	6
2	♂	944	101	10.6	34						
yrs.	♀	846	90	10.6	33						
						19–24	♂	1082[1]	119	11.0	4
						mos.	♀	965[1]	109	11.3	4
3–4	♂	1099	114	10.4	28	3–4	♂	1136[1]	125	11.0	16
yrs.	♀	993	105	10.6	28	yrs.	♀	1035[1]	117	11.3	12
5–7	♂	1143	118	10.4	26	5–8	♂	1200[1]	132	11.0	15
yrs.	♀	1139	119	10.4	23	yrs.	♀	1116[1]	125	11.2	8
8–14	♂	1305	138	10.5	19	11–14	♂	1245[1]	137	11.0	7
yrs.	♀	1158	121	10.5	18	yrs.	♀	1191[1]	131	11.0	3
15–20	♂	1379	151	11.0	17						
yrs.	♀	1248	132	10.6	14						

[1] Estimated values calculated from the absolute and percentage weights of the cerebellum as given by Pfister.

Table 2 shows that at birth the cerebellum is very small and underdeveloped, being only about 5.7 per cent of the total brain weight, while in the adult it has nearly double that percentage. During the first year the cerebellum grows with great rapidity, so that by the end of that time it has reached nearly two-thirds its adult weight; by the end of the second year it has four-fifths

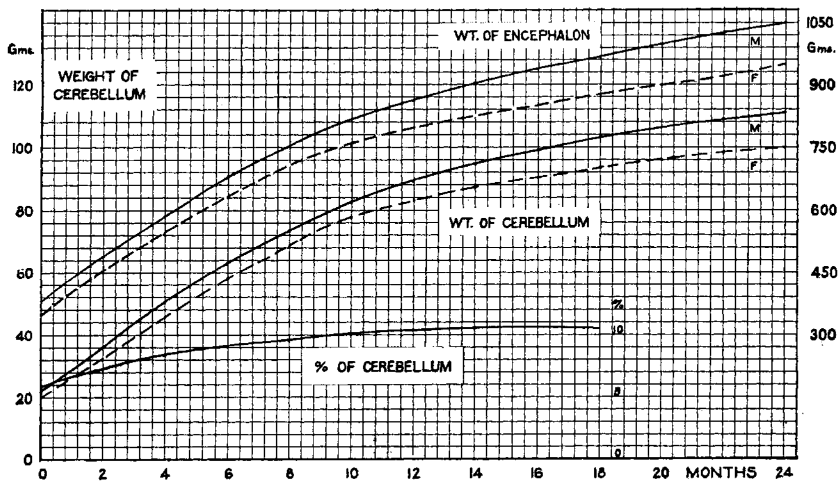

Chart 1 Graphs for the growth of the human encephalon and cerebellum during the first twenty-four months of life. The ordinate values differ for the three records. On the ordinate at the left are the values for the weight of the cerebellum: to the right for the weight of the cerebrum, and within the chart, at the right, for the percentage weight of the cerebellum. The weight of the encephalon is shown by the upper graphs: males; females. The weight of the cerebellum is shown by the middle graphs: males; females. The percentage weight of the cerebellum is given for the first eighteen months by the lowest graph, without distinction of sex. All the graphs have been smoothed.

of its adult weight and the period of rapid growth is over. This appears clearly from chart 1.

As a result of its rapid growth, the cerebellum gains steadily on the cerebral hemispheres until the tenth to twelfth months by which time it has reached approximately its relative weight in the adult. No very marked change in this relative weight is found after the first year.

The absolute and relative weights of the cerebellum for the ages of twenty to ninety years are given in table 3, which is based on the table of weights compiled by Sharpey from Boyd's records.

TABLE 2

This table gives the weights of the encephalon and of the cerebellum as read from the smoothed graphs, based on the observed weights given by Boyd, Danielbekof, and Pfister

AGE	SEX	ENCEPHALON	CEREBELLUM	PERCENTAGE WEIGHT OF CEREBELLUM
months				
0 (birth)	♂	385	22	5.7
	♀	350	20	5.7
2	♂	490	36	7.4
	♀	452	33	7.4
4	♂	585	50	8.5
	♀	545	46	8.5
6	♂	690	63	9.2
	♀	635	58	9.2
9	♂	790	79	10.0
	♀	730	73	10.0
12	♂	860	89	10.4
	♀	795	83	10.4
18	♂	970	103	10.6
	♀	875	93	10.6
24	♂	1055	112	10.6
	♀	950	101	10.6

The variations in the absolute weight of the cerebellum, according to Pfister, amount to as much as 10 grams in the first month, 20 grams in the second month, and 30 grams or more in the third month and thereafter. The variations in the cerebrum are likewise great, but there does not appear to be any constant relation between these variations; Pfister does not find it possible to explain them in terms of body length and weight. At times the encephalon is above weight and the cerebellum below weight, or vice versa; in other cases the encephalon is above or below weight, but the parts are proportionately developed. Chart 2 shows the range of some of these variations, accompanied by the absolute weights of the parts of the brain.

TABLE 3

This table shows the absolute weights of the encephalon and the cerebellum and the percentage weight of the cerebellum with advancing years. Based on Boyd's results as compiled by Sharpey

AGE	SEX	ENCEPHALON	CEREBELLUM	PERCENTAGE WEIGHT OF CEREBELLUM	NUMBER OF CASES
years					
20–30	♂	1360	147	10.8	55
	♀	1241	137	11.0	70
30–40	♂	1369	146	10.7	103
	♀	1224	135	11.0	85
40–50	♂	1356	149	10.9	135
	♀	1216	133	11.0	97
50–60	♂	1347	146	10.8	110
	♀	1225	131	10.7	100
60–70	♂	1318	141	10.7	123
	♀	1213	133	11.0	142
70–80	♂	1292	141	10.9	102
	♀	1172	127	10.8	146
80	♂	1286	136	10.6	24
	♀	1130	127	11.2	75

Pfister states that the relative weight of the cerebellum varies as much as 2 per cent, by which he means presumably that at birth the relative weight would range between 4.7 and 6.7 per cent of the weight of the encephalon, with a similar range of variation for successive periods. My own results based on several groups of cases show that 50 per cent of adult cerebella have weights which are between 9.8 and 11.8 per cent of the weight of the encephalon. The extreme range of relative weights for a given weight of the encephalon, as far as my experience goes, is illustrated by the two pathological cases shown in table 4.

The first case is half of the relative weight for the age of forty days, the normal being about 6.7 per cent; the second case is more than double the average relative weight for the adult, which

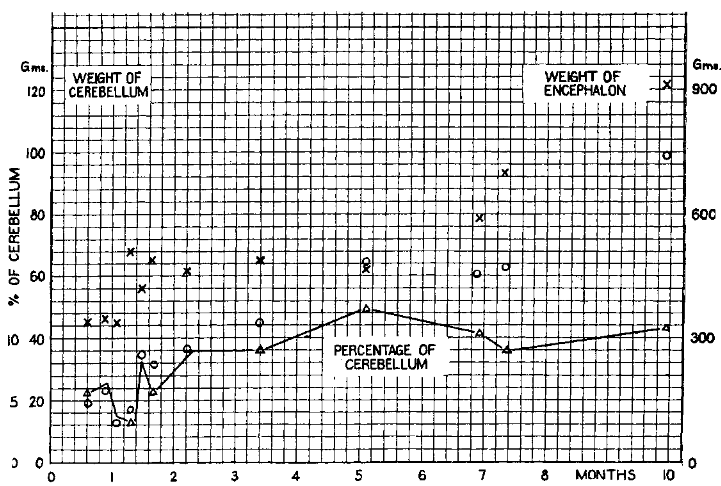

Chart 2 Showing the variations in the weights of the human encephalon and of the cerebellum—both sexes—together with the percentage weights of the cerebellum, during the first ten months of life. The ordinates for the percentage weight of the cerebellum Δ— Δ stand at the extreme left. The ordinates for the weight of the cerebellum O O on the left side just to the right of the foregoing. The ordinates for the weight of the encephalon ×× to the right.

TABLE 4

Two extreme variations in relative weight of the cerebellum (pathological)

NUMBER	AGE	WEIGHT OF ENCEPHALON	WEIGHT OF CEREBELLUM	PERCENTAGE WEIGHT OF CEREBELLUM
		grams	*grams*	
E1	40 days	510	17	3.3
E3	21 years	505	118	23.4

is about 10.8 per cent. It is hardly necessary to add that cases such as these two are very rare. They are to be regarded as due to pathological arrest of development either of the cerebellum or of the cerebrum. The range of relative weights ordinarily found is shown in chart 3.

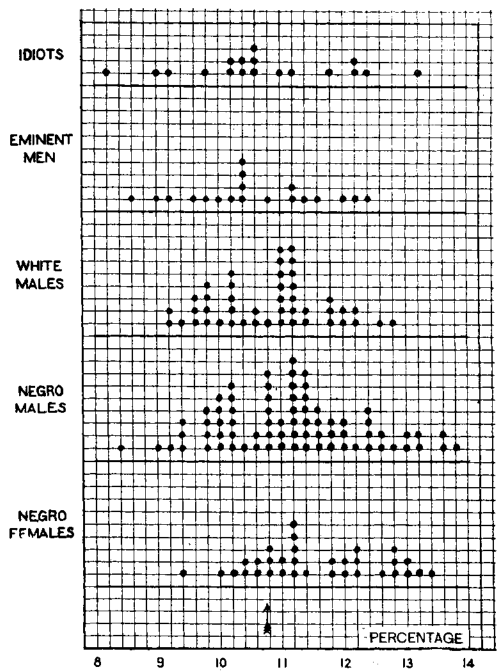

Chart 3 Giving the frequencies of the percentage weights of the cerebellum in five groups of human brains: 18 idiots and imbeciles; 19 eminent men; 45 ordinary white males; 74 negro males; 33 negro females.

The significance of the relative size of the cerebellum has received a great deal of attention since the days of Gall (1807). His view that it was connected with the sex instinct is well known. Leuret ('39) criticised this theory, and in support of his position he presented the weights of the encephalon and cerebellum in stallions, geldings, and mares; from his results I have arranged table 5.

The values given in the table do not seem to indicate a positive correlation between reproductive activity and the relative weight of the cerebellum, but they do seem to indicate a negative one, which would be quite as hard to understand. To throw any light possible on the question, I studied the weights of the parts of the brain in the male albino rat after castration. The data for this purpose were kindly offered me by Doctor Hatai, and for the details of the experiment the reader is referred to his paper ('15). From his results I have arranged table 6.

TABLE 5

The relative weight of the cerebellum in stallions, geldings and mares (after Leuret)

	NUMBER OF CASES	WEIGHT OF ENCEPHALON	WEIGHT OF CEREBELLUM	PERCENTAGE WEIGHT OF CEREBELLUM
		grams	*grams*	
Stallions	10	534	61	11.4
Geldings	21	520	70	13.5
Mares	12	498	61	12.2

TABLE 6

The effect of gonadectomy on the relative weights of the parts of the brain of the albino rat based on the work of Hatai, 1915

NUMBER OF CASES	GROUP	PERCENTAGE WEIGHT OF THE PARTS OF THE ENCEPHALON			
		Cerebrum	Cerebellum	Olfactory bulb	Stem
20	Castrated	62.9	14.7	3.2	19.2
20	Control	62.1	14.7	3.8	19.4

As will be observed from the table, there is no change in the relative weight of the cerebellum of the male albino rat as a result of gonadectomy. In view of the relations in the rat, interpretation of the figures given by Leuret for horses is not easy, but at least it seems clear that his results do not agree with any of the theories so far advanced.

In this connection it is desirable to examine the view of Marshall ('92), who concludes, on the basis of his excellent classification of Boyd's results, that the cerebellum is relatively heavier in females than in males. From his table I have arranged table 7, which shows the variations in both absolute and relative weights in both sexes of different statures for the three decades from twenty to fifty years—the most active period of adult life when any differences due to sex or stature should be most evident, if present at all.

TABLE 7

The weight of the cerebellum according to age, sex, and stature. Based on Marshall's tables

AGE	HEIGHT, INCHES ♂ 69 PLUS ♀ 64 PLUS				HEIGHT, INCHES 66–68 61–63				HEIGHT, INCHES 65– 60–				
	Sex	Number of cases	Weight of cerebellum	Percentage weight of cerebellum	Sex	Number of cases	Weight of cerebellum	Percentage weight of cerebellum	Sex	Number of cases	Weight of cerebellum	Percentage weight of cerebellum	Average percentage weight for each age group
years													
20–30	♂	14	145	10.6	♂	23	151	10.8	♂	15	148	11.3	10.9
	♀	18	133	10.6	♀	32	139	11.5	♀	12	133	11.3	11.1
30–40	♂	23	153	10.7	♂	48	142	10.5	♂	23	133	10.0	10.4
	♀	26	133	10.5	♀	30	136	11.1	♀	15	131	10.7	10.7
40–50	♂	28	148	10.7	♂	56	148	10.9	♂	32	145	11.0	10.9
	♀	32	131	10.8	♀	35	131	10.7	♀	14	133	10.9	10.8
Average.............				10.65				10.92				10.87	
Average for all cases, both sexes....................................													10.82

An examination of the table shows that his conclusion is open to question. The percentage weights of the cerebellum for females are not uniformly higher than for males—to be exact, they are higher in five groups out of nine in the table; in three groups the values for males are higher, and in one group the values for the sexes are the same. Under such conditions, the fact that the average percentage weight of the cerebellum is very slightly higher for females than for males can hardly be regarded in itself as significant.

The figures given by other observers serve only to strengthen the conclusion that there is no adult sex difference in the relative weight of the cerebellum. Bischoff ('80) gives the percentage weight of the 'Kleinhirn' for German males as 12.9 and for German females as 12.8; as his 'Kleinhirn' includes the brain stem, it means percentage weights for the cerebellum of about 10.9 and 10.8, respectively. Meynert ('67–'68) gives values of 11.2 and 11.3 for males and females, respectively. Weisbach ('66–'67) reports the percentage weight of the cerebellum to be less in Slavic males than in Slavic females, the values being 10.7 and 11.0, respectively, while among the South Germans the corresponding values are given as 10.8 (males) and 10.6 (females). No real difference between the sexes is apparent from these figures, and similar results could be given from some other authors without showing any preponderance of evidence on either side.

Chart 3, to be referred to later, shows the relative weights of the cerebellum in seventy-four male and thirty-three female negroes. This chart might be taken to indicate a relatively larger cerbellum in females of that race, but the number of cases is too small to be conclusive.

In my opinion, the evidence at hand is so well balanced that we are not safe in assuming for man any difference in the relative weights of the cerebellum in males and females at maturity, although, as has been pointed out, the female cerebellum may be somewhat precocious in its growth and so may be relatively heavier than that of the male during early life.

The relation of the relative weight of the cerebellum to stature has been examined by Weisbach (op. cit.), and by Marshall (op. cit.). Both agree that as stature increases the relative weight of the cerebellum increases also. If, however, we return to table 7, which, I believe, contains the best available data on the subject, we find, if anything, a lower relative weight of the cerebellum in tall persons. But the average differences are so small and the variations in the values for individual groups are relatively so great that no real significance can be attached to the differences found. We may then, I think, safely disregard Marshall's conclusion as to the effect of stature on the relative weight of the cerebellum.

The relative weight of the cerebellum according to the grade of the intelligence has been studied by Spitzka ('07), who gives a table showing the ratio of the weights of the cerebellum to the weights of the cerebrum in ten ordinary and eleven eminent men, and from this he concludes:

"A glance at the list shows that while in ordinary men the ratios cluster around 1:7.5, among eminent men it is fully a unit higher; that is to say, the cerebrum, or essential-thought apparatus, is relatively more massive, while the somatic organ of motor co-ordination (cerebellum) remains relatively reduced" (p. 300). This sounds very plausible, but let us examine the matter more closely. According to the weights given by Boyd for English males, the average weight of the cerebellum is about 148 grams and the average weight of the cerebrum is close to 1200 grams. Bischoff reports approximately the same figures for German and for French males. On this basis, then, the ratio for ordinary men should be 1:8 instead of 1:7.5, as Spitzka has it; so the superiority of the eminent men is reduced by half. To clear the matter up still further, I tabulated all the cases of eminent men reported by Spitzka, in which the percentage weight of the cerebellum could be determined. These are nineteen in number. I then weighed the parts of the encephalon of eighteen idiots and imbeciles, these, with one exception (table 4), being all of the brains of this class that were available in The Wistar Institute Museum. The results are presented in table 8 and in chart 3.

A glance at the chart and a comparison of the distribution of the percentage values in the different types of cases shows clearly that the number of cases is too small to show exactly the normal probability curve; at the same time, it leaves little room for doubt that the relative weights of the parts of the encephalon do not show significant variations corresponding to different levels of intelligence.

The foregoing conclusion is another reason for doubting the existence of a sex difference in relative cerebellar weight, a difference which has been often connected with a supposed difference in intelligence between males and females.

The problem as to whether there are racial differences in relative weight of the cerebellum has not been adequately studied. However, I have attempted to throw some light on the subject by comparing the cerebella of whites and negroes.

As I have not been able to secure a large number of fresh negro brains for the study of this point, I have had recourse to data given by Mall ('09). Unfortunately, for my purposes at least,

TABLE 8

The relative weights of the cerebellum in eminent men and in idiots and imbeciles

EMINENT MEN, BASED ON DATA FROM SPITZKA ('07)	PERCENTAGE WEIGHT OF CEREBELLUM	IDIOTS AND IMBECILES W. I. NO.	PERCENTAGE WEIGHT OF CEREBELLUM
Pepper, Wm.	8.6	E15	8.3
Letourneau, Chas.	9.1	15310	9.1
Seguin, E. C.	9.3	14942	9.3
Leidy, Jos.	9.7	14880	9.8
Seguin, Edouard	9.8	15145	10.2
Train, G. F.	10.0	15144	10.3
Bertillion, Adolphe	10.2	15113	10.5
Giacomini, Carlo	10.4	15111	10.5
Powell, J. W.	10.4	15320	10.6
Curtice, Hosea	10.4	15298	10.6
Cuvier, Geo. L. C.	10.5	15249	10.7
Pond, J. B.	10.9	15194	11.0
Jeffrey, Lord F.	11.3	15252	11.2
Webster, Daniel	11.3	15122	11.9
Leidy, Philip	11.5	15250	12.2
Fuchs, Konrad H.	11.7	15299	12.2
Coudereau, Auguste	12.1	15214	12.4
Cope, E. D.	12.3	15297	13.3
Allen, Harrison	12.4		
Averages................	10.63		10.77

he does not give the weights of the parts of the brain when fresh, but after fixation. Also he gives the weight of the cerebellum combined with the brain stem. This makes the problem more complex, but I believe I have secured satisfactory and comparable results by resorting to the following procedure:

The brain stem is nearly always approximately 2 per cent of the weight of the encephalon; I have accordingly deducted this amount from the weight given for the combined cerebellum and stem. This gives, with but little error, the weight of the cerebellum alone. From this value I calculated the percentage which the cerebellum is of the encephalon. There remains, however, the question as to the effect of fixation and preservation in formalin on the relative weight of the parts of the brain. According to Donaldson ('94), bichromate changes slightly the relative weights of the parts of the encephalon, so it seems probable that formalin may have a similar effect. I attempted to estimate this effect in two ways. First, I weighed again ten of the brains used by Mall and compared the changes in relative weight of the parts. Five showed increases in relative weight of the cerebellum and stem amounting on an average to 0.2 per cent, that is an increase from 11 per cent to 11.2 per cent, and five showed decreases in relative weight which averaged 0.4 per cent. The maximum change in any case was a loss of 0.5 per cent. Second, I plotted the percentage weights of the cerebellum on the per cent losses in absolute weight of the encephalon to see whether the group would give any consistent curve showing either loss or gain in percentage weight of the cerebellum with loss in weight of the encephalon.

I did this both for the negro brains and for the white ones included in Mall's study. The values for the white males gave a uniformly rising curve indicating a gain in percentage weight of the cerebellum with loss in weight of the encephalon; the values for the negro males did not give a very good curve, but indicated the same tendency as that for the white males; the values for negro females were distributed in such a manner that it was impossible to draw a conclusion.

The changes in the weight of the encephalon during fixation and preservation depend, as Pfister has pointed out ('03), on its condition at the time of fixation, and as the condition of different brains varies widely according to the nature and course of the disease causing death, it is to be expected that a series of brains from a general hospital will show the greatest possible variations in the effects of the fixing fluid. This will apply not only to the encephalon as a whole, but also to the relations of its parts, though perhaps to a less extent. It is consequently wise to use considerable caution in interpreting results based on such material.

To counteract as much as possible the effects of fixation, I have compared the negro brains used by Mall with his white brains—in this way I believe I have as nearly as possible eliminated the effect of changes in the fixing fluid, because the brains of both races were fixed in the same manner and at the same time.

To the brains used by Mall I have added those used by Bean ('06). The two groups do not differ appreciably, so I think no error has been introduced by bringing them together. The larger number is extremely desirable statistically.

The distribution of the percentage weights of these cases is shown in chart 3. The arithmetical average of the percentage weights for the negroes is above that for the whites, and the average for the negro females is above that for the negro males; however, the difference is not a great one and it is not very improbable that a larger number of cases might show the same distribution for the two races. But as far as the results go, they do show a relatively larger cerebellum in negroes. If this indicates anything at all, its significance is probably to be stated in terms of the cerebrum rather than in terms of the cerebellum.

As far as individual cases are concerned, the chart shows clearly that the relative weight of the cerebellum means nothing save in the rarest instances.

THE DISAPPEARANCE OF THE LAYER OF EXTERNAL GRANULE CELLS

Since its discovery by Hess in 1858, the layer of external granule cells has been studied by many investigators. Vignal ('89), in the course of his study of the development of the nervous system, made some observations on these cells and gave us some very good figures showing the histology of the cerebellar cortex at different ages during the fetal period. However, he did not understand the external granule cells; in fact, he thought them pathological, and advanced the theory that they were leucocytes brought to the molecular layer by some inflammation. Since that time there have been several other theories almost as interesting.

At present the external granule cells may be regarded as indifferent cells, some of which become glia cells, while others become nerve cells (Cajal). Of the nerve cells, some migrate to the internal granular layer, while others remain in the molecular layer.

The rate of disappearance of the external layer of cells has been studied in man by Berliner ('05), and by Biach ('09). Their results are shown graphically in chart 4.

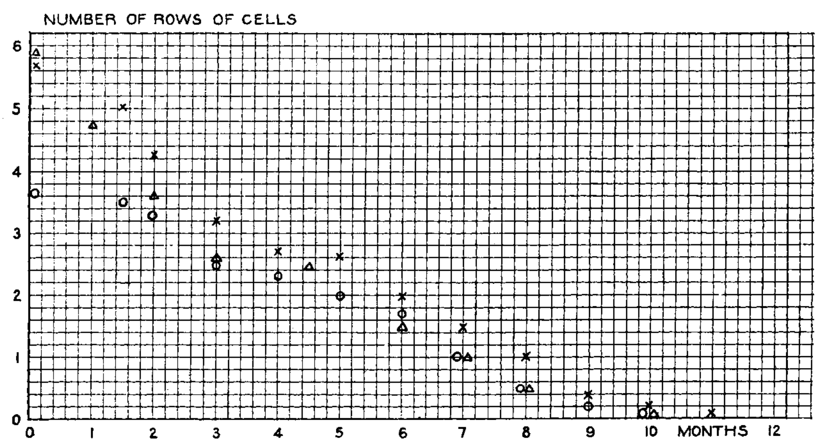

Chart 4 The disappearance of the rows of cells from the external granule layer of man.

Δ Berliner
O Vermis } Biach
× Hemispheres }

As will be seen by consulting the chart, Biach finds that at birth there are about six rows of cells in the hemispheres, and that these cells disappear by about the tenth or eleventh month. In the vermis the number is smaller at birth and remains smaller during the period of disappearance, with the result that the layer has usually disappeared by the eighth or ninth month.

Berliner has not made a distinction between the vermis and the hemispheres, so his results are not exactly comparable with those of Biach. They do, however, follow the same course and leave no doubt as to the rate for the cerebellum as a whole.

I have examined twelve cases with ages ranging from eighteen days to eleven months and my results agree so closely with the curve given by Biach that I have not thought it necessary to modify his statement.

Löwy ('10) has studied the external granule layer in a number of birds and mammals. He likewise finds that the vermis is in advance of the hemispheres in the disappearance of the external granule cells. To this he adds the observation that there seems to be a tendency for the cells to disappear faster in the anterior (cephalic) part of the hemispheres than in the posterior. I have studied this in my cases of human cerebella, and although the difference is not a great one, amounting to about one row of cells usually, I consider it to be fairly distinct in the majority of the cases examined. This, theoretically, is what we should expect according to the localization theory of Bolk ('05–'07).

Takasu ('05) has studied the pig and finds there a difference between the vermis and the hemispheres similar to that already noted.

Addison ('11), working on the albino rat, does not find any conspicuous difference between the vermis and the hemispheres, but he does find that the area anterior to the primary sulcus is somewhat in advance of the area posterior to it. Also he finds the paraflocculus to be most retarded of all. As the paraflocculus has been regarded as the center for coördination of tail movements, this appears to me to be a significant observation.

Biach, in connection with his normal cases, also studied the cerebella of twenty-three infants who had died from diseases tending to produce arrest of general development or other abnormalities in the nervous system. Out of the twenty-three cases, ten showed a distinct retardation in the rate of disappearance of the external granule cells; some showed no great variation from the normal, while others were too old to make it certain that they had not been retarded. It is significant, however, that nearly half of his pathological cases do show a correlation between inferior function and retarded disappearance of the external granules. Later I shall consider more specifically the functional significance of the disappearance of this layer of cells.

THE MOLECULAR LAYER AND THE INTERNAL GRANULAR LAYER

We are indebted to Roncoroni ('05) for a careful and extensive series of measurements on the molecular and internal granular layers of the cerebellum in normal and pathological human cases and in a number of lower animals.

He finds that in general the molecular layer decreases in relative thickness and the submolecular layers increase relatively during the course of evolution.

TABLE 9

The thickness in μ of the molecular and submolecular layers in the human cerebellar cortex (Roncoroni). The sex of the idiots is not stated, but probably four out of the five are males

	NUMBER OF CASES	MOLECULAR LAYER μ			SUBMOLECULAR LAYER μ			MOLECULAR / SUBMOLECULAR INDICES			AVERAGE BASED ON FOREGOING AVERAGES
		Minimum	Average	Maximum	Minimum	Average	Maximum	Minimum	Average	Maximum	
Normal men aged about 30 years	3	250	313	350	150	238	338	100	135	181	131
Idiot, age 20 years	1	225	338	363	150	188	250	135	153	193	180
Idiot, age 9 years	1	275	313	375	150	188	200	147	178	187	167
Idiot, age 20 years	1	250	325	375	113	150	225	144	169	222	213
Idiot, age 25 years	1	275	338	425	125	163	250	150	225	340	207
Idiot, age 34 years	1	188	250	313	125	163	200	133	150	156	154
Women, aged about 45 years	3	200	263	313	138	175	225	138	145	150	150
Woman, age 104 years	1	188	225	250	138	213	250	83	117	150	106

In table 9 I have condensed those of Roncoroni's results which apply most directly to the present discussion. In his paper he gives the minimum, average, and maximum widths of the molecular and internal granular layers, magnified 80 diameters. He has also given a series of the percentage values obtained by dividing the value for the molecular layer by that for the internal granular layer. From this series I have taken, for the sake of brevity, the minimum, mean, and maximum percentages, and have added in a fourth column the percentage obtained from his average measurements of the two layers.

In table 9 I have reduced these measurements to what they were in μ on the slide. His sections were prepared by the Nissl, Weigert, and Müller-platinum methods, so to get the correct values for the thickness of the layers in the fresh cerebellum it would be necessary to correct his measurements by raising them, probably about 15 per cent, to allow for the shrinkage during dehydration and embedding. However, I have not done this in the table. The relative thickness of the layers is of course not greatly affected by shrinkage.

On consulting his table, several interesting relations become apparent. As shown in the last column of the table, the molecular layer is relatively thicker in females than in males, and it is also relatively thicker in idiots than in normal individuals.

TABLE 10

Thickness of the molecular layer in the lateral lobes of the cerebellum during the first two years (man)

NUMBER	SEX	AGE	THICKNESS IN μ
E22	♂	1 mo. 18 days	175
E13	♂	2 mo. 5 days	193
14250	♂	3 mo. 20 days	200
E23	♂	5?	210
E21	♀	7? mo.	235
E8	♂	10 mo. 6 days	290
14428	♂	12? mo.	320
E18	♂	25 mo. 5 days	330

I have supplemented Roncoroni's observations by measuring the thickness of the molecular layer during growth. The results are shown in table 10 and in chart 5, and it may be added that the vermis is ahead of the cerebellar hemispheres in the growth of the molecular layer, as well as in other respects already pointed out. Up to the age of about one year the molecular layer is thicker in the vermis, but after that period I find no appreciable difference in the different parts of the cerebellum.

Krohn ('92) finds that in the asymmetric cerebellum of the cat the molecular layer is thicker in the left hemisphere than in the right. I have studied this relation in eleven human cerebella and have found that in six cases out of the eleven the right molecular layer is absolutely wider than the left, the left is wider in four cases, and the two are the same width in one case. When, however, I divided the values for the molecular layer by those for the internal granular layer so as to get a ratio showing the relative thickness of the two layers, it appeared in ten cases out of the eleven the right molecular layer was relatively thicker than the left, and in the eleventh case the values were identical. It

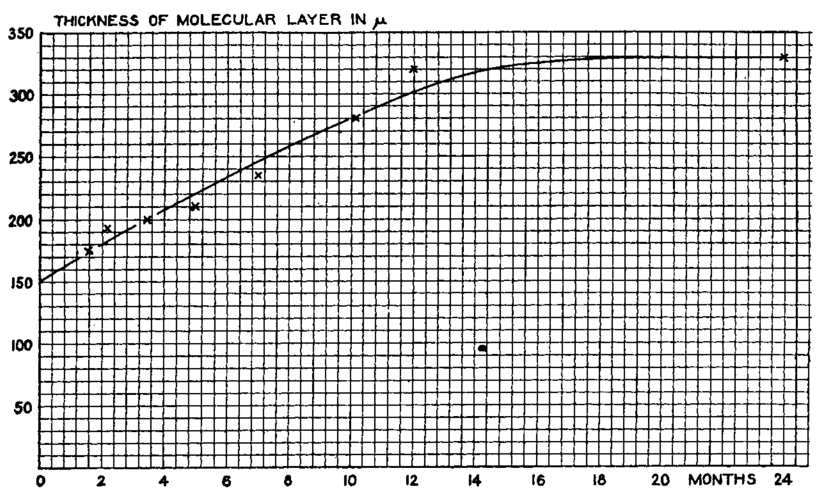

Chart 5 The growth in the thickness of the molecular layer in μ (man) during the first twenty-four months of life.

may be noted also that in only one case was the right internal granular layer absolutely wider than the left. So in man it appears that the right molecular layer is relatively wider then considered in relation to the internal granular layer, and that the left internal granular layer is absolutely thicker than the right. But what functional significance this has is uncertain.

THE PURKINJE CELLS

Growth in size

In the human cerebellum the full number of Purkinje cells is present at birth; they are, however, undeveloped and rather immature in form. The successive stages through which they pass in the growth process have been described in some detail by Cajal and others, but for my purpose it is sufficient to note that by the end of the first year the cells have assumed their adult form.

I have not had satisfactory material for determining the increase in the diameters of the Purkinje cells, but I have made measurements on twelve cases ranging in age from eighteen days to three years. Because of variations in the treatment to which the different brains were subjected, I do not consider the absolute measurements of sufficient value to present them in tabular form. Two results may, however, be stated with a fair degree of assurance. First, the cells are larger in the vermis than in the hemispheres during the first few months of life. Second, the growth in size during the first six months is very rapid, but becomes slower in rate thereafter, and the cells appear to have practically their full size by about twelve to eighteen months. The growth curve has essentially the same form as that shown for the molecular layer in chart 5.

This difference found in the vermis adds to and confirms the other differences already pointed out. There can, I think, be no reasonable doubt that typically the vermis develops in advance of the hemispheres.

The decrease in the number of cells with advancing age

In addition to work already reported, I have made cell counts on the cerebella of sixty-three negroes, whites, and mulattoes of both sexes and of ages ranging from twelve to ninety-two years. All of the material is from The Wistar Institute Museum.

The technique and the method of making cell counts have been the same as that reported in my earlier paper (Ellis, '19). To put the matter briefly, I have made corrections for differences in the size of different cerebella and for the effect of shrinkage of the tissues during dehydration and embedding, so that I have been able to determine the number of cells in similar fractional parts of each cerebellum. These fractional parts have been called equivalent unit areas and designated by EUA.

In this study I have confined my cell counts to two areas in each hemisphere: first, the area anterior to the primary sulcus, and, second, the area anterior to the great horizontal sulcus, or areas 1 and 3, respectively, as shown in figure 2 of my earlier paper, which is here repeated as figure 1.

Cell counts were made for the four areas, two on the right and two on the left, in each case and the sections were also studied in

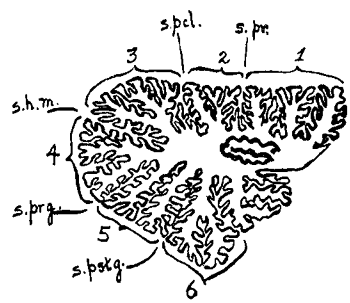

Figure 1

order to estimate the extent to which cells had actually been lost. This is necessary because it is not possible to tell from the number alone whether cells have been lost or are congenitally absent.

After completing the counts I tabulated the results according to age, sex, and color; I have compared the results of the counts for ordinary white males of presumably average intelligence with counts made on white males of superior intelligence; and I have compared also the results for the right and left hemispheres.

As far as my data go, the counts for eleven ordinary white males show no significant difference when compared with the counts for negro males. Neither does any difference appear when the results for the ordinary white males are compared with the results for five white males of superior intelligence. I have accordingly eliminated these two questions of race and mental grade from my discussion. The three conditions remaining, age, sex, and variations between the right and left sides, will be discussed in turn.

Age. The results of the counts for all the cases were tabulated and plotted according to age. But as cell losses are frequently due to disease, I have eliminated those cases for each age which showed the greatest losses, and have retained as the basis for

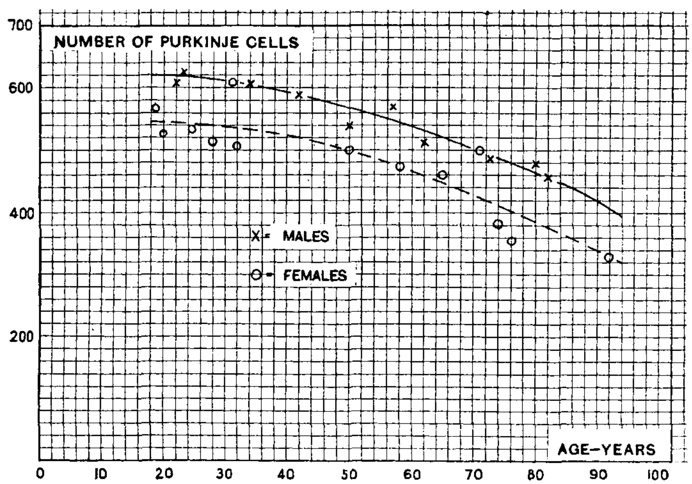

Chart 6 Loss of the Purkinje cells on age (man). X———X, males; O---------- O, females. Based on tables 11 and 12.

the chart only those cases which showed the greatest number of cells and the least indiction of cell degeneration for a given age.

By this method I have eliminated forty-three cases, which left a balance of twenty-seven males and thirteen females. To these, for the sake of greater completeness, I have added three cases, all males, reported in my earlier paper. The process of selection described does not materially affect the form of the curve in the chart, although of course it makes it higher. This, however, instead of being a defect, should give us more nearly the true result for the normal biological loss of cells with age. The results are shown in tables 11 and 12, and in chart 6.

TABLE 11

*Number of Purkinje cells per EUA in the cerebella of human males showing the decrease with advancing age. The cases indicated by the * are taken from my earlier paper*

W. I. NUMBER	COLOR	AREAS				TOTAL	AGE
		R-1	L-1	R-3	L-3		
14476	B	171	147	143	144	605	22
14485*	B	165	181	118	160	624	23
15035*	B	169	151	151	138	609	34
14455*	W	169	150	147	125	591	42
Average...........		169	157	140	142	607	22–42
14482	W	161	134	132	112	539	50
14432	W	147	154	142	126	569	57
14464	B	145	127	103	134	509	62
14459	B	127	124	117	123	491	73
14472	B	119	136	118	106	479	80
14483	B	100	124	133	100	457	82
Average...........		133	133	124	117	507	50–82

TABLE 12

Number of Purkinje cells per EUA in the cerebella of female negroes showing the decrease with advancing age

W. I. NUMBER	AREAS				TOTAL	AGE
	R-1	L-1	R-3	L-3		
14477	150	154	137	122	563	19
14475	153	132	107	132	524	20
15047	147	125	127	133	532	25
14466	128	139	119	132	518	28
15057	168	158	130	156	612	31
15039	128	127	122	134	511	32
Average.....	146	139	124	135	543	19–32
14441	128	132	119	120	499	50
15058	108	122	120	122	472	58
15041	144	118	99	99	462	65
15072	143	128	126	108	505	71
15086	90	90	126	96	402	74
15050	107	103	76	103	389	76
15087	87	83	81	83	334	92
Average.....	115	111	107	104	429	50–92

This set of results agrees with and corroborates the results given in my previous paper. There is a gradual loss of cells with advancing age, beginning normally at about the age of thirty to forty years, although this probably varies in different individuals. The anterior (cephalic) part of the cerebellum, as represented by area 1, suffers more than the more posterior part, as represented by area 3. This agrees with the results found by Archambault ('18).

Accompanying the actual loss of cells there are also degenerative changes in those which remain. Chromatolysis, atrophy, vacuolation, and homogeneous degeneration of nucleus and cytoplasm are found. Pigment is likewise present at times (Dolley, '17, '19), but I have not studied it carefully.

Sex. The sex difference shown in chart 6 is one of which I am not at all confident. As far as the results go, they indicate a greater number of Purkinje cells in male cerebella. Men are of course stronger than women, and experimental psychology shows that they are capable of greater motor skill than are women (Thompson, '03); so it is at least possible that there may be a greater number of Purkinje cells in male cerebella. However, a careful study of the sections used convinces me that the difference shown in the chart and tables is due to a greater loss of cells in the female cerebella examined and that it is not a normal difference. But a further study on better material will be necessary to settle the point.

There is no reason, at present, to think of the difference as due to any systematic technical error.

Comparison of right and left hemispheres

Numerous attempts have been made to explain anatomically the greater motor skill which the average person has with his right (or left) hand. Various estimates indicate that probably about 85 or 95 per cent of the population is naturally right-handed, while the remaining 15 or 5 per cent is left-handed. According to Ramaley ('14) right-handedness is a dominant Mendelian unit character, while left-handedness is a recessive unit character.

If this is true, we should expect to find some anatomical basis for the tendency to use one hand rather than the other.

The relation of the cerebellar hemispheres to the body is not entirely clear, but the weight of the evidence indicates that each cerebellar hemisphere controls the muscular coördinations of its own half of the body instead of being crossed, as is the case with the cerebrum. It is consequently interesting to find that when an excessive number of Purkinje cells is lost as a result of advancing age or as a result of disease, the right hemisphere in most

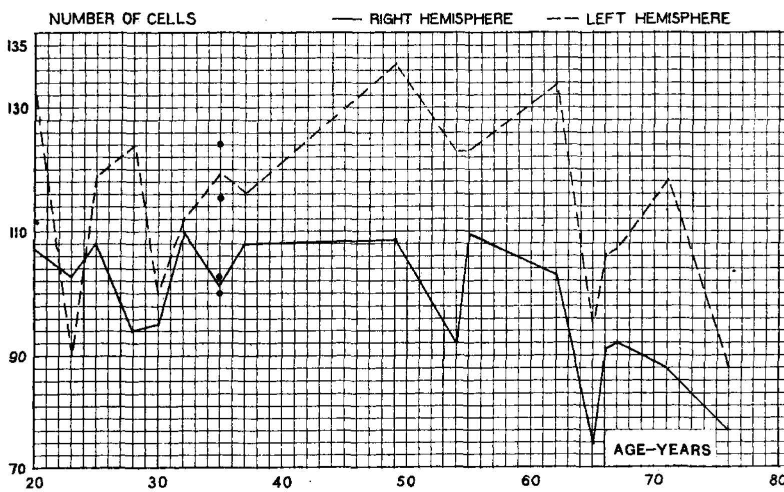

Chart 7 Showing the loss of Purkinje cells on age in the right and left hemispheres of the human cerebellum. ———, right hemisphere; ----------, left hemisphere.

cases is found to have suffered the greater loss—when compared with what is found in more nearly normal cerebella. To demonstrate this, I have selected from my records the eighteen cases which had suffered the greatest losses of cells, and I have shown in chart 7 the numbers of cells in area 3 of the two hemispheres of this group. Whether the greater loss in the right hemisphere is due to use or to some difference in the vascular system, or to both of these factors, cannot at present be determined. In less extreme cases, as shown in tables 11 and 12, the difference between the hemispheres is not marked in old age.

A further examination of tables 11 and 12 will show that the cases with ages of less than fifty years have in half of the cases a greater number of cells in the right hemisphere. But if we eliminate those cases which show the right hemisphere to be noticeably below normal, the difference becomes more apparent. And, lastly, if we observe the highest values for both hemispheres in the tables we find that in only one case, no. 14485, are the values for the left hemisphere as high as the highest values for the right hemisphere; so that although the problem is a complicated one and the evidence is not entirely conclusive, it seems probable that right-handed people start life with more Purkinje cells in the right hemisphere of the cerebellum.

With this conclusion should be correlated the conclusion stated above to the effect that the right molecular layer considered in relation to the internal granular layer is relatively wider than the left molecular layer. As the molecular layer is the zone in which the dendrites of the Purkinje cells ramify, the relatively greater width of the right molecular layer is a further anatomical characteristic to be correlated with the superior functional efficiency of the right half of the body musculature.

THE GROWTH AND DEGENERATION OF THE MYELIN SHEATHS

Sante de Sanctis ('98) studied the development of the myelin sheaths in the human cerebellum during the first three months of life and found that myelination of the fibers occurs earlier in the vermis than in the hemispheres. I have made no special study of the matter, but it is easy, even in preparations stained with Delafield's hematoxylin, to see that the vermis has the fibers more developed.

Löwy ('10) made a comparative study of the disappearance of the external granule cells and the development of the myelin sheath in lower mammals, and he not only confirms the statement of de Sanctis that the vermis develops in advance of the hemispheres, but he shows that the disappearance of the external granule cells, the development of function, and myelination are closely related. This agrees with the general results of Lui

('94), who correlated the anatomical changes in the cerebellum of man and several lower animals with the development of motor control.

The most detailed statement I have found on the growth of the myelin sheaths in man is from Berliner ('05), and I am quoting it in full:

> I have studied more carefully the myelination of the nerve plexus in the granular layer of the vermis. Already in the child of one to two months single myelinated fibers, mostly from the Purkinje cells, can be seen distributed radially; in the fourth month these are more numerous and can be followed to the top of the folium. No myelinated tangential fibers can yet be seen. These appear first at five months; they run below the Purkinje cells and can be seen easier at the bottoms of sulci than at the tips of the folia. In the seventh month the myelinated plexus of the granular layer is well developed; in the ninth month the plexus and the association fibers are still further myelinated; and in the child of fifteen months the association fibers have become still clearer.

From Berliner's statement it will be seen that myelination is taking place while the layer of external granule cells is disappearing and while the child is developing motor control. The growth of myelinated fibers continues for some time, however, at a rather rapid rate after the external granule layer has completely disappeared.

Judging from the results of Engel ('63), there is often a loss or shrinkage of myelinated fibers in the cerebellum during senescence, and this naturally has to be inferred in view of the disappearance of the cell bodies of the Purkinje cells as shown in this paper. To what extent the axones of other cells may disappear or atrophy during senescence I do not know.

THE DENTATE NUCLEUS IN SENESCENCE

Most of the axones from the Purkinje cells in the lateral lobes of the cerebellum terminate in the dentate nucleus, and I have examined therefore the cells of this nucleus to determine what changes take place there during old age. For this purpose I have not attempted to use exact methods, but have simply examined the sections carefully under high and low powers of the microscope.

On the whole, I find that the cells of the dentate nucleus disintegrate and disappear to a much less extent than the Purkinje cells do. In advanced age it is possible to recognize cells in all stages of degeneration and in some cases many cells have been lost. But on the whole, the dentate nucleus appears to suffer less than the cerebellar cortex. With regard to pigmentation, however, the Purkinje cells rarely show the presence of pigment, while many cells of the dentate nucleus show it, and in very old cases few cells are entirely free from pigment.

If we accept the view that this pigment is a product of metabolism and that the failure to eliminate it is an indication of defective function in the nerve cell, we have in the pigmentation of the cells of the dentate nucleus a satisfactory parallel for the actual disintegration of the Purkinje cells. The latter cells rarely show pigment, but, as has been stated, they disintegrate, while the former cells disintegrate to a less extent, but accumulate pigment instead.

THE RELATION OF STRUCTURE AND FUNCTION

In order to correlate some of the growth changes in the cerebellum during the first two years of life, I have prepared chart 8. This shows comparatively the relations of the graphs for the disappearance of the external layer of granule cells, for the increase in the absolute and in the percentage weights of the cerebellum, and for the increase in the thickness of the molecular layer. In each case it will be seen that the period of most rapid growth is completed by the age of twelve months. To this may be added the fact that by that time the Purkinje cells are practically as large as they are in the adult cerebellum. On the functional side, the age of twelve months, or thereabouts, is the time when the child begins to walk. And it is in connection with the increase of functional control that there is an increase in myelinated fibers. The exact relation of myelination and function is, it must be admitted, doubtful; yet there is nothing in the known facts that disagrees with the theory that the myelin sheath is a result rather than a cause of the development of function.

I have pointed out that the vermis is ahead of the lateral lobes of the cerebellum in its early development. This agrees well with the supposition that the vermis is concerned with bilateral movements of the trunk and limbs. The vermis is older phylogenetically than the lateral lobes, and this further suggests that it is the center for the control of the more primitive coördinations of the neuromuscular system.

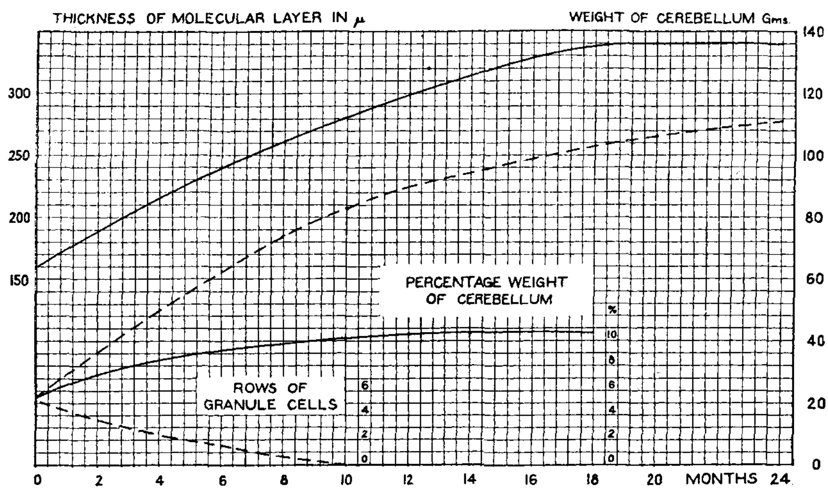

Chart 8 A composite based on charts 1, 4, and 5. The uppermost graph—solid line—gives the changes in the thickness of the molecular layer in μ. Ordinate values at the left. The next below—broken line—gives the weight of the cerebellum in grams. Ordinate values to the right. The next below—solid line—gives the percentage weight of the cerebellum. Ordinate values entered above eighteen months. The lowest graph—broken line—gives the number of rows of cells in the external granule layer. Ordinate values entered above ten months. The grouping of these graphs permits a comparison of several growth changes occurring simultaneously during the first twenty-four months of life.

In that case the earlier development of the vermis agrees well with the fact that the child is able to control many movements of the trunk and limbs before he is able to walk.

In general the head and arm musculature is under control for some months before the child can walk, and this, I think, can be correlated with the earlier disappearance of the external granule cells in the anterior part of the cerebellum.

As far, then, as the growth changes have been studied, they are found to be closely correlated with the development of function.

It is hardly necessary to add here to what has already been said about the correlation between the disappearance of the Purkinje cells in old age and the impairment of motor strength and skill. The two go hand in hand.

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