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JAMES ARTHUR LECTURE ON
THE EVOLUTION OF THE HUMAN BRAIN
1955

CULTURE AND THE STRUCTURAL EVOLUTION OF THE NEURAL SYSTEM

FRED A. METTLER
Professor of Anatomy
College of Physicians and Surgeons
Columbia University

THE AMERICAN MUSEUM OF NATURAL HISTORY
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PREFACE

In 1931 the American Museum of Natural History received a bequest from Mr. James Arthur to establish an annual lecture on the evolution of the human brain. As a result the James Arthur Annual Lecture was established in 1932, with the late Professor Frederick Tilney as the first lecturer. No provision was made for publishing the lectures when the series was inaugurated, and none have been published since under the sponsorship of the foundation. The various lecturers were free to publish elsewhere if they wished. Some of them did, but others for one reason or another did not. Thus some of the lectures which were valuable contributions have not had the distribution they deserved. Moreover, it has been our experience after the delivery of each lecture that there is a considerable demand for published copies of it. It seemed desirable, therefore, even twenty-five years after its commencement to initiate a publication series of the lectures. I trust that the consequent lack of coincidence between the seriation of the lectures and the publications will not prove a nuisance to librarians.

I am happy, indeed, that this new venture can begin with Dr. Fred A. Mettler's stimulating lecture which he delivered in April, 1955. It is a good augury for its success.

HARRY L. SHAPIRO

The American Museum of Natural History
New York, New York

JAMES ARTHUR LECTURES ON THE EVOLUTION OF THE HUMAN BRAIN

Frederick Tilney, *The Brain in Relation to Behavior;* March 15, 1932

C. Judson Herrick, *Brains as Instruments of Biological Values;* April 6, 1933

D. M. S. Watson, *The Story of Fossil Brains from Fish to Man;* April 24, 1934

C. U. Ariens Kappers, *Structural Principles in the Nervous System; The Development of the Forebrain in Animals and Prehistoric Human Races;* April 25, 1935

Samuel T. Orton, *The Language Area of the Human Brain and Some of its Disorders;* May 15, 1936

R. W. Gerard, *Dynamic Neural Patterns;* April 15, 1937

Franz Weidenreich, *The Phylogenetic Development of the Hominid Brain and its Connection with the Transformation of the Skull;* May 5, 1938

G. Kingsley Noble, *The Neural Basis of Social Behavior of Vertebrates;* May 11, 1939

John F. Fulton, *A Functional Approach to the Evolution of the Primate Brain;* May 2, 1940

Frank A. Beach, *Central Nervous Mechanisms Involved in the Reproductive Behavior of Vertebrates;* May 8, 1941

George Pinkley, *A History of the Human Brain;* May 14, 1942

James W. Papez, *Ancient Landmarks of the Human Brain and Their Origin;* May 27, 1943

James Howard McGregor, *The Brain of Primates;* May 11, 1944

K. S. Lashley, *Neural Correlates of Intellect;* April 30, 1945

Warren S. McCulloch, *Finality and Form in Nervous Activity;* May 2, 1946

S. R. Detwiler, *Structure-Function Correlations in the Developing Nervous System as Studied by Experimental Methods;* May 8, 1947

Tilly Edinger, *The Evolution of the Brain;* May 20, 1948

Donald O. Hebb, *Evolution of Thought and Emotion;* April 20, 1949

Ward Campbell Halstead, *Brain and Intelligence;* April 26, 1950

Harry F. Harlow, *The Brain and Learned Behavior;* May 10, 1951

Clinton N. Woolsey, *Sensory and Motor Systems of the Cerebral Cortex;* May 7, 1952

Alfred S. Romer, *Brain Evolution in the Light of Vertebrate History;* May 21, 1953

Horace W. Magoun, *Regulatory Functions of the Brain Stem,* May, 1954

CULTURE AND THE STRUCTURAL EVOLUTION OF THE NEURAL SYSTEM

Two propositions, considered more or less self-evident, have played prominent roles in the consideration of the evolutionary development of man. Indeed, it is often assumed that reference to these propositions is sufficient to decide any doubtful issue as to whether or not man's present structural condition represents an advance over the past. In the first place it has been widely asserted that the size of the brain has steadily increased in those biologic lines leading (and related) to man and that this process has continued until the present and will probably continue through the future. In the second place it is universally assumed that this is or would be a good thing, because, the argument runs, a large brain (especially one with a large frontal lobe) is positively correlated with a high order of intelligence, and the present state of man's development depends upon this alleged cerebral increase.

It will be necessary in the following pages to question the validity of these assumptions, which really are far from self-evident, for there are definite data demonstrating that the size of man's brain has not continued to increase to the present. Moreover, there is good reason to believe that useful or workable intelligence, as we employ the term in day-to-day terminology, is a general aspect of capacity for over-all neural efficiency rather than a localized brain function, and that, in view of the dependence of the individual upon learned cultural traits, the frontal lobe may not be an indispensable substrate for "intelligent" living. I hope then to present certain technical reasons which lead me to question whether *Homo sapiens* can profitably develop a significantly enlarged brain without first undergoing rather radical structural and physiologic alterations in other respects, for it is possible that the size of man's brain might prove to be a limiting factor not merely in his further structural evolution but even in his survival.

Finally I wish to emphasize the role that culture has played in

protecting the individual from his natural environment on the one hand (and thus shielding him from the necessity of developing structural adaptations to it) and, on the other, of creating new environmental demands. I shall conclude with a brief inquiry into the nature of these demands and whether or not the nervous system may be expected to serve as the limiting factor in meeting them.

Has man's brain continued to increase in size and is brain size positively correlated with intelligence?

One of the basic diffiiculties in coming to a decision about the evolutionary trend of the brain is the fact that modern man's brain is far from constant in size, shape, or configuration. This situation has long been known, but people, and scientists are no exception, show a strong disinclination to pay attention to data that do not fit into a frame of reference in which the other data are more or less in concurrence (Craik, 1952).

Many years ago Vierordt (1893) brought together the brain-weight data for different geopolitical groups, which are shown here in table 1. In this table variations of well over 10 per cent in brain weight are obvious, not among markedly different races but among white Europeans. Various reasons could be advanced for such differences. They might be due to genotypic variability, having its basis in racial subvarieties and apart from other somatic variation, or they might be a general reflection of differences in corporeal size. (A variation according to sex is explicit in the table.) Again, such variation might be due to age or correlated with differences in intellectual capacity.

In a consideration of the relation of age to brain volume, which is closely related to brain weight, table 2 demonstrates that the brain, whereas it becomes larger with age, reaches its maximum gross size long before the body does and that, beginning around 50 years of age, it ultimately becomes absolutely smaller.

As a result of such an observation, one would expect that body weight would not be a very satisfactory index of brain size, and table 3 shows that beyond a certain point the relationship between these two variables may be of an inverse nature. Because weight is a poor indication of actual somatic development, stature and degree of muscular development should be correlated with

TABLE 1

ABSOLUTE AVERAGE WEIGHTS (IN GRAMS) OF BRAINS OF EUROPEANS TWENTY TO EIGHTY YEARS OLD FROM DIFFERENT EUROPEAN POLITICO-GEOGRAPHIC DISTRICTS (FROM VIERORDT, 1893)

Investigator	Source of Material	Male	Female
Krause	Hanover	1461	1341
F. Arnold	Grand Duchy of Baden	1431	1312
Reid	Scotland	1424	1262
Peacock	Scotland	1423	1273
Sims	England	1412	1292
Tiedemann	Grand Duchy of Baden	1412	1246
Quain	England	1400	1250
G. H. Bergmann	Hanover	1372	1272
Rud. Wagner	Mixed	1362	1242
Th. von Bischoff	Bavaria	1362	1219
Sappey	France	1358	1256
Huschke	Saxony	1358	1230
Hoffmann	Switzerland	1350	1250
Blosfeld	Russia	1346	1195
Clendinning	England	1333	1197
Dieberg	Russia	1328	1238
Boyd	England	1325	1183
Parchappe	France	1323	1210
Lelut	France	1320	—
W. Hamilton	Scotland	1309	1190
Meynert	Austria	1296	1170
Parisot	France	1287	1217
Weisbach	German-Austrian	1265	1112

TABLE 2

RELATION BETWEEN AGE AND VOLUME OF BRAIN

Age	Number of Cases		Volume of Brain (in Cc.)	
	Male	Female	Male	Female
0– 6 months	29	28	499	478
7–12 months	19	24	772	700
2 years	9	10	929	976
3 years	11	9	1123	1038
4 years	11	9	1190	1049
5– 6 years	8	11	1300	1147
7–10 years	9	12	1333	1204
11–15 years	9	10	1285	1213
16–19 years	13	10	1289	1099
20–29 years	73	43	1223	1148
30–39 years	74	59	1279	1193
40–49 years	77	60	1264	1164
50–59 years	80	57	1275	1146
60–69 years	84	65	1237	1143
70–79 years	70	55	1212	1088
80–89 years	10	23	1164	1072

TABLE 3

BRAIN WEIGHT CONSIDERED AS A PROPORTION OF TOTAL BODY WEIGHT (FROM VIERORDT, 1893, AFTER BISCHOFF)

Body Weight (in Kilograms)	Brain Weight Male	Female
20	—	4.47%
30	3.7 %	3.37%
40	2.98%	2.70%
50	2.5 %	2.29%
60	2.16%	1.99%
70	1.99%	—
80	1.59%	—

TABLE 4

WEIGHT OF THE BRAIN (ENCEPHALON) AND ITS SUBSIDIARY PARTS IN SANE PERSONS, ACCORDING TO SEX, AGE, AND STATURE (FROM DONALDSON, 1895)

(a, above average according to age; s, above average according to stature.)

	Age	Encephalon	Cerebrum	Cerebellum	Stem
MALES					
Stature 175 cm.	20–40	1409	1232	149	28
	41–70	1363	1192	144	27
and upward	71–90	1330	1167	137	26
Stature 172–	20–40	1360	1188	144	28
	41–70	1335	1164	144	27
167 cm.	71–90	1305	1135	142 s	28 a s
Stature 164 cm.	20–40	1331	1168	138	25
	41–70	1297	1123	139 a	25
and under	71–90	1251	1095	131	25
FEMALES					
Stature 163 cm.	20–40	1265	1108	134	23
	41–70	1209	1055	131	23
and upward	71–90	1166	1012	130	24 a
Stature 160–	20–40	1218	1055	137 s	26 s
	41–70	1212 s	1055	131	26 s
155 cm.	71–90	1121	969 s	128	24
Stature 152 cm.	20–40	1199	1045	130	24 s
	41–70	1205 a	1051 a	129	25 a s
and under	71–90	1122	974	123	25 a s

TABLE 5

WEIGHT OF THE BRAIN (ENCEPHALON) AND ITS SUBSIDIARY PARTS IN INSANE PERSONS, ACCORDING TO SEX, AGE, AND STATURE (FROM DONALDSON, 1895)

(a, above average according to age; s, above average according to stature.)

	Age	Encephalon	Cerebrum	Cerebellum	Stem
400 MALES					
Stature 175 cm.	20–40	1378	1192	156	30
	41–70	1354	1170	154	30
and upward	71–90	1333	1158	146	29
Stature 172–	20–40	1363	1186	149	28
	41–70	1305	1129	148	28
167 cm.	71–90	1305	1135 a	142	28
Stature 164 cm.	20–40	1299	1127	144	28
	41–70	1285	1119	139	28
and under	71–90	1216	1047	139	30 s a
325 FEMALES					
Stature 163 cm.	20–40	1220	1056	136	28
	41–70	1215	1053	134	28
and upward	71–90	1240 a	1076 a	136 a	28
Stature 160–	20–40	1189	1027	134	28
	41–70	1216 s a	1054 s a	135 s a	27
155 cm.	71–90	1171	1008	135 a	28 a
Stature 152 cm.	20–40	1141	986	128	28
	41–70	1194 a	1036 a	129 a	28 s a
and under	71–90	1135	985	123	27

variations in cerebral weight, but tables giving such information have not yet been developed. Because brain volume is obviously influenced by age, some correction for the latter factor must be introduced. Tables of this nature have long been available and show a definite positive correlation between brain weight and stature (table 4) when corrected for age (Donaldson, 1895; Dubois, 1914).

Table 4 may be compared with table 5 to see whether the size of the brain is correlated with condition of rationality. It will be observed that no significant difference is disclosed by comparison of these two sets of old figures. Although the validity of these figures has been abundantly contested in the years which have passed since they were compiled, no one has yet been able to bring for-

TABLE 6

BRAIN WEIGHTS (IN GRAMS) OF EMINENT MEN (FROM DONALDSON, 1895, TAKEN FROM MARSHALL AND MANOUVRIER)[a]

Age	Encephalic Weight	Eminent Men
39	1457	Skobeleff, Russian general
40	1238	G. Harless, physiologist
43	1294	Gambetta, statesman
45	1403	Assezat, political writer
45	1516	Chauncey Wright, mathematician
49	1468	Asseline, political writer
49	1409	J. Huber, philosopher
5[0]	1312	Seizel, sculptor
50	1378	Coudereau, physician
52	1358	Hermann, philologist
52	1499	Fuchs, pathologist
53	1644	Thackeray, novelist
54	1520	De Morny, statesman
54	1629	Goodsir, anatomist
55	1520	Derichlet, mathematician
56	1503	Schleich, writer
56	1485	Broca, anthropologist
57	1559	Spurzheim, phrenologist
57	1250	v. Lasualx, physician
59	1436	Dupuytren, surgeon
60	1533	J. Simpson, physician
60	1488	Pfeufer, physician
62	1398	Bertillon, anthropologist
62[?]	1415	Melchior Mayer, poet
63	1449	Lamarque, general
63	1332	J. Hughes Bennett, physician
63	1830	G. Cuvier, naturalist
64	1785	Abercrombie, physician
65	1498	De Morgan, mathematician
66	1512	Agassiz, naturalist
67	1502	Chalmers, preacher
70	1352	Liebig, chemist
70	1516	Daniel Webster, statesman
71	1207	Döllinger, anatomist
71	1349	Fallmerayer, historian
71	1390	Whewell, philosopher
73	1590	Hermann, economist
75	1410	Grote, historian
77	1226	Hausemann, mineralogist
78	1492	Gauss, mathematician
79	1254	Tiedemann, anatomist
79	1403	Babbage, mathematician
79	1452	Ch. H. Bischoff, physician
80	1290	Grant, anatomist
82	1516	Campbell, Lord Chancellor

[a] The entries in this table have been in part revised. Different methods have of course been employed in determining the several weights.

ward conclusive data that the brains of insane persons are customarily smaller or lighter than those of a corresponding "normal" population, although, of course, they may be so.

If we cannot explain variation in brain weight on the basis of rationality or its absence, we may ask whether weight variations not accounted for by sex, age, or body size can be explained on the basis of the possession of unusual intellectual capacities on the part of some of the population. A comparison of the values in table 6, which gives the weights of the brains of certain eminent individuals, with the weights shown in table 1 discloses a range of from 1226 to 1830 grams for eminent individuals between 39 and 82 years of age as compared with 1265 to 1461 grams for average values of samples taken from all over Europe. Moreover, the range encountered in eminence covers the average for insane persons of the same age groups (table 5).

Weidenreich (1946) gives the range of skull capacity for normal individuals in all races of modern man as being from 910 to 2100 cc. As the weight of one cubic centimeter of cerebral tissue is about unity (1.036 grams) and the brain generally occupies two-thirds of the total endocranial capacity, Weidenreich tacitly accepts a weight range of from 625 to 1450 grams as normal. With such figures it would be quite impossible to determine whether any sort of trend in cerebral size has been operative during the last half of the Pleistocene (figs. 1 and 2). Indeed, Weidenreich's range can have really very little meaning even in modern times unless we neglect entirely the influence of age which is operative over a much longer period with regard to skull size (fig. 3) than with regard to brain volume (table 2). We know, of course, that skull volume does not change appreciably between 50 and 90 years in normal individuals, but we have seen (table 2) that the brain does become atrophic. Now we observe that, although the volume of the brain does not increase notably after the first decade of life, head size does increase quite regularly through and even beyond the second decade. (The skull itself thickens in essentially the same period as skull size increases, if we accept Roche's, 1953, figures for the former dimension.) Estimates of endocranial capacity urgently require qualification, in terms of age at least, and it is impossible to be dogmatic about the age of skulls on the basis of the degree of suture closure (Cobb, 1954).

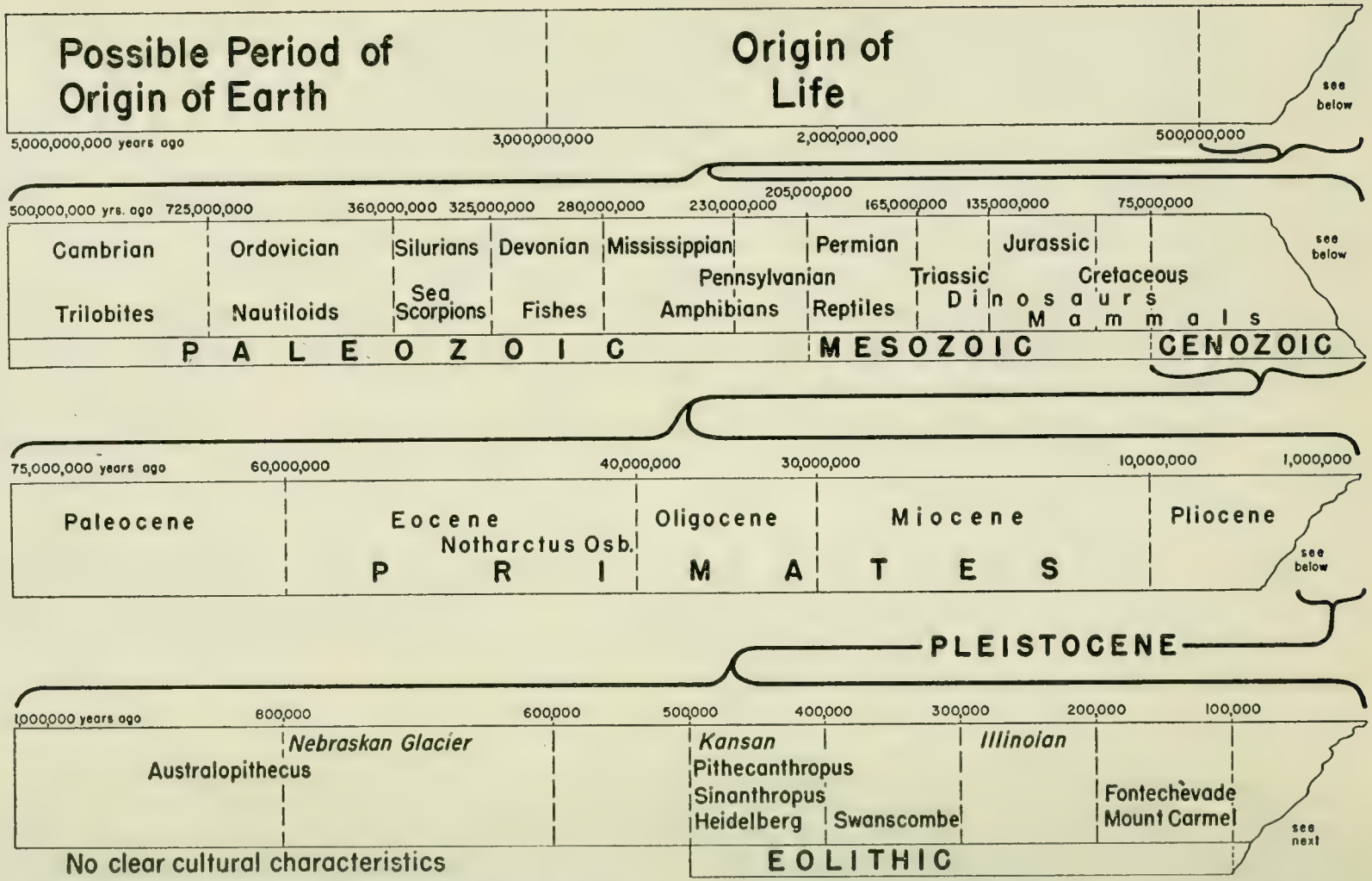

FIG. 1. Approximate time table for origin of man. In second bar graph, right terminal portion of first bar graph is enlarged, as shown by bracketed material. Terminal right portion again enlarged in third bar graph, and so on.

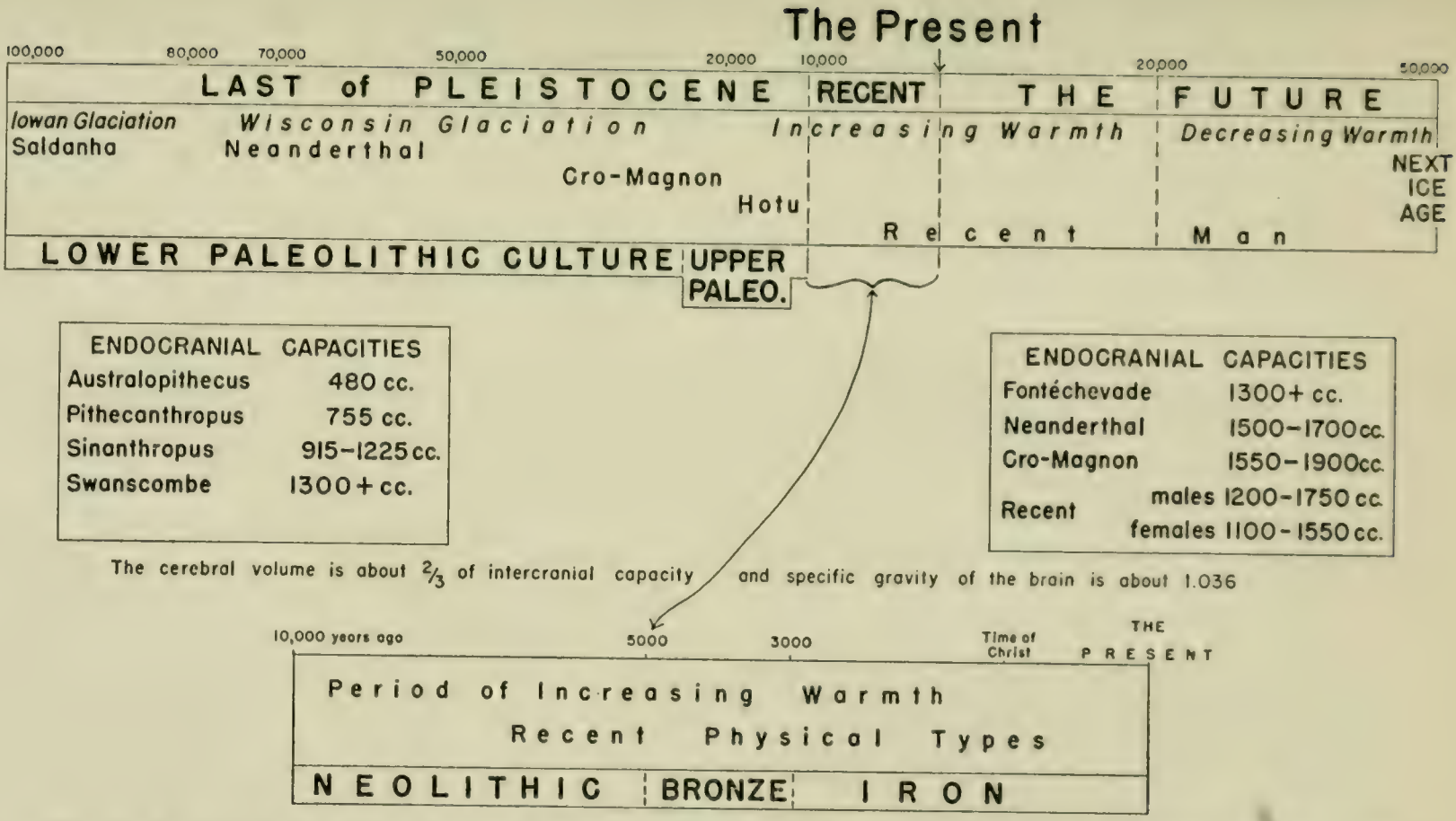

FIG. 2. Paleolithic and Recent periods, together with values of endocranial capacities of Pleistocene anthropoids and man. Terminal portion of last bar graph in figure 1 reproduced in enlarged form.

Measurements of the volume of the brain are themselves not beyond the possibility of misinterpretation. Physical anthropologists are well aware that large brains often hide dilated, water-containing ventricles. Even brain weights may suffer from artifactual error.

Table 7, the source of which shall remain unidentified by me, is an interesting example of incredible nonsense which might have been produced as the result of the operation of rather simple

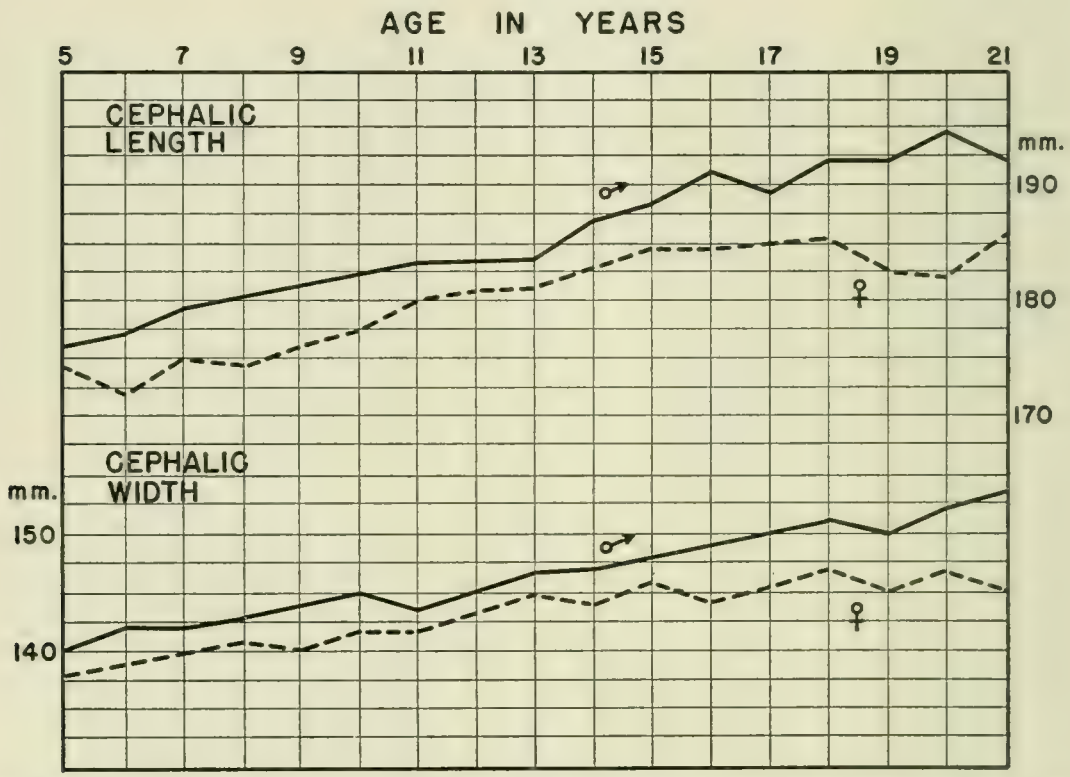

FIG. 3. Age changes in length and breadth of head (from Donaldson, 1895, after West).

artifactual principles, notably the post-mortem changes in weight and volume that brains undergo. It is surprising how easily startling results can be achieved as a consequence of artifact.

Some years ago Lewis Rowland and I set out to determine whether the brains of psychotic persons contain fewer cells per unit of cubic volume than do normal brains (Rowland and Mettler, 1949). When we compared our figures, obtained on material from living psychotics, with the values in the literature for normal brains, we came to the astonishing conclusion that the material from our psychotic individuals quite regularly exhibited not merely the same number of cells as, but *more* than, that obtained

from normal humans! This curious paradox became explicable when we recalled that all the available figures for the "normal" brain were based upon post-mortem material, whereas our specimens had been obtained from living persons during psychosurgical operations. Although all tissues shrink during histological preparation, the post-mortem material had undergone an intervening swelling which occurred after death and which continued during fixation in the formalin.

Fixation-swelling gradually reverses itself, and the brain returns to and then passes below its original size and weight, depending upon how long it remains in a fixative. It is obvious that in instances in which an investigator was particularly interested in what he considered a rare or valuable brain he would study this as soon as it was adequately fixed and thus at the peak of its artifactual increase in size (von Economo, 1929). On the other hand, the brains of such ordinary folk as "laborers" would be left in a common crock to be weighed and measured at leisure—or, in other words, after they had passed the period of swelling and had begun to shrink. Further, such brains would probably have been removed by less careful assistants who may have ripped off the infundibulum and the membranes of the lateral and median cerebellar recesses so that, with shrinkage, all the contained ventricular fluid would run out to be replaced by air during the process of draining before weighing. I suspect forces of such a nature to have been operative in the development of the data shown in table 7.

TABLE 7

EXAMPLE OF MANNER IN WHICH BRAIN WEIGHTS CAN BE EMPLOYED TO BOLSTER AN HYPOTHESIS (SEE TEXT)

Occupation	Number of Cases	Weight	Percentage Over 1400 Grams
Day laborers	14	1410	26.2
Laborers	34	1433	
Attendants, supervisors	14	1436	
Tradespeople, craftsmen	123	1450	42.8
Minor officials	28	1469	48.5
Major officials, physicians	22	1500	57.2

Artifactual confusion due to solicitude for "rare" material can be even more profound. It is the custom, when histologic studies are contemplated, to perfuse the tissue to be removed. Until now we have had very little evidence about how such perfusion solutions influence quantitative studies of neural elements. Professor José Frontera-Reichert of the Department of Anatomy of the Medical School of Puerto Rico has recently shown me figures he has obtained from brains perfused with a variety of mixtures commonly employed for such a purpose. The results clearly indicate that we must reinterpret much "standard" data, for not only do all these fluids engender swelling, but the extent to which cytologic counts of surface elements, such as those in the cerebral cortex, are affected is variably influenced by the magnitude of the radius of the spherical substance which is the brain.

We come therefore to the necessity of concluding that brain size, whether determined by weight or volume, must, like that of other genotypically determined portions of the body, be considered in association not only with factors of handling and age and sex but also in connection with the general bodily characteristics of the individual from whence the material came. There is a direct correlation between the morphology of the brain and race, but that this correlation has any particular meaning in terms of what we call intelligence remains to be demonstrated and, as is shown below, it would be very surprising if a simple correlation could be derived. In attempting to arrive at an opinion as to whether or not modern man's brain has increased in size, we are necessarily forced to deal with endocranial capacities. From what is said above it is clear that a systematic body of data relating encephalon to endocranial capacity has not yet been developed, as this must necessarily be part of the still lacking correlation between brain and body type. Allowing for the shortcomings of the material, we can, however, see if what is available to us discloses any recognizable evolutionary trend.

Endocranial capacity shows variations with regard to sex and bodily development, and these seem to be like those influencing the size of the brain, but we have already commented that the age alterations in endocranial capacity are restricted to the first third of life and progress more slowly than does brain growth. We might expect that, because most primitive races were much

smaller than modern man, they might be anticipated to have had smaller endocranial capacities, and this is true. Cro-Magnon man, who was larger than most moderns, had a larger endocranial capacity (fig. 2). In order for us to know whether or not the brains of any of our predecessors were relatively smaller, we should need to have more satisfactory estimates than we possess about the size and weight of many of these Pleistocene forms. Such estimates are only approachable in *Australopithecus, Sinanthropus,* and Cro-Magnon man. The data with regard to the so-called "giant" races of antiquity are confusing. The size of the bones and even of the teeth of the few widely scattered specimens which have given rise to the supposition that giant hominids existed are massive indeed, but the intracranial capacity, where it is determinable, is slight. Le Gros Clark (1954) has pointed out that these so-called giant forms were probably not unusually tall, and Straus (1954) has even suggested that they are merely pathological specimens. If we attempt to correct for differences in bodily magnitude, we do not emerge with very good evidence that man's brain has been increasing. Figures such as those shown in table 1 illustrate the obvious difficulties that arise in an attempt to correlate brain size with something as meaningless as nationality, for it is clear that genotypic variation is more significant than residence in a particular geopolitical locus. This same difficulty arises when we investigate endocranial capacities, for we have only fragmentary knowledge of the movements of genotypically distinct populations of the past. The recent finding, for example, of a group of fifth-century or sixth-century Finnish skulls averaging 1050 cc. for females and 1185 cc. for males of individuals only slightly over 5 feet tall (Blomquist, 1953) discloses remains quite different from others in the area and suggests that these smaller people may have been enslaved Lapps who were imported from another locus or were the remnants of an indigenous group, possibly to be identified with Procopius' Skrithiphinoi. Not all such older people were diminutives with small brain cases. Moreover, Tilly Edinger, who has delivered an earlier James Arthur Lecture, has demonstrated that if there is such a thing as evolution (increase in size and volume) of the brain, it is not related to body size. Among the only slightly taller tenth-century and eleventh-century Slavs of Bled (5½ feet as against 5 feet 2 or 3 inches for Blomquist's material) the intra-

cranial capacity runs about 1437 cc. for males and 1310 cc. for females (Skerlj and Dolinar, 1950). We must therefore conclude that racial (genotypic) variation has long been, as it is now, the major factor in variation in intracranial capacity.

In some districts man has changed very little since the Paleolithic. Torgersen, Getz, Hafsten, and Olsen (1953) report a Bleivik paleolith that was about 5 feet 4 inches in height and quite similar to modern, mesocephalic Norwegians.

Endocranial casts therefore do not appear to support the notion that the brain of modern man has increased in size. Such casts do

TABLE 8

RELATION BETWEEN ENDOCRANIAL CAPACITY AND ENCEPHALIC VOLUME, ABSOLUTE ENCEPHALIC WEIGHT (IN GRAMS), AND RATIO OF WEIGHT OF ENCEPHALON TO THAT OF BODY FOR DIFFERENT SPECIES

Form	Encephalic Volume/Skull Volume	Encephalic Weight	Encephalic Weight/Body Weight
Homo	*Ca.* 1/1.5	1100–2000	1/30–60
Pitheci			
Simia troglodytes	*Ca.* 1/1.66	209–463	1/14–213
Macacus	*Ca.* 1/2.2	56–145	1/25.8–108.6
Cebus capucinus	—	36–97	1/23–72
Hapale rosalia	*Ca.* 1/2	7.9	1/30
Prosimii, *Lemur*	*Ca.* 1/2.2	14.5–26.3	1/41
Chiroptera, *Vespertilio murinus*	*Ca.* 1/2.2	0.13–0.17	1/30–36.6
Carnivora			
Felis domesticus	*Ca.* 1/2.86	21–35	1/22–185
Meles taxus	*Ca.* 1/3	46–48	1/128–159
Canis familiaris	*Ca.* 1/2.5	54–125	1/37–358
Pinnipedia, *Phoca vitulina*	*Ca.* 1/2.5	302	1/242
Insectivora, *Erinaceus europaeus*	*Ca.* 1/3–4	0.18–3.6	1/43–390
Rodentia			
Mus rattus	*Ca.* 1/2.6–3	1.8–10.0	1/66–194
Lepus cuniculus (domesticated)	—	11.20	1/301
Ungulata			
Sus scrofa (domesticated)	*Ca.* 1/8	105–110	1/630–660
Equus caballus	*Ca.* 1/7	600	1/379–801
Elephas africanus	*Ca.* 1/8–10	2536–4000	1/125
Sirenia, *Manatus americanus*	—	*Ca.* 344	—
Cetacea			
Phocaena communis	—	468	1/38–93
Balaenoptera musculus	—	4700–6700	1/12,000–25,000
Edentata, *Dasypus setosus*	*Ca.* 1/3	18	1/141
Marsupialia, *Petaurus sciureus*	*Ca.* 1/2.2	3–66	1/40–800
Monotremata, *Echidna hystrix* and *Ornithorhynchus paradoxus*	—	16–32	1/80–130

show variations, but these variations are all explicable on the basis of age, sex, and the intermingling of genotypically different peoples. There is no evidence of a selective forward march from a smaller to larger brain. As soon as we come upon modern man, some of his representatives have as large a brain case as those of our contemporaries who we consider to be very satisfactorily equipped with regard to both quantity and quality of cerebral substance.

When it becomes apparent in science that a generally accepted hypothesis has really very little to support it, there is always a tendency to look around to discover who the culprit was who brought the suspect hypothesis into polite company. The background for the notion that man's brain has continued a process of progressive forward evolution up to the present is the same as that which lies behind all considerations of homologous structures, i.e., such structures have a lineage and have remained static, regressed, progressed, or have been diverted into quite different forms for performing essentially the same or very different functions. As man's brain is both absolutely and relatively quite large (table 8), it would seem clear that it has not merely failed to participate in the otherwise general degradation of the human form but has, in fact, undergone positive development. Such a conclusion seems sound enough with regard to the animal kingdom as a whole, but difficulty begins to develop when we draw near to man himself. It is not difficult to admit that the brain of man is superior to that found in fish, or in amphibians, or in reptiles, but even some rather lowly primates have relatively more brain than does man (table 8). The notion that there has been a continuous increase in the size of the brain from early, low primates, directly up to and through modern man is explicit in Broca's studies on intracranial volumes (Broca, 1862), but Retzius (1915) expressed, as the title of his article indicates, a distinct doubt about the validity of such an assumption. We have known for a relatively long period of time that the endocranial capacity of Neanderthal man (1500–1700+ cc.) compares very favorably with that of modern man and that Cro-Magnon man's intracranial capacity (1500–1900 cc.) surpassed present day man's, but these observations were ignored. It was emphasized that *Pithecanthropus* had a low endocranial capacity (775+ cc.) and, when *Sinanthropus* was also

found to have a small brain case, the difficulties raised by the Neanderthal and Cro-Magnon forms were glossed over, although many serious writers failed to subscribe to Broca's thesis. Among these, besides Retzius, may be mentioned Keith (1925), Tilney and Riley (1928), and especially von Bonin (1934). Von Economo (1929) also expressed the opinion that intracranial capacity and intellectual ability need not parallel each other. Von Bonin expressed himself to the same effect by saying that "the conclusion that there has been a lessening of intelligence throughout the ages is hardly acceptable." (He was ridiculing an oblique statement of Martin's, 1928.) Von Economo (1929) and von Bonin both shifted the search for a correlation between intellectual capacity and structural substratum to a new area by suggesting that the active elements in the brain might increase without any increase in total cerebral dimensions. This argument had been implicit in Flechsig's (1896) and Ferrier's (1890) thesis (see below) that particular cerebral loci were of relatively greater importance than others for intellectual activity and in Parker's (1922) emphasis upon the neurocyte as the critical element.[1] It is the former point of view that has enjoyed popularity among physical anthropologists, as it is not possible to determine how many cells existed in a vanished brain but something can be said about the form of the head which contained that brain.

Does intellectual function reside in a particular aspect of cerebral configuration?

Those writers who take the position that man's neural system must necessarily have evolved structurally in a progressive fashion since Neanderthal man and who admit that no such progression can be substantiated on the basis of increase in size or weight are inclined to seek for modern "superiority" in some more subtle alteration. Weidenreich (1946), for example, sought such supe-

[1] This apparently self-evident consideration is not necessarily deictic. There is, for example, a gradual decrease with age in the number of cells per unit volume of cerebral cortex, as Conel (1939, 1951, 1947, 1951, 1955) has shown, and it seems reasonable to assume that a smaller number of strategically situated cells, provided with elaborate synapses, may be more significant than a larger number of inconsequential elements. It is even conceivable that greater metabolic efficiency on the part of a few cells would more than compensate for the potential advantage of number in a more abundant population.

riority in shape. He says, "The height of the Neanderthalian brain is, in all cases, clearly inferior to that of modern man." "Superiority," for Weidenreich, means an increase in prominence of the dorsal convexity above the locus of the junction of parietal and occipital lobes. Because this increase in dorsoventral diameter of the brain occurs in a structure the over-all size of which is not increased, it must be achieved by a reduction in the rostrocaudal diameter. Just why Weidenreich thought such a shift constituted an advance or "superiority" is far from clear. His reasoning devolves from the observation that the development of a more rounded form of the brain is a relatively late development, but Weidenreich must have been aware that the dorsoventral diameter of the human brain is not equally increased in all racial types and that it reaches its greatest natural prominence among plano-occipitals such as the Armenoids and Tyrolese (the Vedas also had a relatively higher cerebrum, as Sarasin has shown), but he did not discuss this situation. Instead he saw in dorsoventral enlargement the possibility that "association" areas might have been selectively enlarged (the fact that they had to be simultaneously rostrocaudally compressed is glossed over), and a highly theoretical speculation of G. Elliot Smith is quoted (somewhat irrelevantly) to provide substance to Weidenreich's hypothesis.

Flechsig was the first to emphasize the supposed relationship between intelligence and what he called "association areas," a term applied to those portions of the brain that are tardy in myelinating and that do not receive any primary afferent system or emit any long motor projection. That such regions perform associative functions is more than probable. That they perform such functions to a greater extent than other portions of the brain is open to question. There is no reason at all to suppose that what are called intellectual functions are specifically dependent upon them.

Weidenreich included in his figures (his fig. 79) endocranial casts from a gorilla, *Pithecanthropus erectus,* Neanderthal man, and modern man, but if he had used the endocranial cast of a chimpanzee it would have been apparent that this animal has a relatively greater dorsoventral cerebral diameter than does modern man. The difference in the relative magnitude of the dorsoventral diameters of the brain of the gorilla and chimpanzee

would seem to be explicable on the basis of difference in the craniocervical angle of these two anthropoids, for the head of the gorilla is carried more decidedly forward than that of the chimpanzee. It is by no means impossible, judging from the pelvic and femoral configuration of early hominids, that they also carried their heads on a wider craniocervical angle than does modern man, and all reconstructions of these forms, such as Coon's (1954) of *Sinanthropus,* show very wide craniocervical angles. Weidenreich did recognize the possibility that brachycephalization was due to adjustment of the head to the erect posture, but his emphasis was on the contention that broad-headedness is an advanced state of development which is still progressing and not on the purely mechanical aspects of the relationship.

While the proportion of short and broad to long and narrow skulls seems to have increased from Neolithic times, it does not seem that this is a universal, irreversible, forward trend that is completely gene-controlled, or that it is correlated with a superior degree of intelligence.

With regard to the tendency towards broad-headedness, it may be pointed out that among modern male Scots short, narrow crania are becoming more numerous (Scott, 1953). In view of the high incidence of anatomic variations (especially those due to modifying influences which operate in the genic environmental sphere or on peristatic fetal-maternal relationships; Fischer, 1952) more work like that of Lasker (1953) and of Otto (1953) needs to be done. May brachycephalization be one of the alterations in body form and size due to a shift in human reproductive habits or to changes in ecological conditions, such as Bartholomew and Birdsell (1953) have emphasized?

Even if we grant that brachycephalization has become an established, progressive feature of contemporary man, we must admit that many groups of earlier men also exhibited this feature. It is easy enough to point out that cultural growth was most rapid among the round-headed peoples of the Mediterranean, but this is merely an *ad hoc propter hoc* argument, and it is chastening to recall that a few decades ago the economically prosperous and supposedly dolichocephalic north Europeans were arguing that long-headedness was positively correlated with intellectual superiority.

In any case, for the original argument to have real weight, the condition of brachycephalization itself still would require to be correlated with superior intelligence. Thus far no data have been brought forward establishing such a correlation. Ordinarily, the basis for the argument in favor of brachycephalization is shifted to some intermediate ground as by Weidenreich's assumption that spherical-brainedness is positively correlated with an increase in the "association" regions of the brain and that these are particularly concerned with intellectual functions. As an example of an "association" region the rostral portion of the frontal lobe has been most frequently cited. There are no easily accessible data to prove that such an increase has occurred with a differential in favor of that region, but even if there were we would still be faced with the difficulty of validating the assumption that these regions are the substrate of intelligence.

Within the past decade a mass of data have accumulated which throw considerable doubt on that assumption. Towards the end of the nineteenth century Gottlieb Burckhardt had the idea that if psychotic persons are bothered by auditory hallucinations one way to get rid of these would be to remove that portion of the cortex in which he thought auditory sensation ended. Burckhardt's (1890–1891) results were not very conclusive, but in 1935 Egas Moñiz (1936) revised the surgical treatment of psychoses in accordance with the hypothesis that it might be profitable to disconnect those portions of the brain most intimately related with complex mental activity. Moñiz chose the frontal lobe, and by 1951 more than 18,600 persons had undergone one or another type of frontal lobe operations. We have had, therefore, considerable opportunity to examine the validity of the belief that intelligence is situated in the frontal lobe. Because this subject was approached with notable bias in favor of the long-accepted supposition that it does, it is not surprising that all the psychologic studies have not been in agreement. This in itself indicates that we are not dealing with the clear-cut correlation everyone supposed existed and expected to find substantiated. It is not necessary to go into the details of the recent findings, but enough is now known to make it clear that an individual lacking both frontal lobes can function quite satisfactorily in our society and that many of what we regard as intellectual traits are not notably im-

paired in such individuals. Consequently, it would appear that the frontal lobe, as such, is not the physical substrate of what our psychological tests of intelligence measure.

Here again it is interesting to enquire how this erroneous concept achieved currency. I have previously explored this curious question (F. A. Mettler, 1949), as follows:

The attribution of changes in personality to frontal lobe damage is not so old as might be supposed. Although some psychic disorders were attributed to cerebral dysfunction even in the early post-Galenic period (C. C. Mettler, 1947) is was not until the second half of the nineteenth century that any evidence was brought forward to suggest that the frontal lobe is specifically concerned with psychic processes. There is nothing in Greisinger's (1867) book to this effect and the suggestion that Harlow's (1848) patient, Phineas Gage, of the so-called "crow-bar case," owed his personality changes (the phrase that he was "no longer Gage," appears in the record; Harlow, 1869, p. 14) to frontal lobe damage was an afterthought on the part of Ferrier. (For Harlow and most of his contemporaries the most significant feature of the case was the survival of the patient, and others, overzealous to defeat the phrenologists, were almost willing to argue that the brain was practically useless in order to achieve their purpose. It is interesting to observe, in passing, that one of the first cases in which a personality change was observed to follow a brain injury was a psychotic case in which the psychosis disappeared after attempted suicide by shooting through the head; Nobele, 1835.)

Welt's (1888) case of Franz Binz of Zürich was probably the first verified example of serious alteration of character and moral behavior due to a frontal lesion, the extent of which was established at autopsy. Franz Binz, like Phineas Gage, changed from a peaceful, gay, polite, and cleanly person to a violently quarrelsome sloven. Goltz, Hitzig, and Ferrier had previously described similar changes. Ferrier (1890) believed that removal of cortex rostral to the electrically excitable area produced "a form of mental degradation which appears to me to depend on the loss of the faculty of attention, and my hypothesis is that the power of attention is intimately related to the volitional movements of the head and eyes," Ferrier attributed the opinion that intellectual degradation may follow lesion of the rostral part of the brain to a number of previous authors, including Brissaud. Welt had been unable to demonstrate any true degradation of intellectual capacity in the case of Binz. Hitzig (1884) also thought that intelligence is impaired by injury of the frontal lobe in the dog, a belief contro-

verted by Loeb (1902), and Bruns could find no evidence of impairment of intellect in one extensive tumor case of his own.

An unpleasant, nasty character was one of the triad of symptoms of release which Goltz felt succeeded frontal lobe changes. [The full triad was (1) general excitement (the capstone of the theory that injury of the cortex brought about a phenomenon of "release" was laid by Charcot, 1876–1880), (2) lack of self-control, (3) violence of spinal and bulbar activity.]

Clownish behavior (*Witzelsucht, mania bel esprit, lazzi, moria*) as a symptom of rostral frontal lobe damage appeared in Jastrowitz's articles of 1888 (Jastrowitz, 1888; see also Leyden and Jastrowitz, 1888; and Bruns, 1892) and formed a part of Bruns' (1897) table of frontal lobe symptomatology. Jastrowitz referred to the condition as *moria*.

Difficulties in the associational process entered the symptomatology of the frontal lobe through the work of Flechsig, who argued that two (originally he said three) "association" centers existed in the brain (a large parieto-occipito-temporal and a smaller frontal one) which gave rise to no projections but only associational fibers, for the purpose of interrelating afferent impulses. Flechsig felt that the frontal association field was primarily concerned with the association of impulses of bodily sense, as contrasted with vision and audition as special senses (he thought of the frontal lobe as containing sensory as well as motor capacities, as indeed its caudal part does), and that injury of it produced defects in personality and self-awareness. Association fibers from it were supposed to deal especially with memory images (Flechsig, 1896). Flechsig's theory was not widely accepted (Oppenheim, 1900) but the theory that psychiatric disorders depend upon an essential difficulty in the associational process long endured in the literature. Thus Bolton (1911) divided psychotic processes into two categories: (1) those in which there is defective control of the processes of lower association, and (2) those in which there is independent activity of the "centers of lower association." He placed apathetic, hebephrenic, and manic syndromes in the first category and illusory and hallucinatory states in the second.

Loss of initiative or apathy as symptoms of frontal lobe disease appeared in Bruns' tabulation and loss of complex emotional behavior probably should also be included here together with defective recognition, due to a degradation in perceptual ability. In contrast to simple apathy, ambulatory hyperkinesia was attributed by Baraduc (1876) as, much earlier, by Magendie, to frontal lobe lesion—specifically by Baraduc to atrophy of the left inferior frontal convolution.

Persistence of fear and the occurrence of panic reactions have been

described as signs of frontal damage, and apparently, in cases of thrombosis of the arteries supplying the frontal region, may be so severe as to amount to delirium tremens. Perhaps these phenomena are to be related with Goltz's listing of release phenomena, though this is far from clear.

Memory defects for the past without impairment of the ability to learn and lack of planning for the future (deterioration of insight) are also listed as results of frontal lobe damage.

It may be justifiably said that these so-called "higher" functions discussed in the foregoing paragraphs are so ill-defined as to be scarcely worth scientific consideration. This depends upon one's point of view. One common criticism of the scientific method as applied to the present sphere is that it has not yielded quantitative support of phenomena which anyone, using merely observation, can easily perceive. Since scientific tests answer only the questions they have been designed to ask, it is, of course, possible that the proper tests have not been devised. On the other hand, it is perfectly possible that these "higher" functions are not functions of the frontal lobe at all or, at best, require damage of very large parts of the frontal lobe in such a way as to compound simple functional deficits into complex patterns of deficit.

The premier question which must receive an affirmative answer in order to conclude that the "higher" functions under discussion are frontal lobe functions, is, Do such deficits invariably appear if the frontal lobe is quite dysfunctional? Under such scrutiny the allocation of most of the preceding phenomena (slovenliness is an exception) fails to be substantiated. We must therefore conclude either that special circumstances, beyond the factor of frontal lobe damage, must be present for their appearance or that they are not true functions.

It becomes clear then that behind the notion that damage of the frontal cortex produces intellectual damage and personality change is a body of data which must be interpreted in a somewhat different light than that which has been employed in the past. We may consider several possibilities. "Intelligence" may be a generalized function of the neural system, or, alternatively, it may be situated in some special locus which has thus far escaped notice. Finally, it is possible that it may not easily be correlated with structural characteristics at all. For example, intelligence must certainly depend on a variety of factors just as does excellence in sports, and excellence in sports depends on the conjunction of the fitness of the individual with the requirements of the sport

chosen. Intelligence presumably also involves not merely an aspect of fitness but the utilization of such fitness in a situation for which it is appropriate. One may question whether there is such a condition as intelligence without specifying the circumstances under which the intellectual skill is to become manifest. Because these external circumstances are obviously very variable, the search for a particular structural substrate would have to be abandoned in favor of a search for a variety of substrata to match the conceivable spectrum of requirements. We may approach the consideration of the possibility that intelligence may be a generalized cerebral function by asking whether Parker's (1922) emphasis on the neurocyte provides us with a useful clue.

Is intellectual capacity directly correlated with the number of neurocytes in the cerebral cortex?

Still another approach to the problem of wherein the supposed superiority of the modern brain may lie is the assumption, already referred to above, that the functional elements of the cerebral cortex, notably its cells, and their functional capacities have increased in number as a result of an increased complexity of folding of cortical surface rather than as the result of an increase in mass. In other words, the free surface of the brain is said to have increased as the result of greater infolding without any increase in the spherical diameter of the cerebrum. Such a situation is certainly possible, and there is a difference among cerebra with regard to degree of convolutional complexity. It is further true that there is a difference between normal brains and the small cerebra of idiots (which are often relatively smooth), but, as in the case of weight or volume, no correlation can be established between degree of gyrencephaly and condition of sanity or intellectual proficiency.

There are two aspects to the problem of whether increased complexity of internal cerebral organization is of possible evolutionary significance. In the first place the fact of such increasing complexity must be established, and in the second place its relation to survival value must be demonstrated. Quantitative estimates of cortical complexity may be expressed in surface area measurements, which are very unreliable, or in terms of the rela-

tion of total volume of nerve cells to volume of cerebral cortex (gray cell coefficient; von Economo, 1926, 1929), or some equivalent of number, such as von Economo's photographic technique or a scanning densitometer measurement (Campbell, 1954). Simplified estimates of the gray cell coefficient can also be worked out on the basis of number, as well as volume, of cells in some arbitrary cubic unit of cortical tissue. Thus the argument that intelligence is related to number of nerve cells can be explored on a localized as well as generalized basis. Such volumetric work is still in its infancy and, I have already noticed, in connection with the discussion of total cerebral volume, some of the difficulties which have beset past computations involving volumetric units. Further, we have no information at all about earlier man and can argue only by comparison of what we find in the brains of different races of modern man and in animals. Obviously there is always a very real danger that superiority will be attributed to some causally unrelated but real concomitant difference which may be disclosed.

The psychologic correlates of the hypothesis that intelligence is a generalized brain function are the theories of vicarious cortical functioning and of mass action. Pavlov took the position that loss of one or another portion of the neural system, and especially of the cerebral cortex, could be compensated for by the extraordinary activity of other portions, the potentialities of which extended beyond their usual function. This principle is demonstrable, but it has limits. Extension of it to the proposition that any portion of the neuraxis (or cortex) can take over the functions of any other portion of the neuraxis (or cortex) is quite unwarranted. Moreover, when such a situation develops, the vicariously mediated activity is likely to be an obvious and, often, poor substitute for the original.

A similar criticism applies to the principle of mass action which is supportable to the extent that neural activity occurs in a frame of reference of totality of function which is distorted by truncation, often in seemingly inconsequential ways. The mass actionists have, however, been less interested in interaction than in the fact that much neural tissue is dispensable. Such a consideration of their work brings us close to the problem in hand. Unfortunately the fact that much neural tissue may be dispensed with does not demonstrate that the function of what has been removed exists

elsewhere, as well as in what has been ablated. It may merely mean that the experimental enterprise is in irrelevant one.

Many persons in the United States not only have been subjected to psychosurgical operations that have removed more or less of the frontal lobe and therefore a considerable proportion of the "association" areas, but these operative procedures have also rendered enough brain non-functional to reduce these individuals to a functioning brain weight not greatly in excess of that of *Pithecanthropus*, depending on what the operated person's brain originally weighed. Nevertheless, as indicated above, such operations may not be followed by any alterations easily detected by psychologic tests. It is true that some patients give very poor performances after operations, but such a situation might be due to the progress of the original disorder for which the operation was done. It is much more significant that many mature patients show no such changes in our society as it is presently organized. The literature contains many impressionistic reports to the effect that such "psychosurgical" operations have adverse effects. Unfortunately we cannot rely on this type of report, but it is true that psychologic tests leave much to be desired by way of conclusiveness. There are limits to what psychologic testing can do, and many patients who refuse to cooperate in a psychologic test situation and cannot be included in statistical evaluations may easily provide the clue to what those portions of the brain that have been removed may "be good for." In social situations, such as those in which we customarily function, the shortcomings of the individual are often compensated for by the social conscience of his fellows. The simple fact that many rather deficient and essentially parasitic individuals move freely and in an undistinguished manner through our protective social structure should not be overlooked in any attempt to explain why persons who have little or no frontal lobe are not merely able to function in our society but are often able to earn very considerable salaries. In a truly competitive and less genteel society the individual who does not or cannot "pull his own weight" or whose wits are less than nimble is likely to succumb fairly early, and this is even more true of persons who do not bestir themselves in existences of a solitary nature. We cannot put this kind of pressure on individuals in psychologic test situations, and our tests consequently lack a certain depth and are devoid of the

vitality which must be of importance to the student of survival values. Nevertheless, the lessons of psychosurgery are clear, and they are to the effect that we have overrated the importance of the frontal cerebral cortex in intellectual function. While it is likely that any one of us could ill afford to part with any cerebral substance if we were transported back to a situation in which we had to retrace the necessity of developing our culture all over again, our modern social system is so arranged that most of us can function at a very low level of efficiency most of the time. The "psychosurgical" data contain another clue of considerable importance and that is that we can more easily dispense with cortical gray matter than with subcortical cellular accumulations. I wish to return to this point farther along.

For the present then we may say that those authors who look for the progress of evolution in the direction of some generalized augmentation of cerebral function, such as might accompany an increase of nerve cells, may be correct, but there is no evidence at all to justify the assumptions that modern man has more such cells in fact than Cro-Magnon, Neanderthal, or even Swanscombe man, and it remains to be demonstrated that there is a positive correlation between number of neurocytes and what passes for intelligence. The position may be granted that a high degree of intelligence is a total function, but it is quite impossible for all or any portion of the cerebral cortex to subserve the function of all other parts.

A high degree of intelligence is certainly not localized in one particular portion of the neural system. It is, or should be, the sum of perfect functioning not merely of the neuraxis but of all other parts of the body. If it is true then that the future of our race depends on the most complete utilization of intelligence, we shall have to look for the most nearly perfect physical individual in order to find the most intelligent.

We all know that matters do not work out this way. We are all aware that the handsome matinee idol may be an unusually vapid individual and that beautiful blondes are often intolerable for protracted periods. The difficulty is, of course, not merely that a physical disability can be readily offset by a cultural advantage but that a disability may actually turn out to be an asset by virtue of its psychological activating quality. We cannot therefore look for

survival of the race in over-all physical perfection. Moreover, as physical defects, such as myopia or a missing extremity, are very easily offset by technological devices, we must search for uncompensable limitations if we are to discover any areas wherein our development will be blocked in a progressive civilization.

Can man satisfactorily maintain a "large" brain?

Proponents of the theory that man's brain has been consistently enlarging have directed very little attention to the anatomic circumstances that are required for the maintenance of such a brain as modern man possesses or to what changes would be required if that brain were to undergo a future progressive increase in size.

Obstetrical difficulties

Obviously, at the very outset of independent existence the head of an infant must, under ordinary circumstances, pass through a birth canal the dimensions of which are unalterably fixed by the size and shape of the maternal pelvis. A not inconsiderable degree of obstetrical difficulty consists in the mismating of genotypically large males with females having a pelvic outlet too restricted for the uncomplicated delivery of the product of such a mating. The margin of obstetrical safety is not so great but that any appreciable increase in the size of the head of the infant would immediately influence the paranatal death rate adversely and markedly raise the incidence of brain injury among neonates. It is quite possible that increased head size and increased pelvic dimensions would occur together. This has been the course of events in the past (fig. 4), but pelvic size is an important selective factor with regard to magnitude of head size in any race and operates in favor of small-headedness.

Oxygen requirements of neural system

The oxygen requirements of the neural system of neonates are different from those of adults. Newborn animals can endure a surprising reduction in oxygen, as anyone who has ever tried to drown kittens can testify. Nevertheless, there are specific limits to such endurance, and it would be interesting to know whether, as seems reasonable, such limits become progressively lower for

neural systems of larger size. I am unaware of any studies on this subject, but we do possess an impressive mass of data which demonstrates that a very considerable proportion of brain-injured children have been damaged because of failure to get oxygen to all portions of the brain during intra-uterine existence, as well as at birth or immediately afterward.

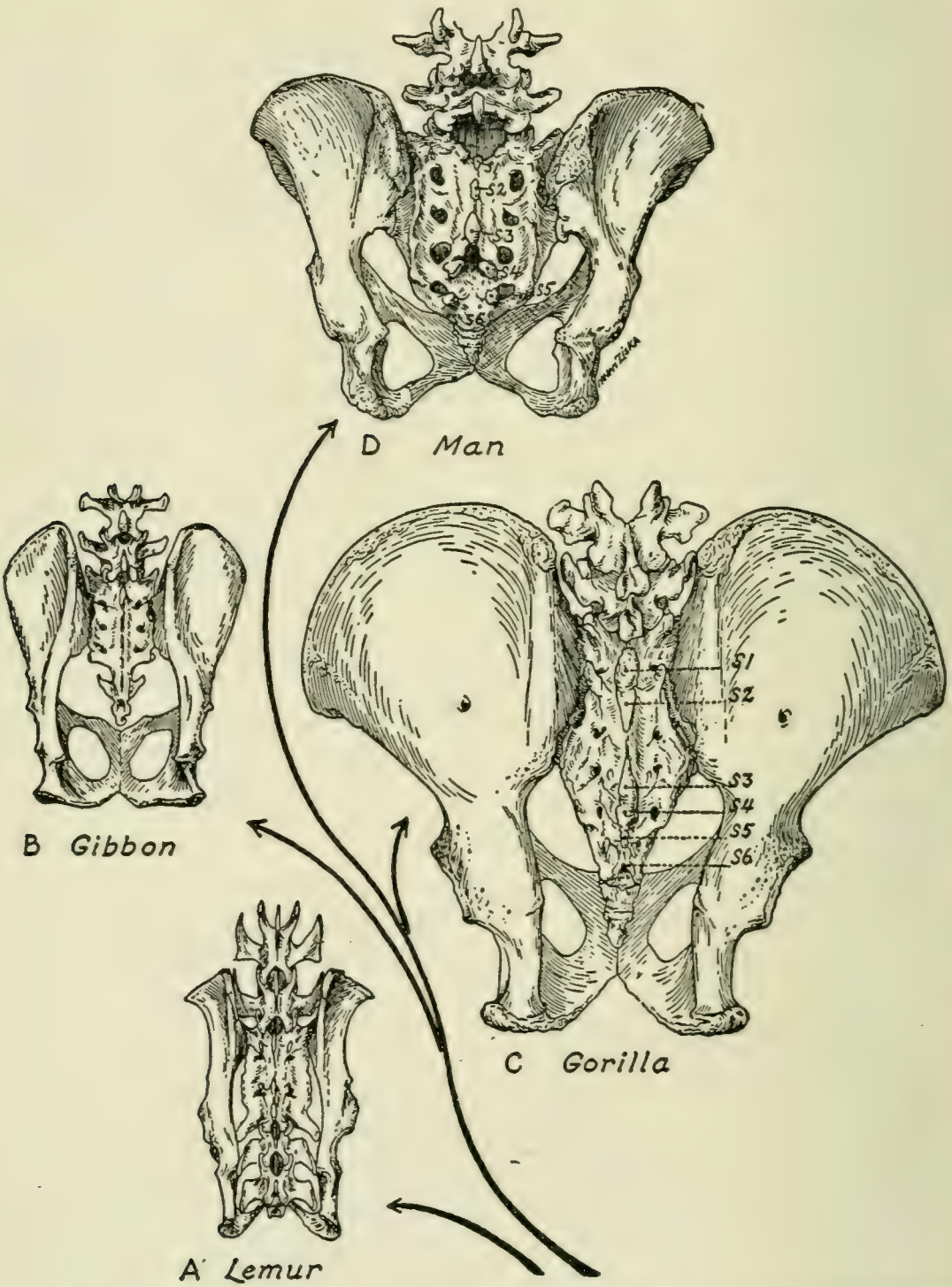

FIG. 4. Progressive widening of the sacrum and pelvis in primates (from Gregory, 1951, vol. 2).

It was long believed that most brain-injured children, the so-called cerebral palsy cases, were damaged during birth, but older doubts have been fortified in recent years by increasing evidence that a great many such children have been born without any notable difficulty in labor. Protracted and complicated labors do result in brain injuries and even deaths, as noted above, but much brain injury occurs before birth as well as during or afterward and as the result of processes the nature of which has only recently been elucidated. Two very important principles have emerged. These are, first, that gross malformations of the neural system almost always have their origin in the very earliest period of pregnancy (often before the mother is aware of her condition) and, second, that alterations in oxygen supply occurring in any part of pregnancy have very drastic effects. Almost any noxious influence that reaches the fetus in its very early, relatively undifferentiated period (especially during the first two weeks after conception) will result in a malformation but after the second month of pregnancy the neural system can withstand many insults, with the exception of oxygen deprivation, which would previously have done irreparable damage.

One possible reason for the precarious condition of the neural system with regard to variations in oxygen supply is probably to be sought in the manner in which blood is carried to the brain.

The brains of all primates are supplied with blood from two principal arterial reservoirs—the internal carotid and vertebral arteries. The ultimate branches of these two principal supplies anastomose at the base of the brain in a circulus arteriosus from which a crown of vessels penetrates and also embraces the brain itself. In very low forms, such as Amphibia, which have quite simple brains, the brain is supplied not only by vessels from a greater variety of sources, but the individual vessels of the brain itself exhibit many intercommunications (Herrick, 1948).

In herbivores and carnivores the situation is not so free as in *Ambystoma* nor so restricted as in the primates. The vascular net of the amphibian cerebrum has been replaced by the terminal vascular design seen in primates, but at the base of the brain the anastomotic pattern has been retained in what is called a rete mirabile, and this is supplied not merely from the vertebral and internal carotid arteries but also receives an abundant supply of blood from the external carotid through ophthalmic and me-

ningeal branches which, in the human adult, do not ordinarily maintain any notable connection with the extracranial vascular arrangements.

In the human embryo an early, freely vascularized stage exists very briefly. During this period all the blood reaching the brain arrives via the internal and external carotid arteries, for no vertebral arteries exist until the end of the second month, at which time the arterial reservoir for the lower (infratentorial) part of the brain is shifted from the carotid to vertebral arteries and the external carotid contribution is gradually cut off.

Thus the arterial plan of the brain of the human infant passes through a series of changes which recapitulate those of lower phyla and, at the end of the second month, the embryo has already been committed to the primate pattern of supply. A very considerable number of developmental errors can occur in this process of recapitulation, but once it has been completed the pattern settled upon must prove adequate for all subsequent purposes, and it is not a pattern into which any considerable margin of safety has been built. From this time onward the brain enlarges and removes its internal substance farther and farther from its all important supply of blood and thus of oxygen. At the same time the tracery of vessels on the surface of the brain is progressively stretched out, and ultimately a rigid encasement for the entire brain develops in which, with little room to spare, any considerable increase in intracranial pressure will serve to prevent blood from entering the skull.

We now know that the brain of the fetus cannot withstand pronounced drops in maternal blood pressure which are not fatal to the mother. The effect of such a drop is to reduce the oxygen exchange through the placenta to a point where the oxygen concentration in the fetal blood is inadequate to maintain nerve tissue situated in those regions where the physiologic factor of safety is small. Such regions are those in the interior of the brain and in the white matter where the vessels are few and thin. Ultimately, if the child does not perish during the period of deprivation, the neural tissues in these regions break down, the vessels traversing them rupture, and a true apoplexy occurs in the fetus.

Phenomena of this type are probably more common today than ever before. Such circumstances can and do occur when pregnant

women undergo surgical operation by modern techniques and could conceivably happen in high speed transport. Other sources of difficulty are infectious processes which impair placental circulation, drugs, and an improper regulation of the atmosphere such as occurs in combustion failures in tight modern houses, or automobiles, or during the breakdown of refrigeration or air-conditioning apparatus.

The problem of cerebral oxygen supply is also a serious one for adults and can be a limiting factor in our further evolution. Many of us are unaware to what extent the necessities of earning a living expose a significant proportion of the working population to neural damage through oxygen lack.

The neural system is very vulnerable to a number of chemical substances. Some of these substances, such as lead and carbon monoxide, are constantly about us, and great vigilance is required to avoid being poisoned by them. Others, such as DFP (diisopropyl fluorophosphate), the still unused "nerve" gas of the Germans of World War II, are unusual compounds which probably are more destructive as military threats to morale than as practical hazards. In an intermediate position are substances such as carbon tetrachloride, methyl alcohol, ergot, and manganese which are potentially dangerous but the use of which is reasonably well controlled.

Approximately a million and a half Americans are chronically exposed to carbon monoxide as an *industrial* chemical hazard. It may be assumed that the number of individuals exposed to this substance, and hazards such as lead compounds, organic solvents, and several of the other chemicals and compounds, is at least twice as great as industrial figures indicate. Moreover, it is probably not without significance that the neural effect of substances like carbon monoxide seems to be due entirely to anoxemia rather than to any special neurotropic action. Even in lead poisoning the initial reaction of the toxic chemical is with inorganic phosphates, a combination that has a very serious effect on the erythrocytes. Primary pathology of the neural system, in lead poisoning, is practically unknown.

The problem of supplying the brain with oxygen is not, however, restricted to the very young or to industrial workers. The third principal cause of death in the United States is major brain stroke. Murphy (1954) has pointed out that "one-half million per-

sons in this country sustain strokes each year, and . . . one and one-fourth million hemiplegic patients are surviving in the hospital or at home."

Study of figure 5 will reveal (incidence of neural vascular accidents) that the number of persons who have vascular lesions in the neural system is appreciably larger than those who show evi-

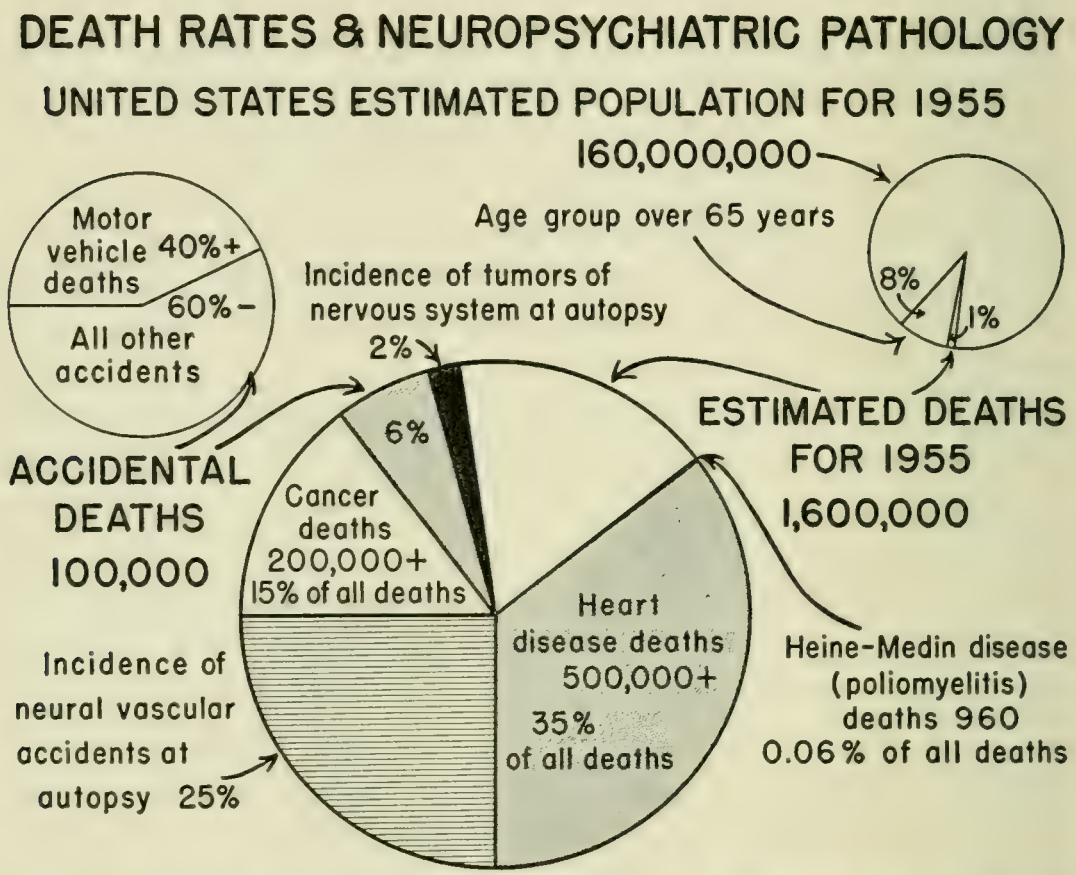

FIG. 5. Relative frequency of different causes of death and also of neuropathology.

dence of such lesions, for such lesions are found in every fourth person who dies. In other words, many persons who will die of other causes and who will show no signs of nervous system damage before they die have substantial damage of the vessels of the nervous system. Had these individuals lived longer they would unquestionably have gone on to show failure of the nervous system.

As our population grows older, an increasing proportion of individuals will inevitably come to a situation in which the vascular supply of the neural system will break down.

All of these considerations point to the possibility that a large brain may not necessarily be a desirable endowment. Indeed, it is possible to experience a certain amount of uneasiness about such

a prospect for it is not at all inconceivable that if man's brain were to increase without substantial modifications, both in his structure and culture, he might be moving in the direction of extinction.

Culture and "intelligence"

It is not often that scientists expend great labor to correlate two variables when the second of these is known to show marked variation in terms of a third, unconsidered variable. Nevertheless, this is exactly what we do when we search for a direct correlation between brain structures and "intelligence," for it is a truism that what we call intelligence is at least as dependent upon nurture as upon nature.

When all the available data have been examined we are forced to admit that no evidence exists to support the contention that man's cultural advance has been due to, or has even been paralleled by, structural changes in his nervous system. The assumptions that the cerebral cortex has become more convoluted or more efficiently organized, by virtue of an increase in the number of nerve cells in it, or because of increase synaptic contacts, are unsupported conjectures, and the belief that human intracranial capacity has undergone steady enlargement is at variance with the actual facts. Since the beginning of the Eolithic period, mankind's neural system has displayed a number of variations on a central structural theme, but no clear trend has become established. Many modern persons seem not to be more abundantly supplied with cerebral substance than any of the Eolithic or Neolithic variants, and indeed most of us have less in the way of brain mass than did Cro-Magnon man who seems not to have been especially successful in the business of survival.

On the other hand it is quite clear that since the Eolithic period mankind has literally inherited the earth. That he owes this inheritance to his culture no one will question, but there has been a tendency to regard culture and structure as essentially separate and antithetical. We speak of physical and social anthropologists, of anatomists, physiologists, psychologists, and sociologists—a literal army of departmentalized scholars, each viewing man from the point of view of his own individual discipline and each insisting upon parcellation.

What in fact do we mean when we admit that, of course, man's

progress has been due to his culture? We may agree (as many have) that this is due to the assumption of the "erect posture, his free-moving arms and hands, his sharp-focusing eyes, a brain capable of fine judgment and decision as well as of keen perception, and the power of speech," as Coon (1954), among others, has pointed out, but all these things were man's in the Eolithic. Man is where he is today not because he has evolved new structural attributes but because he has used the capacities he possessed to provide himself with the means to develop beyond those capacities.

The development of clothing, of tools, of improved means of locomotion, of ways to produce and store food must be looked upon as intellectual accomplishments of the first magnitude. They are especially important in that they came into being at a time when the patterns and mechanisms for intellectual activity so familiar to us were still unknown, when man was still beset by great dangers, could not move far from water, was at the mercy of the sun and snow, and had no accurate records of the past nor clear confidence in the future.

By taking these first steps man had passed beyond the necessity for personal change. He had embarked upon the process of supplementing his evolutionary progress by developing outside himself what other species must attain by personal structure change.

Cultural development nullifies the selective influence of natural environment, by protection from it

Man's forward progress has been characterized by what have been called conquests. In terms of the sciences the implication of such a word is that, whereas man has previously had to come to terms with a physical or biological phenomenon, he has now managed to make himself more or less independent of the influence of such phenomena by virtue of his ability to manipulate the circumstances on which such phenomena depend or that he is at least able to escape from their undesirable effects. In terms of survival, man's knowledge and culture have, consequently, removed him one step farther from the compulsion of his original environment. He is not, of course, freed from obedience to natural law, but he is no longer the inevitable victim of the simple inexorable phenomenon he has learned to manipulate or circumvent. Such a cultural acquisition is the equivalent of an effective structural

modification, but it has the disadvantage that a higher degree of vigilance is required for its effective maintenance.

The cultural acquisitions that free man from dependency on his natural environment are those that protect him from it and that widen his course of action. Science and technological advances operate in this dual manner, and it is to these substitutes for, or supplements to, structural evolutionary change that I now wish to direct attention. Before doing so it is necessary to point out that when cultural continuity is maintained such cultural acquisitions act to all intents and purposes in a society just as though they were genetically determined.

Charles Galton Darwin, the British physicist, has touched upon the biologic equivalence of culture in a rather restricted manner in connection with what he calls "creeds" or what we might call established beliefs (whether rational or not) which result in habit patterns. "A creed," says Darwin (1953), "may have the quality, possessed by the genes of mankind, of being able to produce a permanent effect upon humanity."

Thus it is not merely that aspect of culture that produces science and technologic advances and that removes man from dependency on a restricted environment which may be the equivalent of, or a substitute for, a genetically determined trait, but so also is *any* established course of action, whether rational or irrational. It is obvious that instead of freeing man from the exigencies of his natural environment and increasing his scope of action such an evolutionary change supplement might substitute any kind of abnormal restrictive environment and greatly limit man's scope of behavior.

Evolutionary change supplement

It may be advisable to define more precisely what is meant here by the term evolutionary change supplement and to give some examples. The essential point to bear in mind is that, by virtue of their survival value, human cultural alterations, whether things or thoughts, have come to serve as equivalents or substitutes for structural evolutionary changes, that these cultural alterations, when of a positive nature, protect man from his environment and increase his functional scope, but that they can, from a negative point of view, constitute an adverse artificial environment and severely upset man's structural evolutionary process.

One of the difficulties in dealing with evolutionary changes of any type is encountered in an attempt to separate genetically determined factors from those due to environmental influences. We are all aware that not only are botanical forms severely affected by the climate and soil in which they grow but that the size of animals' bodies and the magnitude of egg clutches are directly influenced by latitude. It is clear that both constitution and environment are active in such variation and that the genetic factors can be operative over a wide, though still definitely limited, range. The non-hereditary influence can be viewed as an evolutionary change supplement.

An important and presently threadbare example of the difficulty in separating genetic and environmental factors is the supposed inverse relation between fertility and level of intelligence. Solution of this problem has been obstructed not merely by a lack of satisfactory methods of measuring intelligence but also by the absence of a clear definition of what is meant by fertility. Are we to understand by fertility the capacity to produce offspring or rather their actual production, i.e., the birth rate? The use of a term such as fertility rate suggests that we are dealing with a genetically determined trait, for that is the meaning of the term in animal husbandry. A moment's reflection soon discloses, however, that local variations in the human birth rate involve cultural, environmental, or, in other words, non-genetic influences to as great an extent as, if not greater than, the actual capacity to produce offspring. Moreover, even the capacity to produce offspring may be influenced by such environmental factors as diet or radiation.

We come therefore to the realization that not only can we not say that what we measure by intelligence tests is entirely genetically determined but that even the birth rate is notably influenced by environment. Viewed in such a light we become aware that what at first sight seemed an interesting correlation between two genetic traits turns out to be no more profound an expression than the simple statement that ignorant persons display their ignorance in reproductive habits as well as in other ways.

Another difficulty in distinguishing between nature and nurture arises when we deal with such behavioral phenomena as become manifest in the interaction of the individual and its milieu. Are these the result of heredity or environment, or do they occupy

an ambivalent and intermediary position? Not all evolutionary changes are obviously structural, although probably all depend on some type of structural change. As an example of what is meant by saying that not all evolutionary changes are obviously structural, it may be pointed out that the migratory habits of birds are not directly structurally self-evident. Nevertheless such habits, like all physiologic behavior, depend on a morphologic substrate and are therefore genetically determined, to some degree at least. In some behavioral patterns of birds, as in the tumbling of pigeons, both hereditary and what might be termed cultural factors are involved. For practical purposes newly emergent behavioral phenomena (having survival value and appearing relatively constantly in a population) whether of a simple physiologic or complex and apparently social nature may be considered solely genotypically determined evolutionary changes if they manifest themselves in their essentially important character in individuals of the species which have been reared in isolation.

More interesting is the position occupied by non-transmissible behavior patterns. These form, of course, a large part of the material of social behavior and, in man, reach the complexity of a definite culture. Social anthropologists have made it clear that culture is itself a product of evolution and undergoes all the usual aspects of evolutionary development. More recently attention has been directed to the fact that the culture produced by man constitutes an artificial environment which exerts a selective factor upon its creator. In other words it becomes itself a selective determinant. Many examples of such a situation might be cited. Man has created many machines on which his present culture is dependent. These machines call for certain behavioral traits in their operators. Operators failing to exhibit these traits or exhibiting them in common with other inconsistent traits not only fail to derive any benefit from the machines (and therefore fall behind in the socio-economic struggle for supremacy) but may in fact injure themselves (and often other persons near them). Again, individuals residing in areas that have long served as emigration sources and never as attractions to immigrants display, as the result of progressive personality selection, psychologic traits essentially different from those seen in newly opened frontier or prospecting communities.

It is not necessary to belabor the point that culture is at once

a product and a determinant of selection, and it certainly has been adequately emphasized that the culture of a species may protect individuals who would otherwise be unfit for survival. I am not so sure that the broader aspect of this principle, notably that it shifts the emphasis for selection from the structural to the cultural level, has been sufficiently emphasized among morphologically minded individuals. (The shift to a culturally determined environment tends to result in differential reproduction in selected genetical systems as a result of weighting cultural adaptation more heavily in the struggle for survival than physical adaptation.) The fact that the physically unfit have had increasing opportunity to survive has been a cause of concern to many writers, but the fact that even greater opportunities for survival have been provided for the culturally adept seem not to have been recognized.

A species that can enhance its sensory capacity by instrumentation and its motor capabilities by technology is under no selective stress at the structural level, and structural modifications in such directions will have little survival, and therefore selective, value. On the other hand the individual who fails correctly to interpret the indicators of our technological civilization will soon be eliminated from this in one way or another.

Not all cultural variants have survival value any more than do all structural variants, but to those cultural elaborations that transcend the selective effect of organic (or important genetically determined behavioral) changes I have chosen to apply the term evolutionary change supplements. Behavioral patterns, not genetically transmissible, that have definite survival significance for the species are evolutionary change supplements. Various names could be applied to such developments, and it could be said that they are merely culture. They certainly are cultural alterations, but it would not be sufficient to characterize them in such a way solely, for not all culture, as has just been pointed out, has positive or negative survival value for the species or even acts as a selective force. Moreover, such a name would obscure the fact that these particular aspects of culture tend to encourage structural variation and protect the total species from specialized evolution. Neither would it be correct to consider particular cultural features simple supplements of evolutionary structural changes, for they also supplement behavior patterns. To call them evolutionary

supplements would be to ignore the fact that they are also determinants of evolutionary processes. The phrase evolutionary change supplements does not entirely satisfy me, and I am sure additional objections, beyond those I have pointed out, can be raised by others.

One of the most interesting aspects of evolutionary change supplements is that they not only free a species from the forces that result in structural evolution but, by tremendously increasing intraspecies variability, they make it possible to develop very great potentialities for structural evolution. This is the result of a variety of influences, among which preservation of many more mutations than would otherwise survive is only one. Another is, of course, the tendency for cross breeding which is seen in most protective and permissive environments. These two factors are mutually reënforcing, because with the genetic reservoir greatly expanded as the result of mutation, cross breeding will result in further intraspecies variation.

There has been an almost uniform tendency to look towards the most highly developed examples of *Homo sapiens* as holding the hope for the future of our species, and it is certainly true that, as our culture is presently organized, the ability to develop evolutionary change supplements seems to be the only requirement for progress. The more we can control our environment and devise new ways to manipulate it and make it work for us the less we shall have to do with our own soma. Nevertheless, I can conceive of a situation in the brightly burnished and explosive future in which the capacity to survive in a very primitive environment might be the most import characteristic *Homo sapiens* could display, and the most valuable members of the species may prove to be those who are presently far down the scale in social acceptability.

Types of neural system supplements

To list all the supplements that have been developed for the neural system would constitute a complete catalogue of our cultural necessities and conveniences, but it is worth paying some attention to the areas in which such supplementation has been maximal and minimal.

It is customary to divide neural function into various types of

categories which more or less overlap. Thus we can speak of autonomic and central neural functions, of spinal and cranial nerve functions, or of sensory, internuncial, and motor activities.

One might suppose that the greatest cultural developments would be in those spheres characterized by the capacities for nicety of sensory discrimination or degree of motor performance. It is certainly true that little or no cultural sophistication exists in areas such as olfaction, gustation, or vestibular function or in pedal dexterity, as contrasted with manual, but the great mass of cultural developments seem to be primarily directed towards supplementing the autonomic functions of the body and to the avoidance of actual discomforts. Mankind appears to be more interested in homeostasis at the social as well as the biologic level than hustling, and in ease than exertion.

Another generality which emerges in connection with what types of neural system supplements have and what have not been developed is that relatively little development has occurred in those areas in which the race as a whole is not naturally proficient. Thus there is great variation in the ability of persons to discriminate between gustatory sensations, and gustatory or olfactory sensory experiences would make very poor communications media. As a consequence, such experiences play an almost completely nonobjective role in our culture. The implication seems clear that culture tends to develop around average natural attributes, which is in line with what we know about the tendency for social organizations to level off the hills of exceptional ability and fill up the valleys of deficiency.

The demands of the future

There have been many guesses advanced as to what the world of the future will be like (Shapiro, 1933). We can be sure of little in this regard except that we can confidently expect more of what we are already are aware. This being the case, it is safe to say that the world of the future will be full of technological advances, toxic hazards, high velocities, synthetic foods, and radiation dangers, all of which sum up to what man regards as improved material advantages and which result, in fact, in increased isolation from the natural environment of the physical world. It is an interesting observation that the nervous system is relatively resistant to many of these technological alterations. Notable exceptions exist with

regard to oxygen deprivation, which we have already noticed, and with regard to nutrition.

The neural system has no capacity to store appreciable quantities of food substances, enzymes, and minerals, deficiencies of which produce not only pronounced reversible functional changes but actual structural deterioration which may not be entirely reversible

Man has been remarkably adaptable in connection with his diet, being exceeded, from the point of view of omniverousness, by the hog alone. It might be expected that quite low forms would exhibit a greater versatility in ability to absorb nutriment and therefore to survive than does man, but the case seems to be quite otherwise, for it is enough to place some insects upon an unfamiliar though satisfactory type of food in order to starve them to death. Still, man's very omniverousness seems to have been achieved at the cost of a loss in the ability to discriminate between good and bad, or even poisonous, food. It is very difficult to fool felines or canines about their food in spite of their domestication, and it is even more difficult to fool an ape, but man possesses little ability to select what is good, and reject what is bad, from natural sources. This ability is more notable in the very young than in older individuals. Taste and olfaction are both of rudimentary significance in man and deteriorate quite rapidly with age. Tests on primitive peoples and groups, such as the Lapps, who are located away from the central streams of culture do not support the notion that the olfactory or gustatory senses of these people are any more acute than those of people with more advanced and centralized cultures. Among all groups of modern man there is great individual variability in olfactory and gustatory sensitivity. In general about one-third of any population sample is practically anosmic and ageustic, but even those individuals who exhibit a good sense of smell and taste show little ability to live off an unfamiliar terrain. Modern man's nutrition provides an interesting example of the manner in which evolutionary change supplements function and is affected by a wide range of cultural and economic factors which will probably exert increasing degrees of pressure as the pressure of population density continues to increase. The essentially irrational role that culture plays in food habits and preferences has been explained by many serious and competent writers, and the extent

to which processed, "substitute," and "supplementary" food products have supplanted natural foods has clearly been demonstrated to be dependent on the disinclination of people to expend the time and trouble in bringing the latter to the table. Psychiatrists have also shown the extent to which eating and eating habits have become substitutive functions unrelated to the actual bodily need for food as nutritive material. All these circumstances suggest areas requiring attention in the future in order to make certain that the neural system man has is adequately provided with the material it needs in order to function at peak capacity.

Another difficulty arising from foods,
from the point of view of the neural system,
is the not inconsiderable danger
of actual poisoning

Here again the economic factors involved are especially compelling. Tremendous quantities of insecticides, fungicides, dye products, and hygroscopic agents are carried forward in food products brought to the table. It is rather pointless to inveigh against the possibility of poisoning ourselves, when our society is organized in such a manner as to force the producer to use dangerous materials in order to maintain the small margin of profit that keeps him in business, when we beat Federal, state, and county budgets down to such a level that no really efficient job of inspection can be done, and when the consumer himself (or shall I say herself) shows a strong disinclination to select safer food products which require time and labor in bringing them to the table.

The opportunity for modern mankind to poison himself does not begin with food and end with war. It covers a wide variety of possibilities encompassing practically all circumstances in which modern man comes in contact, from the cradle to the grave, in his technical environment.

The modern world is full of accident
and technical hazards

As the individual grows older and becomes ambulatory, his neural system runs the risk of new conflicts with our culture. Although the death rate of children in the first decade of life has

been greatly lowered, this lowering has been due to a reduction in the mortality from disease, not because of more satisfactory safeguards against accidents. One might suppose that the children of well-educated, solicitous, and careful parents would have a lower death rate than the children of parents with little or no education, but what little information we have on this subject (and it is old) does not bear out that common assumption (Lennox, 1924). There is, of course, a higher death rate in slum areas, but many factors other than the lack of protection of children are involved in such communities. There can be little doubt but that the pattern of development of the nervous system (the insatiable and direct curiosity and lack of care and foresight as well as of understanding, all directly related to the manner in which the human neural system develops ontogenetically) is responsible for the high death rate from accidents.

Infection

The period about 10 years of age is one at which neurological infections are especially likely to occur. At that time the individual has attained, in most modern cultures, full adult mobility but only partial immunity. It is, moreover, an age at which intracranial neoplasms, which may have been present from birth, now begin to become manifest. The brain reaches its maximum volume about the tenth year of life, but the cranium does not acquire its fullest size with the end of the second decade at which time the brain occupies about two-thirds of the endocranial volume. There is therefore a critical period of maximum endocranial filling at about the end of the first decade.

Behavioral disorders

With the advent of adolescence, psychiatric disorders become distressingly more frequent and, for those who see in such conditions overt manifestations of biochemical disturbances, the metabolic shifts attendant upon a changing hormonal situation are conceived to provide the basis for this rise in incidence. While it is probable that the origin of severe psychiatric disturbances begins long before adolescence, it does seem to be true that in many endocrine disorders, such as myxedema, which begin with birth the more serious aspects of intellectual deficit are cumulative.

Thus, the myxedematous child who has not received thyroid medication prior to the second decade of life usually has a permanently damaged neural system.

The witlessness of childhood passes into the riskiness of adolescence

It takes the human being a long while to develop a sense of caution and to achieve a respect and understanding for, and of, destructive machinery. The primary killer of the first decade of our race continues as the principal cause of death throughout the second decade. If childhood is the age of simple curiosity and exploration, adolescence is the period of experiment and manipulation. It is at this latter age that the neural system is exposed to a new and serious though still fortunately minor peril—habituation to drugs. All such habituations (whether heroin addiction, alcoholism, barbiturates, or phenanthrene habituation—the smoking or coffee habits) are all essentially neural habituations, and the only real difference between the coffee drinker and morphine addict lies in the urgency and nature of his dependency, both dependencies being dictated through and by the nervous system.

With the development of adulthood and the acquisition of full muscular power certain inadequacies of our evolutionary state become apparent

Sensory acuity has already begun to fail before the individual has gone far into the third decade, and there is a marked degree of deterioration in the condition of the teeth which, if it were not offset by cultural skill, would soon exert a marked limiting influence upon many individuals.

Sensory deterioration, though perceptible, is not yet incapacitating, but the active physical life of the second and third decade soon discloses that man's assumption of the upright posture has been achieved at the risk of an essentially unstable vertebral column. In quadrupedal infraprimate species the vertebral column forms a rather simple horizontal arch of the classical type in which the highest point is in the center and the central vertebrae behave much like keystones. In the lower primates such as the fossil lemur, *Notharctus,* or recent baboon the vertebral column has

not become organized in such a way as to introduce any appreciable risk into its stability. In man, however, the situation is greatly altered, and a double or sigmoid curvature has replaced the original arch. Where this curvature is free, as in the cervical and lumbar regions, anteroposterior displacements in the elements of the column are not uncommon, with the result that the contained spinal cord and nerves may be damaged. Sudden compressive forces, such as may occur in directional change in high speed travel, greatly increase the probability of such structural failures. It may be asked why this feature of human structure should be a greater hazard at the present time than it was in an equestrian society. There is no doubt that ruptured or herniated nucleus polposus, as this condition is called, was a common cause of trouble for our carriage-riding predecessors, but a torso well-splinted by abdominal and back muscles properly developed by horseback riding is not particularly vulnerable to this disability. We are not, however, making comparisons here between the twentieth and nineteenth centuries but between the quadrupedal, semiquadrupedal, and erect postures. Sciatica, the name by which this condition was known to our forbears, has been a familiar feature of the literature of medicine from earliest times, and there is every indication that the unstable dynamics of our vertebral column, although long known, constitute a definite contemporary hazard to the safety of the neural system in view of the demands of high speed travel and the lack of opportunity to maintain a properly exercised axial musculature.

Radiation

While it is probable that all of the population of the future will be subjected to more or less potentially dangerous radiation, it seems likely that adults will be subjected to more intense and prolonged exposure than the young or aged. Fortunately the neural system is peculiarly resistant to the effects of radiation, and it is only by radiation during early intra-uterine life that any notable effect would be produced.

Warfare

There seems to be no particular reason to suppose that the neural system would be particularly vulnerable to bacterial or

biologic warfare. We are not well prepared from the point of view of public defense against biologic attack, but (with the exception of certain improbable parasitic infections, such as by trypanosomes or cysticerci) most populations are naturally well protected, as the result of natural, or easily acquired, immunity against infections of the neural system. The case is quite otherwise with regard to chemical warfare.

Physical disturbances

One might suppose that physical disturbances would adversely affect the neural system, and they do but not preferentially and, in the case of some agents (such as vibration caused by pneumatic drills), to a lesser extent than joint surfaces, tendon sheaths, and bony structures. Some physical disturbances, notably decompression and the thermal extremes of runaway industrial processes, may disturb the neural system extensively though in an indirect manner. Heat stroke and freezing occur only after there has been a breakdown in the heat-regulating mechanism, such as sweat-gland fatigue or failure of the metabolic processes to cope with a reduction in environmental temperature. Aviation black-out is due either to lack of oxygen or to gravitational or centrifugal force manifesting itself differentially with regard to the body and its circulating blood, and in such a way as to result in regional anemia.

Character of the nerve cell

Although the neural system is the physical substrate for many delicate perceptual and adaptive processes, it is not a fragile and precarious tissue but a tough apparatus. Nevertheless it must have the means to maintain itself by food and oxygen in a minimum condition. In respect to the need for food and oxygen, we have not advanced far in 500 million years. Our nerve cells still require to be bathed in an aqueous, nutrient, oxygen-containing medium much like their Cambrian progenitors required, and this would appear to continue as a definite limitation upon the future.

Until quite recently we were of the opinion that mature nerve cells of the central neural system could not regenerate. We knew that the distal processes of neurocytes could and did regenerate, but it seemed as though the fibers inside the spinal cord and brain were devoid of this property. Moreover, when cells situated there

were seriously damaged they seemed to be unable to recuperate and usually perished.

Such a situation now appears to be due to factors outside the nerve cell itself. Probably it is caused by the overenthusiastic activity of elements associated with the more sedately behaving nerve cells which are as frequently thwarted by the reparative activity of these associated elements as by the original traumatic situation. Anyone who is blessed with well-meaning but meddlesome relatives will appreciate the predicament of the neurocytes!

We now know that neurocytes will survive in tissue culture when removed not only from the body of embryos but even from that of adult humans. Moreover, such cells regenerate their broken processes and attempt to establish a kind of communal relationship. In my own laboratory we have found that such cells do not merely survive but are capable of being excited by electrical stimulation. Electrodes so small their tips cannot be seen under the microscope can be constructed and inserted within the cell in order to study its internal behavior! The study of the electrophysiology of single nerve cells grown outside the body has therefore become an actuality, and we have a tool with which to study the metabolism of the various elements of the nervous system *in vitro*. In this way the effect of drugs, vitamins, and other chemicals on such cells can be investigated directly. The possibility of the isolation of individual cell types is also within our grasp, and the construction of an artificial nervous system from real, living neural elements is a very definite possibility of the future.

How the nervous system breaks down

There is another way in which we can approach the problem of what the future has in store for the nervous system. Instead of attempting to identify the substances and conditions that place definite limits on its ability to function, we can try to determine what the most common types and causes of neural disintegration have in common. We have three major sources of information on this subject—mortality and morbidity statistics and autopsy findings. The figures on morbidity statistics can be profitably augmented by data on industrial hazards, absenteeism, the incidence of accidents, and the manner in which medical (and dental) services are utilized.

Necropsy statistics (fig. 5) lead us to believe that of the persons

who will presumably die this year one-third will have notable damage of the nervous system. Mortality statistics are misleading, because the actual cause of death in a case of apoplexy may be pneumonia. It is for this reason that the autopsy findings on unselected cases are more informative as to the true extent of neural damage. By far the largest number of these neural lesions are the result of failures of blood supply to the nervous system. One-quarter of all dead persons show notable damage of this nature. Of such cases one-third have had actual hemorrhages, whereas the remain-

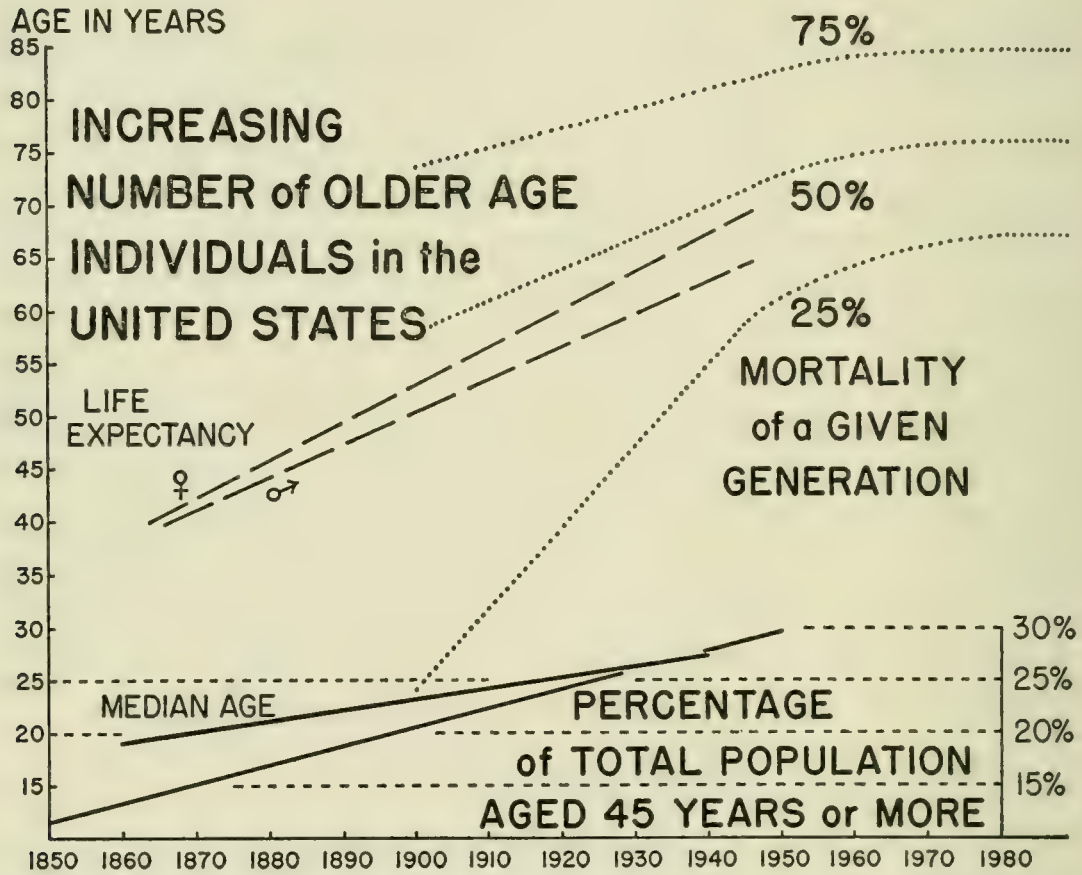

FIG. 6. Composite of three more or less independent graphs (data obtained from Joseph Zubin from Dublin, Lotka, and Spiegelman, 1949; and from Statistical Bulletin of the Metropolitan Life Insurance Co., 1949, vol. 30, no. 10, pp. 1–3; 1952, vol. 33, no. 3, pp. 1–3; 1953, vol. 34, no. 4, pp. 1–2). Lowermost line on lowermost graph shows percentage of total population aged 45 or more from 1850 through the present; median age for same period shown in upper left line in same area. Life expectancy for individuals of both sexes and born in various years shown by two dashed lines in center of graph. In upper right quadrant, three dotted lines show times at which generations born in various years from 1900 through the present exhibited a 25, 50, and 75 per cent mortality. Thus, of the generation born in 1900, 25 per cent were dead at age 25 (or 1925), and half are dead now. By 1972 three-quarters of that generation presumably will have died.

der exhibit softening and death of neural tissue as a result of inadequacy of blood flow.

Of the 33 per cent of autopsy cases with neural lesions, about 25 per cent is therefore accounted for on the above basis and the remaining 8 per cent is accounted for by approximately equal proportions (2%) of tumors, trauma, malformations, and infections of the neural system.

Six per cent of all deaths are due to accidents each year, and a large proportion of these must be considered due (in more than one sense) to neural failure or inadequate function from the point of view of natural selection.

In summary then, although trauma of the neural system is especially lethal and although a surprisingly high percentage of tumors and malformations are found in the neural system and it is rather susceptible to infection, the overwhelming cause of destruction of neural tissue is failure in blood supply.

Morbidity statistics reveal a much higher percentage of persons to be affected by neuropsychiatric disorders than are found to contain evidence of neuropathology at death. This is not due to such a simple matter as the fact that not all neuropsychiatric disorders depend on obvious organic substrate, for there are many lesions demonstrable after death that are not accompanied by obvious interference with function. This is because the nervous system, like other bodily tissues, contains a certain amount of spare material.

About 3 per cent of the population of the United States suffers from neuropsychiatric disorders which are ongoing and serious (table 9), other than deafness, blindness, and old age. Of this number of persons by far the largest proportion suffer from psychiatric or convulsive disorders.

Although advanced age is not in itself a disease, in the common sense of the word, there are few persons who have passed the age of 65 who do not exhibit a certain amount of psychomotor deterioration. At the present time about 8 per cent of the population is 65 years or older (fig. 5).

A figure of 10 per cent would therefore be a very conservative one for persons exhibiting impaired neural function. If one included persons who are deaf, mute, and/or blind, or who are suffering from some temporary neuropsychiatric impairment, an estimate of 20 per cent would not be too high for that proportion

of the population which at any moment must be considered unable to participate in the true type of activity on which survival would depend if the protective mechanisms of society were to break down. If, because of military urgency, such protective mechanisms were ineffectual for a protracted period, this entire segment of the population might very well succumb.

While the effect of morbidity due to neuropsychiatric disorder is non-adaptive behavior, it is not easy to explain what the most important cause or causes for such disorders may be, because when we speak of a psychiatric disease we really are only applying the term to non-adaptive behavior and the term must necessarily

TABLE 9

PREVALENCE OF ONGOING SERIOUS NEUROPSYCHIATRIC DISORDERS IN THE UNITED STATES

Demyelinizing diseases		
Total	8,000	5/100,000
In northern latitudes	6,000	10/100,000
Cerebral palsy (major congenital defects)	500,000	300/100,000
Born annually	11,000	
Expected mortality in infancy	1,500	
Expected life institutionalization	3,000	
Remaining in society	6,500	
Convulsive disorders (epilepsy)	750,000+	500/100,000
Serious psychiatric disorders	2,800,000	1,750/100,000

be relative. It is sometimes said that complexity in civilization "causes more mental breakdowns." This is probably not true, but it is certainly true that non-adaptive behavior has less social significance in less complex societies and that what Coon has called the paleolithic organization of social life can tolerate such behavior more easily than a highly specialized urban culture. The incidence of psychiatric morbidity rises in urban communities not because such communities contain or produce more "breakdowns" but because they extrude non-adaptive individuals more vigorously than do agricultural communities and because such individuals succumb in non-supportive environments. This is just another way of saying that culture exerts its own selective effect, and we have therefore come again upon the ubiquitous manner in which evolutionary change supplements operate. In very primitive, unorganized societies psychiatrically ill individuals soon perish. In

simple, organized societies they may not only survive but may be treated as privileged persons. In highly competitive societies they are protected but extruded if they possess no useful skill or creative ability. It is surprising to what extent society is able to absorb aberrant behavioral patterns which are not merely non-contributory but frankly aberrant, providing the individual exhibiting the pattern has something useful to offer the community.

Ordinarily an environmental situation admits of only one directional developmental tendency. There is only one "ideal." In a regulated, variable environment a number of different ideals may be tolerable and the individual traits which go towards the development of such different ideals may be mutually contradictory or even antagonistic or destructive.

A scientifically organized, mechanistic society must necessarily depend on the creative ability of its reflective minds, and these must operate in the relatively free and unhurried milieu which is itself destroyed by the very machine and increased productivity which the reflective mind creates. We all know creative engineering geniuses whose preoccupations with generalities and principles result on the one hand in constant and almost daily scientific and mechanical advances and whose preoccupations, on the other hand, also make them practically unfit to drive a simple automobile. Traits such as rapid reaction time and the ability to develop generalities, both of great value to our society, are not necessarily present in the same individual, nor does the same individual necessarily exhibit one of these traits throughout his lifetime.

In a rigid and obligatory environment individuals departing from the requirements of the environment are ultimately obliterated. In our social organization the accident-prone driver can travel in public conveyances, obtain a chauffeur, stay at home, move to an isolated community, or even obtain repeated respite from obliteration through the technical skills of the medical profession.

Not only does the manipulation of environment lead to great intraspecies variation by the preservation of variants and mutants and provision for these to procreate, but interbreeding among all the members of the species is facilitated.

For the individual who considers himself the prototype of the future and the fittest human this is a dismal prospect indeed. For

the biologist such shuffling about constitutes no real alteration in the species, because the moment such an elaborated species is brought into direct contact with a compulsive environment all the irrelevant variants are promptly eliminated.

It would appear that while man's cultural development has tended on the one hand to preserve variants that will ultimately prove to have been useless it will also have the effect of guarding the species by having protected it from the commitment of specific evolutionary specialization. Not only has average man remained unspecialized but he has, in the process of domestication, become a result as well as a manipulating factor of that process and now presents a bewildering degree of variation not merely at the structural but also at the behavioral level, to the consternation of obstetricians and delight of psychologists.

Conclusion

Attention has been drawn to the fact that there is no good evidence to support the assumption that man's neural system has undergone any progressive alteration in the direction of greater size or complexity since the middle of the Pleistocene. It was at this period that cultural development became manifest, and the hypothesis is advanced that, with the advent of culture, man achieved a degree of independence from his environment and was therefore no longer under the necessity of developing structural modifications to survive. Consideration is drawn to the fact that the culture man has created has itself become a selective factor in his development and has resulted in great variation in the species.

It is pointed out that man's nervous system has some definite structural and functional limitations and that structural evolution in the direction of a larger or more complex neural system would require the movement of the species form into a direction in which the factors of structural and physiologic safety are already very narrow. Evolution of the species, in the sense of improvement in living conditions and extended and continued manipulation of the environment, would consequently appear to have to occur at a cultural rather than structural level. The specific structural limitations placed on man's neural system appear to be those that animal forms have inherited from the earliest Paleozoic, notably

the necessity of a cell living in an aqueous medium to obtain oxygen and food.

In its broadest sense structural evolution may be regarded as a process that really gathered momentum and significance when unicellular organisms became combined into complex bodies in which the component cells assumed specialized functions. In so far as later forms are concerned, this process appears to have been extended by the cooperation of complex individuals in social systems. There is nothing novel about a comparison of the social order in which individuals are the subsidiary units to biologic bodies in which cells are the units, but, within the culture man has developed, there seems to be no clear, general recognition of the fact that a social order implies that individuals must accept the principle of specialization and cooperation and that neither the individual nor the system can achieve maximum efficiency if the subsidiary elements of the system insist that they can accomplish any and all tasks in the social order. Certainly, if there is to be any considerable evolution in which the neural system is to participate, it is quite clear that individual neural systems must draw upon the cultural reserves of the order, and this implies specialization on the part of particular individuals.

Before putting down the subject in hand, I should like to call attention to the fact that a recognition of the cooperative function of the individual involves a radical revision on the part of the individual in the concept of the "I" and "not I." A high degree of cooperative activity cannot be achieved in the presence of a strong sense of distinction between what is the concern of the individual and what is not. On the other hand a marked weakening in the ability to distinguish between the "I" and "not I" can have serious psychiatric consequences.

How does the neural system determine what is a part of the self and what is not? It is not possible to develop this consideration to any extent at this place, but it is not difficult to demonstrate that identification of the self with substance involves to a very large extent the degree of personal satisfaction the individual can obtain from such substance. Under such circumstances my glasses are much more significant to me than the last toe of my left foot. Our cultural development has progressed therefore to the point where we can easily place a higher evaluation on an item of technological

achievement than on a part of our own body. This would seem to be a rather interesting way of raising the question whether evolutionary progress may not be moving not only faster but more significantly in the area of culture than structure.

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Paleoneurologic, Neoneurologic, and Ontogenetic Aspects of Brain Phylogeny

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Frederick Tilney, *The Brain in Relation to Behavior;* March 15, 1932

C. Judson Herrick, *Brains as Instruments of Biological Values;* April 6, 1933

D. M. S. Watson, *The Story of Fossil Brains from Fish to Man;* April 24, 1934

C. U. Ariens Kappers, *Structural Principles in the Nervous System; The Development of the Forebrain in Animals and Prehistoric Human Races;* April 25, 1935

Samuel T. Orton, *The Language Area of the Human Brain and Some of its Disorders;* May 15, 1936

R. W. Gerard, *Dynamic Neural Patterns;* April 15, 1937

Franz Weidenreich, *The Phylogenetic Development of the Hominid Brain and its Connection with the Transformation of the Skull;* May 5, 1938

G. Kingsley Noble, *The Neural Basis of Social Behavior of Vertebrates;* May 11, 1939

John F. Fulton, *A Functional Approach to the Evolution of the Primate Brain;* May 2, 1940

Frank A. Beach, *Central Nervous Mechanisms Involved in the Reproductive Behavior of Vertebrates;* May 8, 1941

George Pinkley, *A History of the Human Brain;* May 14, 1942

James W. Papez, *Ancient Landmarks of the Human Brain and Their Origin;* May 27, 1943

James Howard McGregor, *The Brain of Primates;* May 11, 1944

K. S. Lashley, *Neural Correlates of Intellect;* April 30, 1945

Warren S. McCulloch, *Finality and Form in Nervous Activity;* May 2, 1946

S. R. Detwiler, *Structure-Function Correlations in the Developing Nervous System as Studied by Experimental Methods;* May 8, 1947

Tilly Edinger, *The Evolution of the Brain;* May 20, 1948

Donald O. Hebb, *Evolution of Thought and Emotion;* April 20, 1949

Ward Campbell Halstead, *Brain and Intelligence;* April 26, 1950

Harry F. Harlow, *The Brain and Learned Behavior;* May 10, 1951

Clinton N. Woolsey, *Sensory and Motor Systems of the Cerebral Cortex;* May 7, 1952

Alfred S. Romer, *Brain Evolution in the Light of Vertebrate History;* May 21, 1953

Horace W. Magoun, *Regulatory Functions of the Brain Stem;* May, 1954

Fred A. Mettler, *Culture and the Structural Evolution of the Neural System;* April 21, 1955

Pinckney J. Harman, *Paleoneurologic, Neoneurologic, and Ontogenetic Aspects of Brain Phylogeny;* April 26, 1956

PALEONEUROLOGIC, NEONEUROLOGIC, AND ONTOGENETIC ASPECTS OF BRAIN PHYLOGENY

It is an honor to have been invited to deliver a James Arthur Lecture on the Evolution of the Human Brain. Our discussion is the twenty-fifth in an annual uninterrupted series which began in 1932, so that it may be of interest to refer at the outset to the topics discussed in previous lectures, in an attempt to distill some of the spirit of the series.

One finds, of course, that the phrase "evolution of the human brain" has been afforded a rather wide interpretation. The majority of the previous speakers seem to have followed the lead of the inaugural lecturer, the late Professor Tilney, and have discussed behavioral aspects of brain structure and function. Several speakers were neurophysiologists and dealt with recent findings (often their own) on the way the brain carries out its manifold operations. A third group discussed one or another of the three different ways of looking at brain evolution, which receive consideration in this presentation, namely, the study of brain history as revealed by a consideration of fossil brains (paleoneurology); of comparative anatomy of contemporary brains (neoneurology); and of the embryological development of the brain (ontogeny).

Both comparative anatomy and embryology have long been regarded as evolutionary sciences, in the sense and to the extent that both give us information about the ancestry of the animals studied. In comparative neurology we often arrange the brains of animals in what we call a phylogenetic

series. It is common to hear, read, or utter such phrases as "the brain from amphioxus to man," or "up from the ape," or "from fish to philosopher." Certain of the smaller modern primates are commonly referred to as "prosimians," with the implication, at least, that the predecessors of the monkeys resembled the lemuroids of today, and that when we study the brain of the bush baby or the potto, it is tantamount to studying an ancestor of the rhesus monkey or the Hamadryas baboon. Embryology, in accordance with the well-known if now somewhat repudiated law of biogenesis, is certainly an evolutionary science if "Ontogeny recapitulates phylogeny." If such were the case, man in his embryological development would pass through stages which would accurately recall his evolutionary history.

But the law of biogenesis is in sufficiently bad repute nowadays that, out of consideration for our embryological colleagues, it is only fair to state that the dictum as originally expressed by Haeckel (1847) has been considerably modified by the embryologists of our time. It seems also fair to say that the general idea of recapitulation still has a powerful effect in the directing and interpreting of embryological as well as evolutionary studies. As with many generalizations, the reception accorded the biogenetic principle has been colored by the emotions and attitudes of the times. When originally propounded, biologists were sufficiently eager to embrace it that many did so rather uncritically. Later, when the fire of controversy surrounding the evolutionary concept had moderated somewhat, a reëvaluation was in order, and the weight of opinion against its obvious defects threatened to destory the usefulness of the "law" altogether. At the present time it seems that a middle ground has been approached,[1] and it is rather generally recognized

[1] A good discussion of the current status of biogenesis is by Hobart M. Smith (1956).

that, although ontogeny does not recapitulate phylogeny, *sensu stricto*, there is nonetheless likely to be a connection between certain phylogenetic events and certain of the ontogenetic events that have been preserved for posterity in embryology. In such cases, embryology provides phylogenetic insight of crucial significance and is indeed evolution reënacted.

If comparative neurology and embryology could tell us what the facts of evolution really are, it should be possible to give a fairly satisfactory account of the evolution of the human brain; or, for that matter, of many animal brains representative of the major classes and orders of the vertebrates. But, just as embryologists have come to realize the limitation of biogenesis, so also have biologists come to appreciate that modern animal types do not form a phylogenetic series. Rather, these represent the end products of evolutionary processes which may have been proceeding along independent lines for, in some instances, millions of years. According to current concepts, the various orders of placental mammals have had a separate evolutionary history for as long as 70 million years. To regard the series rat, cat, monkey, and man as phylogenetic is warranted only if rat, cat, and monkey stages can actually be verified among human ancestral types. The demonstration of such ancestral types depends ultimately on the science of paleontology and cannot be separated from it. In like manner, the sequence from embryo to fetus to newborn to adult is not *per se* a phylogenetic sequence, regardless of how many ontogenetic facts there may be which relate to phylogeny. The important point is that we cannot tacitly assume this relationship. We can only inquire whether a particular ontogenetic change has any phylogenetic counterpart or not. Embryology is an evolutionary science only to the extent that known embryological stages have been compared with the facts of phylog-

eny as revealed in the fossil record. In like manner, comparative anatomy is an evolutionary science only after it has been integrated into the science of paleontology.

The data of comparative neurology, then, and of neuroembryology provide only indirect evidence concerning evolution. In such circumstances, we can hardly discuss the evolution of the human brain in any rigorous sense and not refer to the direct evidence of paleoneurology—that segment of science that rests on the solid rock of fossil remains.

Fossil Brains

Of course, the brain, like other soft parts, does not really fossilize. Nonetheless, there exists during life such an intimate relationship between the exterior of the brain and the interior of the skull, that the latter may be molded to the brain's image. If an ancient skull came to rest in a muddy stratum, which subsequently hardened into rock, the rocky interior of the cranium may form a natural cast, with similar contours and surface markings to those of the brain. Such a natural cast can be exposed by the chipping away of the cranial bones, and is one form of fossil brain. Artificial endocasts may also be made after removal of the cranial contents, with the use of a variety of molding materials. In either case, the study of endocranial casts provides the basic data for the paleontology of the brain, although, in addition, considerable information about the size of the brain may be obtained from a study of the skull itself, and inferences about habits or behavior may often be drawn from a study of other portions of the skeletal remains.

Fossil brains were first described by Cuvier in 1804[1] and

[1] The author is indebted to Dr. Tilly Edinger (1956) for this reference which was discovered by her and had not been previously published.

received sporadic attention during the nineteenth century. It has been only in the present century, however, that paleoneurology has come into its own as a productive and appreciated branch of science. Even at the present time many workers in the field of neurology seem largely unaware of the contributions that paleoneurology offers. There does appear to exist, however, an increasing awareness on the part of the general public of the promise of paleontology in general and paleoneurology in particular—related, no doubt, to educational programs such as those carried out in the American Museum, as well as to the publicity afforded by the press to recent fossil finds.

The longest rigorously documented ancestry among mammals is that of the horse, and, thanks to Dr. Tilly Edinger, the brain of this animal is also better understood from the standpoint of its history than is any other form. The usefulness of generalizations concerning the evolution of the brain derived from comparative anatomy and embryology can actually be tested because of the many years of patient study by Edinger, which is summarized in her monograph on the evolution of the horse brain (1948). Edinger has, in fact, provided us with a model for the study of brain phylogeny by demonstrating that once paleoneurological data are available, one can speak with authority about evolution and at the same time test the working hypotheses inherent in the facts of comparative anatomy and embryology. Edinger found that certain evolutionary trends indicated by the study of modern forms are, in fact, substantiated by paleontology; other trends, however, are only partially verified and require modification. A rather significant number of observations revealed by the study of fossils would not have been expected from the study of contemporary animals.

Edinger's work is significant, not only because it has contributed new facts, but also because it has done so much to

provide a place for paleoneurology. A tendency to be superficial about phylogeny had grown up in comparative anatomy, and her studies have required us to be more realistic. Neoneurology and neuroembryology have much to contribute to evolutionary science, if we retain our critical faculties while constructing our hypotheses and synthesize our findings with those of the paleontologist. In fact, both neoneurology and embryology have actually been strengthened by paleontology, in that the broad generalizations derived from the study of modern forms have been largely validated by reference to fossil remains arranged in historical sequence.

Let us see, then, what the bold outlines of the evolution of the human brain appear to be.

The Phylogenetic Record[1]

Until rather recently, the fossil record of the primate order was very fragmentary. The resurgence of interest in primate paleoneurology, however, as well as several recent rich strikes of fossils, now permits the following tentative sketch of man's history.

Precursors of the primates are thought to have been small, arboreal, shrew-like creatures which gave rise to the primitive tarsiers and lemurs of the Eocene. The lemurs rapidly became a specialized and separate group and persist today as lemurs. According to one view, the many tarsiers of that period evolved, independently of the lemurs, from the shrew-like precursors of the primates. In the opinion of these specialists, however, the tarsiers are derived directly from lemurs before specializations had appreciably modi-

[1] In this outline, I have drawn freely from the works of Sir Wilfred E. Le Gros Clark, an anatomist who has become sufficiently at home in paleontology to be generally recognized as the international authority on the history of the primates.

fied their generalized structure. In any case they progressed to forms that foreshadowed the monkeys during the 25 million years of this period. The succeeding period, the Oligocene, witnessed the appearance of the true monkeys which branched out throughout the world, but the descendants of which are likewise simian rather than anything else. It appears, then, that the monkeys, as the lemurs, became an offshoot and that they have thrived away from the main line.

The earliest apes also appeared in the Oligocene and can be found in each succeeding period. They are believed to have taken two separate lines: one, the now familiar sideline that leads to the highly specialized apes of today; and the other, the more conservative generalized line from which human precursors are derived. At some period between the Miocene and the Pleistocene (perhaps in the intervening Pliocene), the human stock is believed to have started its own specializations—brain, skull, and upright posture. Current opinion favors the possibility that Miocene apes gave rise to Pliocene intermediates that resemble, perhaps, *Australopithecus* which, in turn, developed into the Java and Peking hominids of the Pleistocene. These forms were eventually transformed into types similar to modern man. An interesting point about this sequence is that at almost every step of the way (except for the final stages) the brain has progressed less rapidly than the body.[1] There have been apes with monkey brains, and *Australopithecus* had remarkably human general skeletal characteristics but an ape-like brain. One can single out, from the general fossil records, tarsier-, monkey-, and ape-like brains in what appears to be the line of human development and

[1] The final steps of human evolution took place in a relatively short time, geologically speaking, during which the brain expanded at a more rapid rate than it had in its previous history.

thus provide some solace to the comparative neurologists who have been seeking to unravel the secrets of primate evolution over the years by a scrutiny of "graded series" of contemporary brains.

The Ontogenetic Record

We may continue with human embryology. Here we will have recourse mainly to the studies of the Minnesota school of anatomists which provide us with a good general picture of the ontogeny of the human brain. Most of this material was collected under the leadership of the late Professor Scammon (1933) and has been well summarized in the studies of Dunn (1921) and of Grenell and Scammon (1943).

A number of interesting facts have emerged from this work which seem pertinent to our present discussion. As is well known, the brain parts do not develop with equal speed. The older portions (as we are accustomed to think of them from both paleontology and comparative anatomy) are relatively larger in the beginning and become superseded (in size, at least) as ontogeny proceeds. Thus, the hind brain and midbrain represent a preponderant bulk of the encephalon in early development, only to be overshadowed by the forebrain later. Likewise within the forebrain itself, the older parts, such as the "rhinencephalon," are not only relatively, but apparently in certain instances also absolutely, smaller in the adult than in the embryo and fetus. The emergence of the forebrain and its newer parts is not the only striking feature of human neuroembryology. It is matched, and to a certain extent surpassed, by the evolution of the cerebellum as well. The cerebellum not only becomes dominant in later fetal life, but in point of fact en-

joys its greatest period of relative growth during the last stages of the fetal-newborn period which in the human actually represents a terminal developmental phase, for the fundamental brain plan in the human is well established by the end of the first year of postnatal life.

If phylogeny is recapitulated in ontogeny, one should expect that the fossil record would show a relatively great development of both forebrain and cerebellum. However, the forebrain should slacken in development at the end, and the cerebellar increase would persevere to provide the finishing influence in the production of the brain of modern man. It is important to note that so much attention has been paid to the forebrain in general, and to the neopallium in particular, that the late relative emergence of the cerebellum, which is one of the most conspicuous volumetric events in ontogeny and has been clearly described both by Dunn and by Grenell and Scammon, seems very little appreciated. On this basis, the cerebellum appears to merit as much attention and study in the human evolutionary scheme as the forebrain itself. Interestingly enough, the late emergence of the cerebellum as a predominant structure in mammalian and primate evolution receives considerable support from both comparative anatomy and paleontology. If one takes particular note of the expansion of the lateral parts of the corpus cerebelli in primates, it is evident that, particularly in anthropoid apes and man, the so-called hemispheres reach their greatest size and complexity. As the scale is ascended, this lateral expansion develops concurrently with, and probably under the influence of, newly developed incoming pathways to the cerebellum, such as the cortico-ponto-cerebellar connections.

Paleoneurology tells a similar story. Brains of the prehuman predecessors, so far as these can be identified, are less well developed in both forebrain and cerebellum than

are those of modern man. Unfortunately, however, the final stages are not clear. When more fossil material is available and when this particular point is subjected to inquiry, we may expect an answer to the question raised by the ontogenetic data, i.e., Did the forebrain as a whole retain its pre-

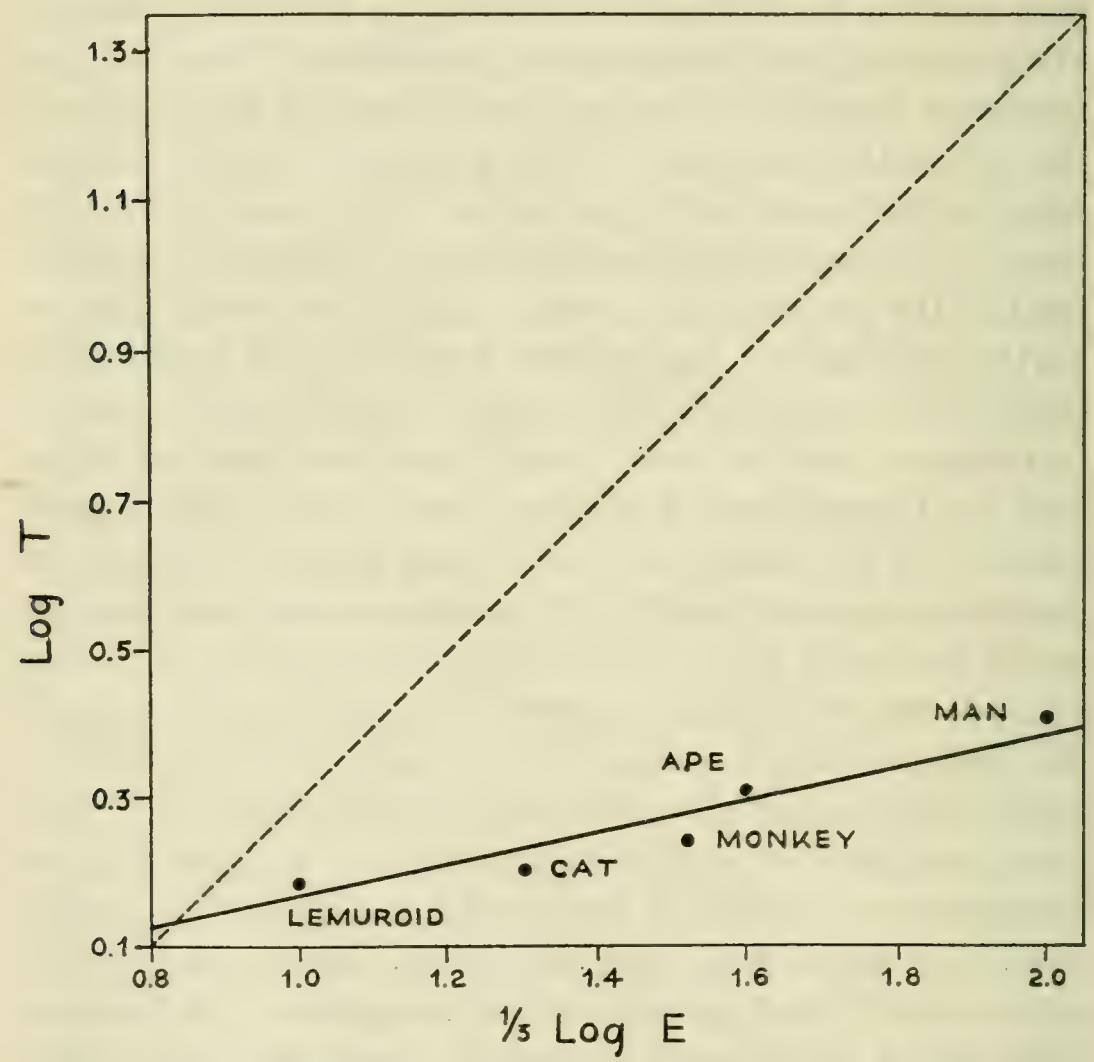

FIG. 1. Double logarithmic plot showing the relationship between increase in thickness of the isocortex to the increase in size of the brain. Logarithms are employed in order that relative change can be emphasized. The logarithm of thickness (log T) is plotted against a comparable dimension of the brain; i.e., one-third of the logarithm of the brain weight (1/3 log E). It will be seen that the rate of increase of isocortical thickness, although steady from lemuroid to man, is relatively slight, falling well below the slope of the dotted line which indicates value-to-value expansion. (From original in Harman, 1947a, p. 163, fig. 1.)

ponderating tendencies throughout evolution, or did it yield this vaunted privilege to a "downstream" structure, the cerebellum, during the terminal period when the brain of *Homo* finally became indistinguishable from that of *Homo sapiens?*

The emergence of the forebrain and cerebellum in embryology is associated with a marked furrowing or fissuration of the outer surface of these structures. Although many parts of the brain are increasing during this period, such fissuration is a familiar developmental phenomenon in only some of them. Those brain parts that exhibit increased fissuration, however, do so not only during embryological development, but also in the phylogenetic series of both the comparative anatomist and the paleontologist. The significance of fissuration appears to depend on the structural plan of the brain parts in question; that is to say, fissuration occurs in an enlarging brain part when increase in volume is accomplished without significant increase in thickness. The phenomenon is consequently especially characteristic of brain parts which form the surface or cortex, although certain interior structures (e.g., dentate nucleus and inferior olive) also exhibit the same phenomenon. Data documenting this explanation of fissuration have been supplied from comparative neurological studies, as illustrated in figures 1, 2, and 3.

Why should the cortex increase more in its surface than in its thickness? Apparently, the thickness of the cortex is a rather constant dimension, just as cell size is a rather constant dimension. Once a certain degree of maturity is attained, the brain enlarges by multiplication of cells or by expansion of intercellular space, rather than by increase of the individual elements. Further, the cerebral and cerebellar cortices achieve a relatively stable vertical structure early in development before much fissuration has occurred. In-

creases in the cortex thereafter are accomplished largely by lateral expansion, rather than by enlargements in depth. This means that the cortical, or fissurating, parts of the brain expand by means of an increase in the number of vertical units and/or by a sidewise swelling of such units. One would expect, then, that increase in brain size would be correlated, especially in later development, with increased fissuration. Such is actually the case with the cortex as judged by paleoneurologic, neoneurologic, and ontogenetic criteria.

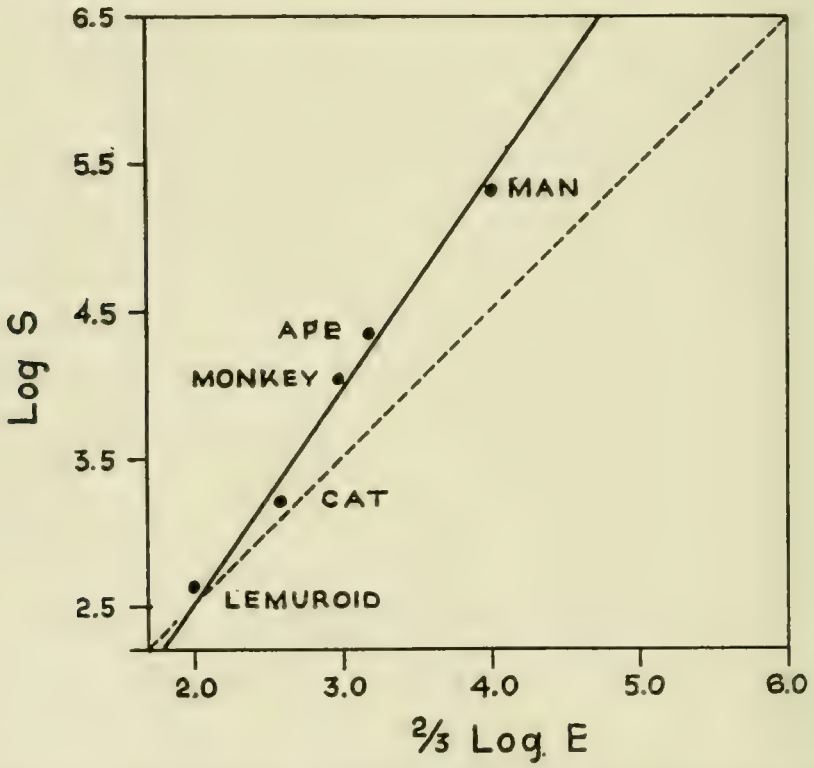

FIG. 2. Double logarithmic plot showing the relationship between increase in surface of the isocortex to the increase in surface of the brain. The logarithm of isocortical surface is plotted against two-thirds of the logarithm of brain weight. It will be seen that the rate of increase of isocortical surface is relatively great as compared to the corresponding dimension of the brain. (From original in Harman, 1947a, p. 164, fig. 2.)

The phenomenon of fissuration is relevant to the present discussion, not only because it is a striking feature of development, but also because, if our interpretation of the

phenomenon is correct, we should be able to draw some inferences concerning what occurs within the fossil brain. If thickness of a cortical sheet is such a constant dimension in a fissurating cortex, then the degree of fissuration, the surface area, and the over-all size of the brain (all of which may be judged from endocasts) may provide enough data to allow a guess at cortical volume. If such is the case, a new dimension could be added to paleoneurology, a science that hitherto by its very nature has been largely a study of the brain surface.

So much for the folding of the neopallium. What of its phylogenetic growth and of the growth of other parts of the brain? Tentative answers to questions pertaining to phylo-

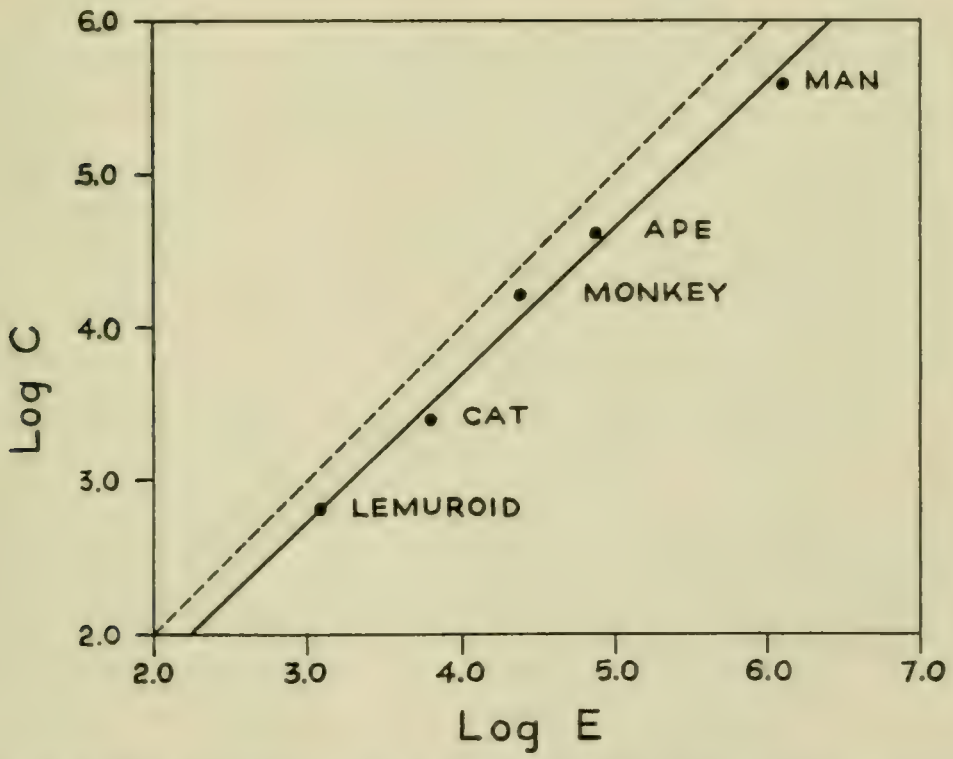

FIG. 3. Double logarithmic plot showing the relationship between increase in isocortical volume and increase in brain volume. The dotted line has been drawn at an angle of 45 degrees from the horizontal in order that the slope of log C to log E may be interpreted. It will be seen that the relative increase in isocortical volume matches the relative increase in the over-all size of the brain. (From original in Harman, 1947a, p. 165, fig. 3.)

genetic growth can be provided by comparative anatomy and seem to us to be best supplied by quantitative studies. We wish to place special emphasis on the importance of measurement to comparative neurology, because in the past all too many generalizations have been put forth in this area without recourse to data. Of course, many parts of the brain of many animals have never been subjected to quantitative analysis, but such data as are available appear to indicate certain trends which, in turn, may ultimately be correlated with fossil findings.

Neoneurologic Data on the Growth of the Brain

In figures 4, 5, and 6 are graphed some data reported by the present author some 10 years ago, which allow us to compare the "phylogenetic growth" of the neocortex as judged by comparative anatomy with the growth of the brain itself. One striking feature emerges from these data, i.e., within orders of mammals, the increase in size of the neopallium is a remarkably constant phenomenon, the neocortical volume tending towards a constant percentage of the total brain volume in both Carnivora and primates (figs. 4 and 5). A phylogenetic increase or hierarchy on a percentage basis is evident only if separate orders are compared, as is done in figure 6. For example, percentages for the Rodentia are approximately 30 per cent; for the Carnivora, between 40 per cent and 46 per cent; and for the primates, from 46 per cent to 58 per cent. It seems to me that these data are consistent with the paleontological fact that various orders have been separate for a long time, that years ago the brain plan within groups was roughed out, and that subsequent evolution took place without destroying the fundamental pattern. The same situ-

ation, indicated in these studies, which presents the interrelationships of brain parts as an orderly unfolding within groups, has also been found in our studies of the basal ganglia (Harman and Carpenter, 1950), and receives further support from the work of von Bonin (1948). The latter author has demonstrated that if the surface of the frontal lobe (a structure that is highly regarded for its preëminence in man)

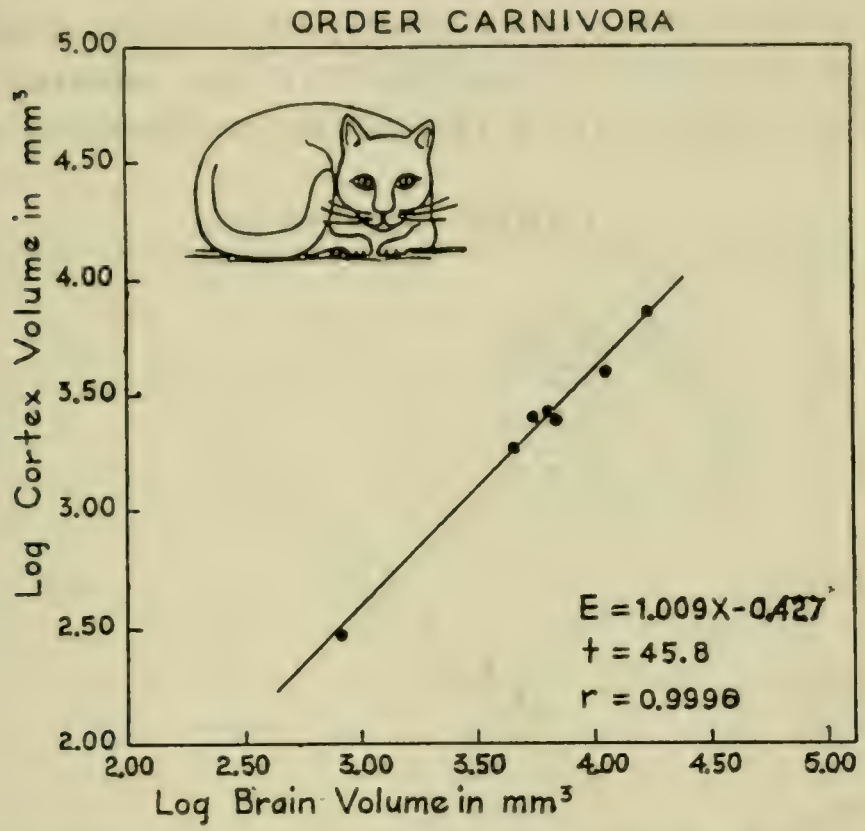

FIG. 4. Double logarithmic plot showing the relationship between isocortical volume and brain volume in Carnivora. It will be seen that the relationship is rectilinear and that the slope of the line approaches 45 degrees, indicating great internal consistency of brain parts within the carnivores. (Data from Harman, 1947b.)

is compared to the surface of the total cortex in a double logarithmic plot, a markedly rectilinear relationship exists from marmoset and lemur through monkeys and apes to man. However, in contrast to the neocortical-brain relationship, where percentages tend to remain the same within

orders, there was a steady increase in the ratio (from 0.09 to 0.33) in favor of frontal cortex from marmoset to man. Thus, although the situation in frontal cortex and in neocortex as a whole may appear at first glance to be comparable, as the graphs are rectilinear, a basic difference exists in the slope of the lines. In both cases the rate of change appears to be governed by law, but the results are not the same. Man's isocortex is, by per cent, not remarkably different from that of other primates, but his frontal lobe is, although an analysis of how this may have occurred indicates that it was the result of a continuous change or trend

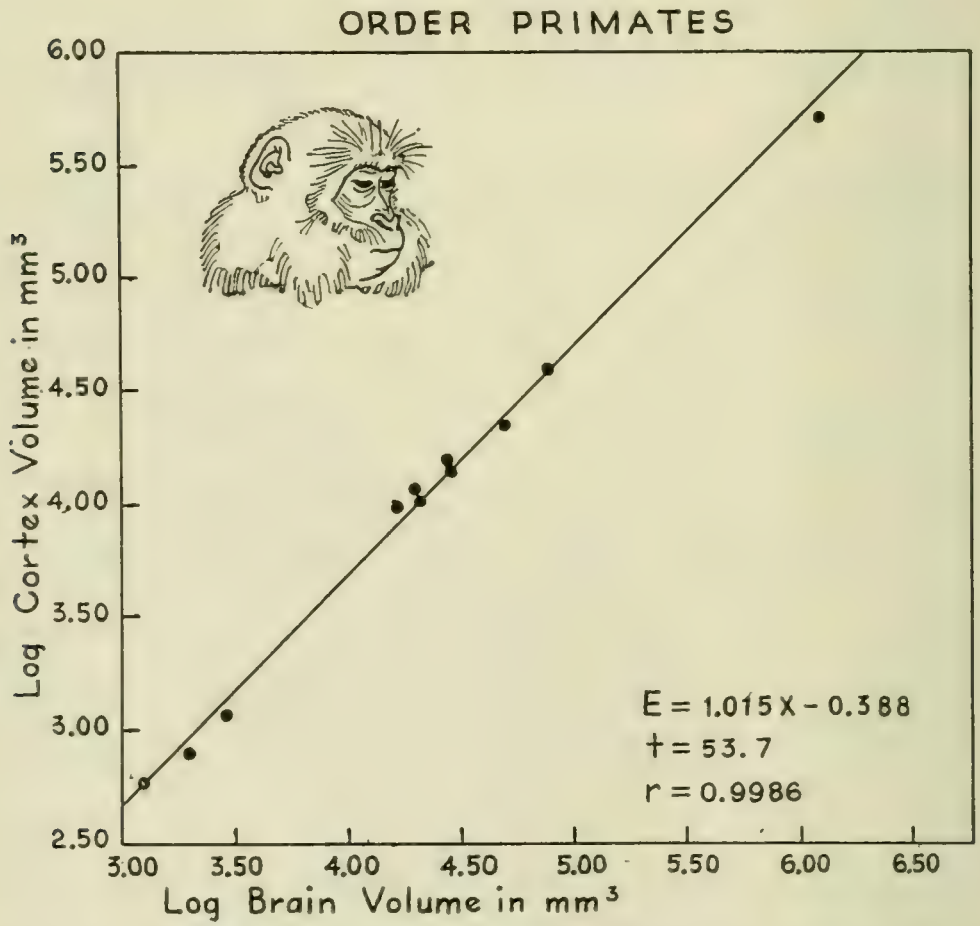

FIG. 5. Double logarithmic plot showing the relationship between isocortical volume and brain volume in primates. The similarity between this graph and that of figure 4 is evident. Apparently the isocortical-brain relationship within primates shows the same consistency as does this relationship within carnivores. (Data from Harman; 1947b.)

throughout the primate stock. Percentage-wise, then, Brodmann (1912) may have been justified in pointing to the "overwhelming development of the frontal lobe" in man, as also may von Bonin when he came to the seemingly contrary opinion that Brodmann's charts illustrated "a very simple case of relative growth, and that man has precisely the frontal lobe he deserved, by virtue of the overall size of his brain."

Further contributions to a quantitative analysis of relative brain growth have been made by the extensive measurements on brain parts of different mammals carried out by Riley (1928) some years ago. He dealt entirely with ratios or coefficients, and restricted his attention to the midbrain, hind brain, and cerebellum. His method was to compare the cross-sectional area of a brain tract or group of nerve cells to the cross-sectional area of the region of the brain in which it was found, as has been done with the spinal cord by several authors who have compared relative areas occupied by the gray and the white matter at various levels. In all, Riley compiled coefficients for some 14 components and arrived at some suggestive conclusions. The increase in the new parts of the midbrain and hind brain and cerebellum is apparent if primates are arranged in the conventional series. The importance that many of the structures that exhibit relative growth have in the organization of motor behavior is quite evident; the pyramid, the ponto-olivocerebellar system, the neocerebellar nuclei, their outflow and midbrain connections, all reach their highest ratios in the human brain. Older structures, such as reflex centers in the midbrain for hearing and vision, and the older centers of the hind brain dealing with those primitive spatial orientations present throughout vertebrates, decrease throughout and are lowest in the human brain. The centers in the hind brain that serve to relay sensory information to higher cen-

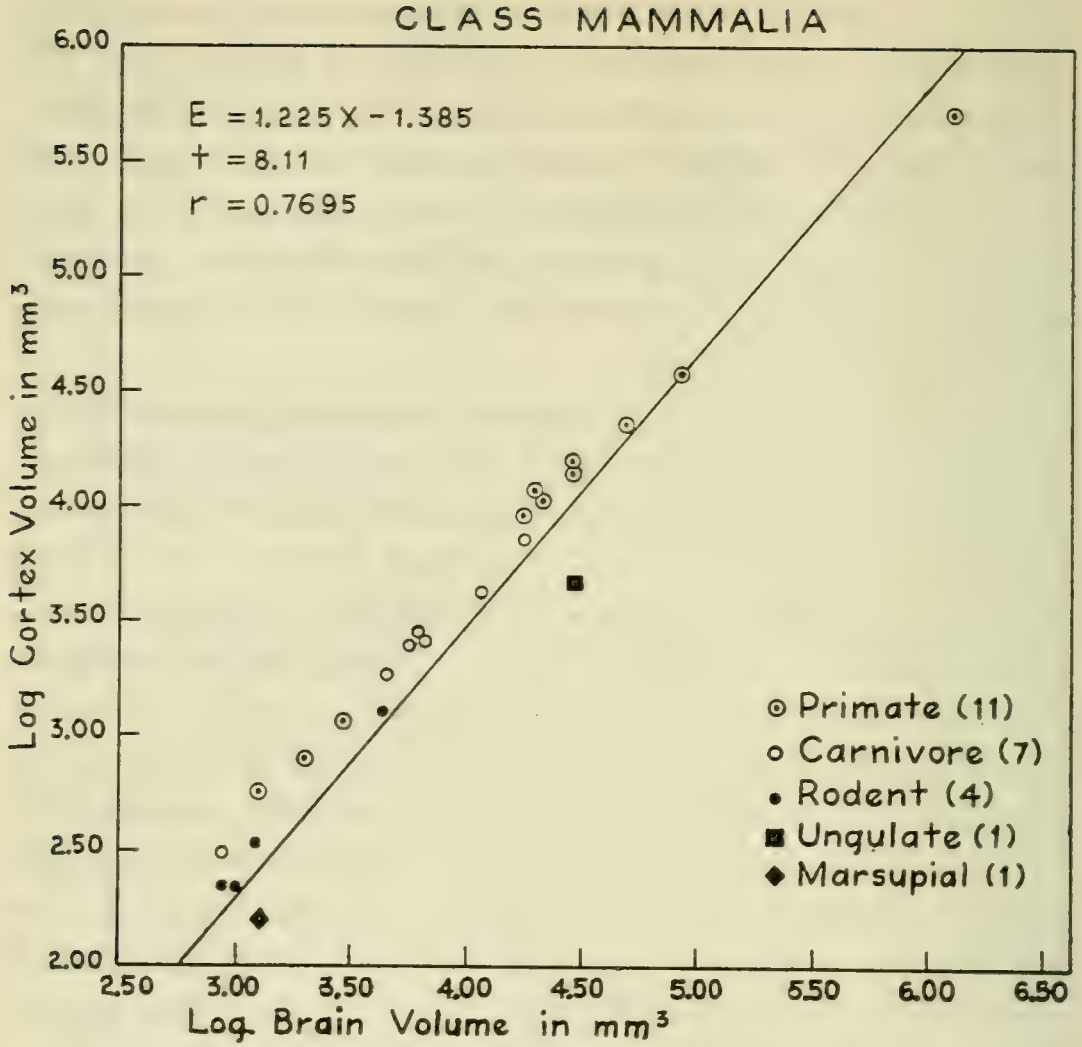

FIG. 6. Double logarithmic plot showing the relationship between isocortical volume and brain volume in different mammals. Although there is a general trend towards an increase of both cortex and brain throughout the mammalian class, if brain increase is used as the basis for comparison, considerable differences exist in amounts of isocortex between animals of different orders. Thus, in the lower left-hand corner a marsupial, a rodent, and a primate of the same brain size have markedly different cortical volumes. Throughout the plot, wherever points have the same position on the X axis, it will be noted that the values on the Y axis always favor the primate. (Data from Harman, 1947b.)

ters from the extremities are of interest. The relay centers for the lower extremities are relatively constant, whereas those for the upper extremities show a steady increase and, again, reach the highest value in the human brain. The fact that man became an armed hunter, tool maker, and fire

maker early in history finds its correlation in the phylogenetic measurements compiled by Riley.

To date, no correlations have been advanced that differentiate highly civilized man from more primitive races. Comparative anatomy and embryology have been able to account to a certain extent for differences between man and other primates but not among members of the human species. We are forced to the realization that the methods are probably of value only in the broad sense. So long as we remain in this wide realm and do not overtax our methods or stretch our data, quantitative studies on the growth of the brain may be expected to yield data of importance, if only to the question of evolution in reference to the origin of species.

A Look Ahead

Our previous discussion has presented data on the growth of the human brain drawn from embryology, comparative anatomy, and paleontology. As more paleontological information becomes available, we should be better able to single out the forms of modern animals that most closely simulate stages of evolution and to assess more accurately what steps in ontogeny recapitulate phylogeny. Yet it now seems evident that all these studies must of necessity be carried out at relatively coarse levels of observation and therefore will be able to give hardly more than a generalized account of what has occurred. In spite of this fact, it also seems likely that anatomists and paleontologists will persevere until the picture of man's development (rough though it may be) has been completed. We might conclude here, but we will not because we are tempted to look ahead a bit and inquire how the general picture obtainable by the above methods of study can be supplemented by other and new techniques.

During ontogeny and also phylogeny (as judged by comparative anatomy) a number of characteristic changes occur in the cells and tissues of the brain. Chief among these are blood supply, cell form, and that intriguing phenomenon called myelination. Judged both by ontogenetic and phylogenetic criteria, a general plan of increasing differentiation and complexity has been found in the way in which the blood vessels establish themselves with respect to the central nervous system. The phylogenetic and ontogenetic growth and modification of nerve cells and the cell bodies and processes also follow a general plan of increasing complexity. The formation of myelin, a lipoprotein complex laid down on the surface of the nerve fiber and having important interrelationships with it, appears to be related not only to the taxonomic position of the animal, but also to the stage of embryological development and the phylogenetic antiquity of the fiber in question. For reasons such as these, the microscopic structure of neural tissues may acquire phylogenetic significance, and, if such is the case, exciting times are ahead. The vision of the microscope as we have known it for most of the present century has now been significantly extended by the development of electron microscopy. We can only guess at what correlations will emerge when comparative cytology has had the use of this new, powerful tool for a few more years. Certainly this vista is an intriguing one, because the electron microscope can do much to bridge the gap between the level of microscopic observation and the molecular level and thus allow for elucidation, in a very fundamental sense, of those differences and similarities that have resulted from the formation of new species and that have been responsible for them.

The Molecular Level

A science that deals with the biochemical growth of organisms and of organ systems, including the nervous system, has now reached the stage at which symposia are beginning to appear. Had I been more courageous, I might have discussed the biochemistry of the developing nervous system in the present lecture. In spite of this lack of temerity, I am encouraged to point out that just as we are on the threshold of a science of comparative cytology at the ultramicroscopic level, so also are we now witnessing the development of this science at the molecular level, i.e., with respect to the physicochemical composition of protoplasm in animals of different species and at various stages in embryological development. The concept of brain evolution that lies ahead, then, is one that promises to deal with the very crux of the matter, and these new approaches should provide increasing insight into the basic mechanisms responsible for the production of the modern brain, that is, for the growth, differentiation, and development of the functioning nervous system within the functioning organism.

Conclusion

All the studies referred to in the present paper are cooperating towards giving us a comprehensive picture of the development of *Homo sapiens*. However, it must be evident that the human being we are attempting to recreate is something of an abstraction. As anatomists, we might be content to present the story of man's origin, which would apply to the first creature who could be classified as *Homo sapiens,* an event that may have occurred some 200,000 years ago. A

great deal of evolution seems to have occurred since, and it is a matter of considerable regret that this most important aspect of man's development (civilization and its effect on its architects) has been dealt with here so lightly. Fortunately, Mettler (1956) and Shapiro (1957) have both considered this problem with insight and skill.

What, then, can we make of the human brain at the present time? It is something of a morphological anomaly, which has attained great size and complexity in a relatively short period of time. Yet throughout history primates have always been distinguished by the size of their brains. As Le Gros Clark points out, the increased brain power of the primates has allowed for the keeping of generalized and primitive features along the main line of human descent. The retention of these primitive characteristics has allowed for great structural plasticity and facilitated adaptation. Man's torso and extremities seemed to have been prepared in advance, so that in the final stages of development the brain and the skull were the structures chiefly involved.

In the course of phylogenetic development, as judged by paleontology, comparative anatomy, and ontogeny, certain structures (the neo-, or new, parts) have become more prominent, somewhat at the expense of older structures. However, such phylogenetic changes as have been analyzed appear to follow simple laws of relative growth so far as rates are concerned and can usually be correlated, by rather elementary mathematical procedures, with the over-all size of the brain. Ontogeny and comparative neurology are in good agreement with paleoneurology so far as general principles are concerned, but there is an obvious need for more complete paleontological information before many comparisons of a quantitative nature can be attempted. A happy thought in this connection for those who still concern themselves with the physical facts of development (and one developed here)

is that the surface of the brain appears to be a very significant dimension so far as the neocortex is concerned. Because the cortex is such an important part of the brain, and because it is in respect to surface that most comparisons with fossil forms must actually be made, we await with renewed interest new fossil findings in the primate series.

It is not unreasonable to expect that man's brain will continue to study itself so long as *Homo sapiens* shall last. We must reserve to the imagination and judgment of man himself how long this shall be and what role the human brain will play in the determination of its duration.

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JAMES ARTHUR LECTURE ON
THE EVOLUTION OF THE HUMAN BRAIN
1957

EVIDENCE OF PRENATAL FUNCTION OF THE CENTRAL NERVOUS SYSTEM IN MAN

DAVENPORT HOOKER

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Davenport Hooker, *Evidence of Prenatal Function of the Central Nervous System in Man;* April 25, 1957

EVIDENCE OF PRENATAL FUNCTION OF THE CENTRAL NERVOUS SYSTEM IN MAN[1]

The first of the definitive organs of the vertebrate to separate from the germinal disc are the neural folds, which, following closure, develop into the central nervous system. In as much as the general course of embryonic development in vertebrates occurs in a head-to-tail direction (Kingsbury, 1924), the cervical portion of the neural tube begins differentiation into nervous tissue before its caudal end has been completed. As the neural tube extends caudally, the somites, from which some trunk musculature (and certain other elements) will develop, appear as subdivisions of the dorsal mesoderm, hitherto unsegmented. Other trunk musculature arises from the ventral unsegmented mesoderm.

The cardiovascular system, which begins differentiation at almost the same time as the neural tube, precedes all other organ systems in attaining initial functional capacity except, apparently, in certain sharks (Wintrebert, 1920).

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The neural tube, however, which begins its formation before any muscles have appeared, requires a relatively long period of differentiation before reaching its first capacity for function. Hence the more cervically located trunk muscles become capable of contraction on electrical or direct mechanical stimulation before motor nerves establish effective connections with them. As the motor system develops in advance of the sensory, reflex activity does not appear until still later.

Mention has been made of the general head-to-tail direction of embryonic differentiation. Recognition of this trend was criticized by Kingsbury (1924), who recognized that this "law of cephalo-caudal differentiation" was general only. Actually, from the beginning of closure of the neural folds in the neck region, the central nervous system has two directions of differentiation, one involving the spinal cord, the other the brain itself. The upper cervical region is the starting point for both directions of differentiation, the first passing caudally, the second rostrally. Hence, for the nervous system and its associated structures, it is more accurate to refer to the two as the "cervico-caudal" and the "cervico-rostral" directions of differentiation, respectively (see Hooker, 1954). The cervico-caudal direction of differentiation is the more significant in early central nervous system function during embryonic life because its development, like its function, precedes that of the cervico-rostral.

Microscopic examination of the developing nervous system is, of course, important. However, it cannot be the final arbiter of certain of the finer points in fixing the exact time at which functional levels of morphological maturation are attained. For example, excellent as are modern techniques and microscopes, they cannot establish the time when synapses between neurons become functional. For that, it is necessary to supplement microscopic examination with

functional studies. Hence a combination of morphological and physiological techniques is advantageous in any investigation of the development of the nervous system and of its functional capacity at any specific age.

It is obvious that there can be no capacity for function not permitted by the level of structural differentiation. In broad terms, structure determines the capacity for function. This is true whether one is considering the entire organism or only its parts.

It should also be obvious that the functioning of a whole organism is its behavior, at whatever age it may begin to exhibit activity. The behavior of an adult human being is exceedingly complex, but it is still "structure in action." It is no part of the present discussion to attempt an analysis of adult human behavior. Fortunately, it is not necessary. A recent book, "The evolution of human nature" (1956), by the dean of comparative neurologists, C. Judson Herrick, presents the case as only that master can do it. All that is attempted here is a presentation of some of the findings of a study of certain aspects of human fetal behavior, set into enough of its phylogenetic background to permit interpretation of the clues offered as to the functional capacity of the embryonic and fetal nervous system.

The fact that developing organisms exhibit activity, and hence behavior, has long been known. However, the exact nature and sequence of these activities, their similarities and differences throughout the vertebrate scale, and their implications as indexes of the structural development of the nervous system have been submitted to truly scientific study only within the past half century or so. Much, but by no means the entire story, is now known about embryonic and fetal activity, the so-called "overt behavior" (Hooker, 1944) of developing vertebrate forms.

It must be borne in mind that overt activity, that activity

expressed through the skeletal musculature, is only a part of the behavior of any organism. Behavior is essentially the interaction of a living organism with its internal and external environments. Both these environments are closely interrelated, so closely as to be virtually inseparable. Each may affect responses of the organism as soon as their elements have attained functional capacity. Overt behavior, produced by the nervous and muscular mechanisms of the body and taking the form of bodily movement, is the more evident kind of behavior. There is, however, a covert behavior, largely hidden and unseen, going on within the organism and affecting the nature of overt behavior. Covert behavior is largely the response of the internal organs to changes in the external or internal environments. By means of many enzymes and hormones and by the muscular activity of the internal organs themselves, any organ may affect others, including the nervous system, and hence may have a profound effect upon overt behavior. Behavior is thus an expression of the activity of the entire organism, an interaction of all its parts with its varying environments, both external and internal.

When adult organisms are dealt with, it is difficult in any situation to assess the roles played by the elements of covert behavior. If this be true in man, where introspection is possible, how much more difficult is such assessment when one is dealing with animals that cannot communicate! In both man and other forms, a variety of methods must be employed to determine the contribution of the various internal organs to the sum total of behavior.

With the young embryo, the assessment of behavioral components may be somewhat easier. In the development of an individual embryo, the primordia or *anlagen* of the various organ systems tend to appear in a characteristic sequence. As is noted above, the cardiovascular system is the first to

reach a functional level in most vertebrates. This is a system essential to the life of the organism and in older animals one highly sensitive to changes in either the external or internal environments. However, in so far as is now known (and admittedly little is known about it) the early cardiovascular system appears to have little effect, other than sustaining the living organism, on the activity of other systems that appear at about the same time. In the light of our present imperfect knowledge, other organ systems affect activity to no greater extent in the embryonic period.

Embryonic respiration is carried on by gills for a long time, if not permanently, in certain animal forms. In the mammals, it is accomplished by means of placental interchange. The early alimentary canal is digesting yolk or, in the placental mammals, engaged in differentiation, while nutritional duties are cared for by the placenta. The urinary systems begin to function early (Guthmann and May, 1930), but there is no evidence to indicate that they have an effect on overt behavior in early fetal life. Hence the embryo offers an ideal opportunity for our observing the functioning of the muscular and nervous systems, relatively unhampered by other complicating factors.

Unfortunately, it would require greater space than is here available to review the work that has been done on the overt behavior of the various classes of vertebrates. To that end, reference can only be made to an earlier publication by the present author (1952). However, it is essential to review, though all too briefly, the embryonic development of overt behavior in that amphibian for which the most complete study has been made. This is the salamander, *Amblystoma,* which was the subject of intensive study by the late George Ellett Coghill from 1906 until shortly before his death in 1941.

Coghill presented his findings in a long series of papers

between 1909 and 1936. These are rather adequately summarized in his University of London lectures, "Anatomy and the problem of behaviour" (1929a). To test reflexes, Coghill used human hairs as the tactile stimulator. He has described a series of physiological response stages in *Amblystoma* and thoroughly worked out their underlying structural basis. These stages, with their characteristics, are as follows:

1. The premotile stage, in which no contraction of any muscle can be elicited by any method of stimulation. The muscle has not as yet differentiated to a structural state that permits function.

2. The non-motile stage, limited to those embryos in which certain muscles, located in the neck region, are sufficiently differentiated to respond to electrical or direct mechanical stimulation, but do not contract on tactile stimulation of the integument in any region of the body. At this time, no reflex arc has developed to the functional level.

There is strong presumption that, towards the end of this non-motile stage in *Amblystoma,* there is a brief period when electrical stimulation of appropriate areas of the spinal cord would excite the motor nerves to cause muscle contraction. It is certain that the motor nerves precede the sensory in their differentiation and that they are well developed and connected with the muscles in the cervical region at the latter part of this stage. Such muscular activity as a result of stimulation of motor nerves is well known in fishes, birds, and mammals, but apparently Coghill did not test for it in *Amblystoma,* as his primary interest was centered on the development of reflex activity.

3. The early flexure stage, characterized by the first reflex activity, follows abruptly on the last. Gentle tactile stimulation of the integument in the neck region causes a sharp bending of the head, almost perpendicular to the body

axis. The response is "typically away from the side stimulated" (Coghill, 1929a). Those embryos that at first exhibit ipsilateral flexion of the head, or even irregular laterality, eventually react contralaterally.

4. The coil stage, in which the caudally expanding muscle differentiation and motor-nerve connections with the muscles transform the localized neck flexion into a coil of the body, almost always to the contralateral side. Despite the caudally increasing spread of the neuromuscular connections, the sensory elements in the integument remain localized for some time before also expanding the reflex arc system towards the tail.

5. The S-reaction stage, "characterized by reversal of a flexure before it is completed as a coil" (Coghill, 1929a). As one flexure passes caudally along one side of the trunk, another appears in the neck region on the opposite side of the body and also passes caudally, to be succeeded by a third on the first side of the trunk, and so on, for a limited period. These waves of contraction, passing down the opposite sides of the body to slip off the tail, throw the trunk into alternating S- and reversed S-formations. A sinuous motion of the trunk is thus produced, which quickly becomes stage 6.

6. The swimming stage, as the tempo of passage of the alternate flexions increases and as they are longer continued. Then the young larva swims in sinuous fashion.

Several facts should be noted relative to the last four stages, those in which reflexes were elicited. In none do nervous elements above the medulla play any role in the responses. This was demonstrated by Coghill (1929a) by his severing the central nervous system at the level of the otic vesicles. In all cases observed, the commissural mechanism decussates, carrying the nervous impulse to motor cells on the opposite side of the spinal cord.

The earliest reflex response is localized in the neck region because, as Coghill pointed out, it is only here that motor-nerve connections to functional muscles have developed. As new motor connections are established seriatim in a caudal direction, the response spreads caudad. Hence it is obvious that all the functional reflex mechanism of the embryo responds to each effective stimulus. Because of this fact, Coghill termed these responses "total patterns."

As Coghill determined, the total pattern plays a significant role beyond the early stages. When the gills and then the extremities appear (first the forelimbs, later the hind limbs), these are moved only with the trunk during the sinuous movements of the body. They continue to do this for some time before they become capable of moving independently of the trunk, that is, before local reflexes of the limbs appear. Local reflexes are made possible by the development of additional nervous elements, chiefly motor, within the central nervous system. Coghill spoke of them as "partial patterns" which were "individuated" from the total pattern. However, Coghill was convinced that in *Amblystoma* the total pattern was always "dominant" over the partial patterns, though inhibited during the activity of local reflexes.

This concept of the development of behavior in *Amblystoma* is now generally accepted. Some of the original objection to it was based on the fact that the concept seemed to parallel the point of view of *Gestalt* psychology, which has not enjoyed universal acceptance. However, the great amount of detailed evidence furnished by Coghill was close to irrefutable.

Coghill believed that the concept of total pattern and partial pattern derived from his studies on *Amblystoma* established a principle basic to the development of behavior in all vertebrate forms. As he stated (1929a), "There is nothing

in our knowledge of the development of behavior to indicate that the principle does not prevail universally in vertebrates, including man." To test this belief, he set two of his students at Kansas, Swenson and Angulo, to the problem of the development of behavior in the fetal albino rat. The preliminary results confirmed Coghill's belief that his principle of total pattern and partial pattern held good for that form. Other persons who worked with him directly and still others who began studies quite independently on other vertebrates secured results which aligned them with the Coghillian concept.

However, not all students of embryonic behavior agreed with the Coghillian concept of behavioral development. Swenson had become impressed by the explosive activities of rat fetuses when the umbilical cord was ligated (1928b), a phenomenon often seen in many mammals but not in man. In the rat (1928a), he thought he recognized "simple movements." After he had left the Wistar Institute, he stated (1929) that local, "simple movements" could be elicited from rat fetuses and conceived of these as forming the building stones of behavior, which grew by the addition of one "simple movement" to another into the characteristic behavior of the organism. Windle and his coworkers, after tentatively agreeing with a Coghillian sequence in their first study on cat embryos (Windle and Griffin, 1931), became interested in local movements which could be elicited by certain specialized types of stimulation and swung over to Swenson's thesis.

Many investigators have studied the development of behavior in the embryos of a wide variety of vertebrate forms. Divergent conclusions have been drawn from the results secured. However, most fall into one or the other of two concepts, either into the concept of total pattern and partial pattern outlined by Coghill, or into the unit-plus-unit idea

originally put forward by Swenson and espoused by Windle.

No one, least of all Coghill, imagined that all animals in all vertebrate classes would develop their behavior exactly as does *Amblystoma,* any more than one would expect that all animals in these classes would develop structurally as does *Amblystoma.* There are great structural differences between animals within a class and greater between those in different classes. The question, however, was and is, Do all vertebrates, whatever their class and however greatly their adult structure and their adult behavior may differ, go through their early development, both structurally and behaviorally, in a sequence that has a definite, essential, basic similarity in principle or does each have a development that is unrelated to any developmental principle?

If one shifts the emphasis from the manifest differences between adults and later fetuses of vertebrate forms to their possible basic similarities in embryonic life, too much confirmatory evidence exists to deny that there is a definite basic principle continuously present throughout the morphological development of embryos in all vertebrate classes. This is, perhaps, best illustrated in the development of the nervous system itself. No "higher" form repeats the adult stage of any "lower" form, as the long-since discredited "recapitulation theory" once maintained, and equally there is no basic similarity in the method of development of vertebrate and invertebrate animals (see Meyer, 1935). If, however, there is a common basic principle governing the structural development of all vertebrate embryos, the question whether there also exists a common basic principle in vertebrate functional development very naturally arises. Indeed, it is forced upon us, if structure determines function.

Unfortunately, the work to date in this field offers no unequivocal proof one way or the other. Many investigators,

perhaps a majority, have offered evidence consonant with the view that there is a basic principle of structural development at work in the early embryos of the vertebrate series and that early functional development consequently also proceeds along similar lines, allowing for class, generic, and specific differences. Among those whose results and interpretations seem to favor such a point of view are: Pankratz (1931) on the rabbit; Tuge (1931) on the terrapin; Angulo (1932–1951) on the rat; Coghill (see Herrick, 1949, p. 96 *et seq.*) on the toadfish; Tuge (1934, 1937) on the pigeon; Youngstrom (1938) on *Rana, Bufo,* and other anurans; Barcroft and Barron (1939a, 1939b) on the sheep; Wang and Lu (1941) on *Rana;* and Smith and Daniel (1946) on the loggerhead turtle. The evidence furnished by these investigators has been highly favorable to the assumption of Coghill that the concept of total and partial pattern determined for *Amblystoma* applies to the embryonic functional development of other vertebrates.

However, others have opposed this concept. Some, such as Swenson and Windle (the latter in his papers after 1931), have embraced the concept of the cumulative union of "simple movements" to form behavioral patterns, though admitting the probable truth of the Coghillian sequence for *Amblystoma,* but for that genus only. Still others believe that each form is different from all others in the formation of its own pattern of behavior. Kuo (1932, 1938), working on chick embryos, rejected both the Coghillian and Windelian concepts. The results secured by Coronios (1933) on cat embryos afforded some support to the existence of a Coghillian sequence in that form. However, neither Coronios nor Carmichael, under whose direction the cat fetal studies were made, has any particular sympathy with the total-pattern ideas of Coghill. Carmichael himself (1934) made probably the most thorough study of reflexogenous

areas as yet undertaken on any fetal form. He used the fetal guinea pig, and his results are both interesting and instructive. As interpreted by him (and, indeed, in actuality), they do not support the total-pattern concept. Bridgman and Carmichael (1935) continued the work on guinea pigs. Again, their results do not support the total-pattern concept, but indicate that independent (though in no sense "simple") movements may occur at almost any time in fetal life in that form.

Brief reference has already been made to the views of Windle and his associates, but their evidence cannot lightly be brushed aside. More than 20 communications between 1930 and 1950 have adequately set forth the views of their senior or sole author on the basis of studies on fetuses of cat, rat, guinea pig, and man. Windle has not only championed the concept that behavior is primarily built up by the progressive addition of "simple" reflexes secondarily integrated into a functional whole, but he has also claimed that the total-pattern type of response can be secured only from mammalian fetuses suffering from oxygen want (Fitzgerald and Windle, 1942). The effects of anoxia are considered below, but it should be stated clearly here that most neuro-embryologists consider the integrative processes in the nervous system to occur in normal development as a primary procedure, antedating the beginning of functional capacity in any part of the nervous system.

A factor that often may prove puzzling in the interpretation of results is the exact nature of the stimulus applied. Coghill used human hairs to apply tactile stimulation to his *Amblystoma* embryos. In the Pittsburgh human fetal studies, discussed below, both human and horse hairs were used as stimulators. These were very carefully calibrated on a delicate balance to insure that the maximum pressure exerted did not exceed 10, 25, 50, or 100 milligrams or 2, 5,

or 10 grams in each category. Other investigators have used steel and fiber needles, scalpels, forceps, camel's hair brushes, glass rods, metal probes, and even cactus thorns. Light stimulation can be applied with such instruments, if sufficient care be taken, but there is no way of proving that the stimulation was light in any given case. Windle implies (1944) that strong stimulation is required to elicit movements of the early type obtained in the Pittsburgh studies, but we have elicited them routinely with hairs having "pressure values" of from 10 to 50 milligrams. It is not the pressure of a single "spot" type of stimulation that evokes responses, but the brushing of the stimulator over the reflexogenous area that elicits reflexes. This affords spatial summation over a series of sensory endings.

The mammalian embryonic integument is thin, and the underlying muscles may readily be excited to contraction by pressure exerted upon them. Direct mechanical stimulation of even small groups of muscle fibers may sometimes be seen through the semitransparent skin. In the Pittsburgh studies, hairs with "pressure values" of 50 or 100 milligrams were often used, but every embryonic response has been tested at some time, often repeatedly, with 10- or 25-milligram hairs to prove the exteroceptive nature of the resulting reflex and to establish the identity of its character under both conditions.

The problem of oxygen want or anoxia in mammalian fetal studies has already been mentioned. Without question, the best way in which to observe mammalian fetal reflexes is with the fetus in the opened uterus with intact placental connections, but without deep maternal narcosis. These conditions impose the serious problem of immobilizing the mother animal. Swenson (1925), Angulo (1932), Windle and Minear (1933), and others have accomplished this by producing maternal brain anemia by ligating blood

vessels to the head in the rat and other small mammals. Barcroft and Barron (1939a, 1939b) used spinal anesthesia on their sheep.

Few investigators of human embryos and fetuses have been able to observe them with intact placental connections. Where the specimens for observation are secured by operation, the welfare of the mother is paramount, especially as such operations are performed only for the most compelling medical reasons. In spontaneous premature deliveries, the fetal portion of the placenta ordinarily separates before examination of the fetus can be completed. Separation of the placental connections and consequent removal of the fetus immediately impose a number of additional complications, chief among which is anoxia.

The effects of anoxia are definite, and, to date, little has been accomplished in the way of combating them. If the time between beginning placental separation and the initiation of observations is short (not longer than one and a half to two minutes), even the very young human embryo may exhibit activity which we have come to recognize as characteristic for its age. Then there ensues a gradual slowing of responses, though they are still characteristic. Eventually, within a matter of seven to 10 minutes for young embryos, and longer, up to 20 minutes, for somewhat older fetuses, all activity ceases. When respiration may be established, observations may be greatly prolonged beyond these time limits. It is usually possible to establish respiration on at least a temporary basis when the fetus is about 23 weeks old.

The belief of the Pittsburgh investigators that the reflexes elicited by tactile stimulation are normal is based on two considerations. In the first place, these reflexes form a continuous series consonant with the morphologic development of the fetal nervous system as shown by Hogg (1941),

Humphrey (1952, 1954, 1955), and Brown (1956a, 1956b). Second, a careful study of the literature on reflexes that undergo progressive anoxial states indicates that, so long as reflexes can be elicited, they are an entirely normal expression of the functional capacity of the reflex arcs involved (Humphrey, 1953). It should be stated, however, that progressing anoxia does suppress the most recently developed reflexes so that all exteroceptive responses disappear in the reverse order of their development (Angulo, 1935; Humphrey, 1953; Hooker, 1954). Consequently, reflexes observed as anoxia increases do not necessarily indicate the most recent functional development. Only those reactions observed immediately upon delivery most nearly indicate the functional capacity of the age level considered.

Another factor which must be given careful consideration in the observation of human embryos and fetuses removed from the uterus or seen *in utero* is the effect of maternal anesthesia on the specimen being observed. Anesthetics used in the operations pass readily through the placenta in most cases and may have widely varying effects on the fetus. These range from the abolition of all fetal responses, as is the case with heavy doses of the barbiturates, to no discernible modification of movement or response, as in the case of local or spinal novocaine. Maternal anesthesia under local or spinal novocaine, with only Demerol and atropine sulphate as preliminary medication, is undoubtedly the optimum for the observation of operatively removed fetuses. As the selection of drugs for premedication and anesthesia is exclusively the prerogative of the surgeon, many fetuses have been tested under less than optimal conditions. However, anesthetics, like anoxia, do not appear to alter the essential character of the reflexes elicited, but rather to suppress more recently developed reactions (see Humphrey, 1953).

At least as important for fetal observations as anoxia or anesthesia is the care used in handling mammalian fetuses of the younger ages. These are delicate organisms, easily injured by even slight added pressures exerted on them. Such injury materially shortens the period of reactivity, although it does not alter the character of those responses that are elicited.

It is also essential that avian and mammalian embryos and fetuses be maintained at temperatures close to those of their incubation or intra-uterine environment. Chilling will cause activity to cease within a very short time. For this reason, early mammalian fetuses must be immersed in a constant temperature bath of physiological saline or other isotonic solution at all times. However, we have observed that slight variations from normal temperatures appear to facilitate the activity of human fetuses.

Isolated accounts of observations made on single human fetuses have appeared in the literature for over a century. Usually these fetuses were observed under quite unfavorable conditions. Hence the recorded results are open to question.

The first series of scientific observations of human fetuses was that of Minkowski, summarized in his publication of 1928, though begun in 1920 or earlier. He studied some 75 human cases, and his observations are the classic foundation of human fetal studies. The work of Bolaffio and Artom (1924) was unfortunately not always done under favorable conditions.

In the autumn of 1932, it became possible to begin a study of human fetal reflex behavior in the Department of Anatomy at the School of Medicine of the University of Pittsburgh. Those who entered on these studies are greatly indebted to many of their clinical colleagues in several of

the hospitals of that city and its environs for the opportunity to observe fetuses that became available, some prematurely delivered spontaneously, some derived from operations to conserve the life of pregnant women. During this period of over 24 years, 149 cases have come to observation, ranging from six weeks of menstrual age to a postmature of 45 weeks. In the following account, menstrual age estimated from the Streeter (1920) tables is used. This age is two weeks, plus or minus two or three days, longer than actual age, which of course cannot be determined.

As is mentioned above, morphologic methods of study do not permit the determination of the time when functional synaptic relations are established. The appearance of the various reflexes themselves, therefore, offers the most satisfactory evidence of function in the central nervous system of the human fetus. Consequently, in the following description of these reflexes the reflex arcs that probably function are mentioned in many instances.

In human embryos, the area of integument first sensitive to tactile (exteroceptive) stimulation and capable of eliciting reflexes is restricted to that portion of the face about the mouth and the lateral aspects (alae) of the nose. The receptor nerves from this region belong to the maxillary (V_2) and mandibular (V_3) divisions of the trigeminal (V) nerve. This restricted area of sensitivity gradually expands until, at about 14 weeks, it more nearly corresponds to that of the adult supplied by these two divisions.

The first reflex elicitable by stimulation with 10- or 25-milligram hairs in the restricted perioral region of the face occurs from the middle of the seventh week to the beginning of the eighth week. It consists of a contralaterial flexion of the neck. At this time the embryo is 20 to 23 mm. in crown–rump (CR) length. Only a few such reflexes have been observed, and not all fetuses tested in this age range

exhibited responses. Fitzgerald and Windle (1942) report having observed this type of response in two cases. No case of an ipsilateral response has been seen before eight weeks, but such does occur occasionally at the latter age. It is, of course, possible that it may occur earlier, but it has not been seen in the few reflexes so far elicited. It should be borne in mind that this and other accounts of human fetal activity

TABLE 1

FIFTH CRANIAL NERVE REFLEXES IN THE HUMAN EMBRYO AND EARLY FETUS: SOMATIC REFLEXES, 1

Menstrual Age in Weeks	Region of Stimulation	Divisions of V Involved	Nature of Response
7½	Perioral	V_2 and V_3 (limited)	Contralateral flexion of neck (avoiding)
7½–8	Perioral	V_2 and V_3 (limited)	Contralateral flexion of neck and uppermost trunk, with at most slight quivering of upper extremities
7½–8½	Perioral	V_2 and V_3 (expanding)	Chiefly contralateral flexion of neck and upper trunk, with extension of both brachia at shoulder and slight rotation of pelvis towards contralateral side, all movements becoming more pronounced and trunk flexion extending farther caudad as 9½-week age is approached
10½	Perioral	V_2 and V_3	Contralateral trunk flexion, with occasional trunk extension
11–12	Perioral	V_2 and V_3	Relatively constant trunk extension, with medial rotation of both brachia and head rotation away from stimulus; returning to contralateral flexion when anoxia increases

can record only observed movements. As the Pittsburgh studies have progressed, it has been necessary to revise both the repertoire of reflexes observed and the earliest age at which they have been seen.

As the eight-week period is attained (table 1), the extent of the trunk response to stimulation of the restricted maxillomandibular region spreads caudally to include the uppermost part of the trunk. This caudal expansion of the neuromuscular mechanism capable of responding to stimulation in the perioral skin area continues until, by 8½ to 9½ weeks, the entire trunk is involved in the usually contralateral response. During this period also, the area of integument sensitive to stimulation increases in extent, although it does not attain the typical distribution of the maxillary and mandibular divisions of the trigeminal until 11 to 11½ weeks.

During the expansion of the neuromuscular mechanism between 8 and 9½ weeks, the trunk flexion becomes more complete and, though discernible at 8½ weeks, pelvic rotation is increasingly evident from that age to 9½ weeks. Although the trunk flexions are predominantly contralateral during this period, ipsilateral flexions occasionally occur.

As the trunk response extends below the shoulders, both brachia extend (move backward) at the shoulder joint. The arm extension is quick, and the brachia return to the resting position before the trunk. At this time, there is no movement at the elbows, wrists, or in the hands. In one case observed at 8 weeks (22.6 mm. CR), the brachia appeared to "quiver," as though their neuromuscular mechanism were almost, but not quite, at the point of participation in the contralateral flexion of the trunk. The brachia move only with the trunk, having no capacity for independent movement before 10½ weeks, and then only seldom.

It is during this two-week period between 7½ and 9½ weeks of age that the method of stimulation must be most carefully controlled. Even what appears to be rather light stimulation of the integument over the trunk muscles may exert enough pressure to result in their direct mechanical stimulation. It is therefore imperative to test with truly light tactile stimulation, although the movements that result from direct stimulation can readily be distinguished from reflexes. Muscle contractions evoked by direct mechanical stimulation of the musculature are localized, ipsilateral, and without the accompaniment of other elements of the typical reflex, such as brachial extension or pelvic rotation.

Little change in the nature of the trunk reflexes elicited by stimulation of the perioral region of the face occurs between 9½ and 10½ weeks of age. As the latter age is approached, however, there is a tendency for the trunk flexion to give way to trunk extension. At first, trunk extension appears only occasionally in a series largely consisting of contralateral trunk flexions. By 11 or 12 weeks, trunk extension has become the predominant type of body-wall (somatic) muscle reflex elicited by stimulation in the area of sensory supply through the maxillary and mandibular divisions of the trigeminal nerve.

At this age also the brachial movement accompanying the trunk response changes to a medial rotation, rather than an extension, of both brachia, but there is still no movement at elbow or wrist as a part of the arm response elicited by trigeminal nerve stimulation. The head has also altered the nature of its response. It now rotates so that the face is removed from the stimulus by this means, rather than by merely flexing laterally. This type of response continues, with little alteration, as typical of the human fetus until 13 or 13½ weeks of age.

That certain fibers of the trigeminal nerve constitute the earliest receptor pathway to develop in the mammals has been demonstrated morphologically by Windle (1932, 1933) for the cat, by Angulo (1951) for the rat, and by Windle and Fitzgerald (1937) and by Humphrey (1951, 1952, 1954) for man. It has been confirmed physiologically by Barcroft and Barron (1939a, 1939b) for the sheep and by the Pittsburgh investigators (Hooker, 1939, 1942, 1944, 1952; Hooker and Humphrey, 1954) for man.

Humphrey, by a microscopic study of serial sections of a number of human fetuses, was able to determine the fetal age at which fibers of the spinal tract of the trigeminal nerve reach the spinal cord (1954) and add new evidence regarding the ultimate point of termination of its three divisions at spinal cord levels (1951, 1952, 1954). By 8½ weeks, maxillary and mandibular fibers were found, in one case, to reach the cephalic part of the fourth cervical segment of the cord and, by 9½ weeks, ophthalmic fibers appear to extend as far caudalward as do those of the other two divisions (1954). Of more interest from the standpoint of fetal activity is Humphrey's observation that, by 6½ weeks, all three divisions of V have reached the first cervical segment and, by 7½ weeks, the age at which the earliest reflex in response to perioral stimulation has been observed, these fibers have grown throughout the first and into the second cervical segment of the spinal cord (1954). Later, the maxillary and mandibular fibers, those first responding to stimulation, outdistance the ophthalmic fibers in their growth caudalward, but by 9½ weeks the ophthalmic fibers have reached approximately the same caudal levels as the others.

Even before the spinal tract of the trigeminal reaches the spinal cord, Windle and Fitzgerald (1937) noted that commissural fibers were well developed in the upper cerv-

ical levels of the spinal cord. At 7½ weeks, when the first reflex has been observed, these commissural fibers, connecting the area of termination of the spinal tract of V with the contralateral ventral horn motor neurons, are well developed, as Humphrey (1952) has shown. Consequently Humphrey (1952) suggested that this pathway constitutes the reflex arc whereby contralateral flexion in the neck region occurs in response to perioral stimulation. Similar commissural connections with the contralateral spinal accessory (XI) nucleus enable the sternomastoid and trapezius muscles to participate in producing this reflex. Later, when the face is rotated away from the site of stimulation, either collaterals from these commissural fibers or internuncials between V and the ipsilateral nucleus of XI will aid in producing the rotation.

We know from the results detailed above that there is a reflex arc system which becomes functional at about 7½ weeks in the human fetus. The maxillary and mandibular divisions of the trigeminal nerve serve as the receptors of this arc which finds effector neurons in the contralateral cervical spinal nerves as well as in the contralateral spinal accessory nerve. These maxillary-mandibular reflexes, so far described, affect only the trunk musculature and hence have been denominated as somatic in character. They form an expanding type of trunk response with upper and lower extremity participation only in conjunction with the trunk movements. They are, then, the counterparts of Coghill's total-pattern responses (see p. 8). However, beginning at about 9½ weeks, certain local facial reflexes (table 2) make their appearance. At this age, of course, not all the trunk responses to be elicited by trigeminal stimulation have fully developed.

The first local facial response to appear is active but incomplete opening of the mouth by lowering of the mandi-

TABLE 2

FIFTH CRANIAL NERVE REFLEXES IN THE HUMAN FETUS: LOCAL REFLEXES OF THE FACE

Menstrual Age in Weeks	Region of Stimulation	Divisions of V Involved	Nature of Response
9½	Edge of lower lip	V_3	Active mouth opening by lowering of mandible
10–10½	Upper eyelid	V_1	Occasional contraction of orbicularis oculi muscle
10½	Rima oris	V_2 and V_3	Deglutition
11	Upper eyelid	V_1	Occasional contraction of corrugator supercilii muscle
12½	Tongue and/or rima oris	V_2 and V_3	Momentary lip closure and, if repeated, deglutition
12½–13	Upper lip or, rarely, lower lip	V_2 and V_3	Contraction of orbicularis oculi muscle
13	Rima oris	V_2 and V_3	Maintained lip closure
13–14	Upper lip and nose ala	V_2	Contraction of quadratus labii superioris muscle and rotation of head away from stimulus
17	Upper lip at rima oris	V_2	Protrusion of upper lip
20	Lower lip at rima oris	V_3	Protrusion of lower lip
22	Rima oris	V_2 and V_3	Simultaneous protrusion and pursing of both lips
29 or before	Rima oris	V_2 and V_3	Audible sucking

ble. This reflex is elicitable at about 9½ weeks, following stimulation of the edge of the lower lip. It has been elicited only by stimulation of the mandibular division of the trigeminal nerve. The sensory fibers of this division (V_3) pass through the spinal tract of the trigeminal to the spinal nucleus of V, thence by intermediate neurons to the ventral horn motor neurons of the first three cervical nerves which innervate certain suprahyoid and infrahyoid muscles participating in mouth opening (Humphrey, 1954). In as much as there is no indication of activity of the facial nerve (VII) until 10 to 10½ weeks, when there is "squinting" of the eyelid (see below), and no indication of action over the motor fibers of the mandibular division of the trigeminal before 12½ weeks, when mouth closure occurs, the incomplete mouth opening at 9½ weeks is probably unrelated to the action of muscles innervated by either of these nerves (VII or V_3).

Within a few days thereafter, at 10 to 10½ weeks, the area of integument over the upper eyelids becomes sensitive to tactile stimulation. This region, along with the forehead, is supplied with sensation by the ophthalmic division (V_1) of the trigeminal nerve. Restricted at first to the upper eyelid, very light tactile stimulation of this area causes a "squinting" of the eyelid, a contraction of most of the fibers of the orbicularis oculi muscle. When it is first seen, the eyelid "squinting" is only occasionally elicitable, but becomes constant by 11 to 12 weeks. At 12½ to 13 weeks, an eyelid "squint" has been observed to follow stimulation of the upper lip or, rarely, of the lower lip. In this case, the reflex arc consists of sensory fibers of the maxillary division of V, or more rarely of those in the mandibular division, the impulse passing through internuncial neurons to the facial nerve (VII).

At 10½ weeks, also, repeated stimulation of both lips

sometimes, though rarely, causes swallowing. Though deglutition may at times be elicited under certain conditions from this age on, it is not frequent until near the middle of gestation. If better tests are found, it is quite possible, however, that swallowing might be more frequently observed than it has been heretofore.

By 11 weeks, that is, shortly after the eyelid "squint" has first been seen, the sensitive area supplied by the ophthalmic division of the trigeminal spreads onto the forehead. Stimulation over the upper eyelid or near the eyebrows may then cause occasional scowling. Both "squint" and scowling become quite constantly elicitable as reflexes when the upper eyelid is stimulated by 12 weeks. These reflexes would presume the functioning of intermediate neurons between the spinal nucleus of V and the facial nucleus (Humphrey, 1954).

Opportunities to test the tongue do not often present themselves, as the mouth is rarely open sufficiently for the tongue to be touched without at the same time stimulating the lips. The earliest that tongue stimulation has definitely been accomplished is at 14 weeks, but it is possible that it may yet be carried out at an earlier age. Tactile stimulation of the tongue at 14 weeks resulted in its withdrawal. Sensory fibers from the anterior two-thirds of the tongue, the only region so far stimulated, pass along the lingual nerve (V_3). All the tongue muscles concerned with its retraction are innervated by the hypoglossal nerve (XII). Hence by 14 weeks, if not before, evidence exists for a functional reflex arc consisting of V_3-internuncial neurons-XII.

By 12½ weeks, also, stimulation of the maxillomandibular complex at the rima oris causes momentary lip closure and, if repeated, has elicited swallowing. This is evidence of the ultimate passage of trigeminal nerve impulses to the facial nerve (VII) for the lip closure and to the glossopharyngeal

(IX) and vagus (X) nerves for the swallowing. By 13 weeks, stimulation of the rima oris may cause maintained lip closure. At this age as well, the first active mouth closure by mandibular movement has been observed on stimulation of the lower lip alone. This activity is additional evidence of trigeminal sensory (V_3) connections with the motor root of V, via internuncial neurons. The motor root of V accompanies the fibers of the mandibular division to the muscles of mastication.

Between 13 and 14 weeks, depending on the level of maturation of the neuromuscular mechanism in the particular fetus observed, general trunk responses to stimulation of the maxillary and mandibular divisions tend to cease in large part, as mentioned above. From this time on, stimulation of any of the skin areas supplied by the trigeminal nerve causes chiefly local reflexes. At this age also, stimulation of the side of the upper lip and the wing (ala) of the nose elicits contraction of the quadratus labii superioris muscle which elevates the upper lip and the ala of the nose, producing what has earlier been referred to as a "sneer" (Hooker, 1952, etc.). The effector element in this reflex is again the facial nerve (VII). It may be noted that the various branches of VII become functional not all at the same time but in a somewhat seriatim manner. Ordinarily, the response consisting of elevation of the upper lip and nasal ala is accompanied by rotation of the head, which carries the face away from the stimulus.

Rotation of the head, turning the face away from the stimulus, is an avoiding reaction, as was the earliest head movement, contralateral flexion, seen at 7½ weeks and older ages (see Coghill, 1916; Angulo, 1932; Hooker, 1952; Humphrey, 1952, 1954; Hooker and Humphrey, 1954). Each of these responses, and each equally effectively, separates the sensitive area of facial skin from the stimulus. At

13 to 14 weeks, the same avoiding reaction by the turning of the face away from the stimulus is seen as a local reflex, without other trunk participation, and not as a part of a general trunk response. As a component of the quadratus labii superioris reflex, head rotation is none the less produced by a reflex arc originating in V_2 or V_3 and passing through intermediate neurons to contralateral cervical nerves, as it was at 11 to 12 weeks, when it was part of the trunk response.

It might be pointed out here that reflexes elicited by stimulation of the mucous membranes of the lips and tongue (opening of the mouth, tongue movements, deglutition, lip closure, and mouth closure) are successive phases in the development of the feeding responses (Hooker and Humphrey, 1954). The remainder of the phases in the development of feeding responses may be covered briefly. At 17 weeks, stimulation of the mucous membrane of the upper lip causes that lip to protrude. No protrusion of the lower lip, upon its stimulation at its edge, has been observed before 20 weeks. Between 12½ and 20 weeks, the lower lip merely closes. However, at 20 weeks, both lips protrude on stimulation of the rima oris and, at 22 weeks, are pursed as well. The earliest that sucking movements have been observed in this study is at 29 weeks. There is some clinical evidence that sucking movements may occur earlier, although by no means all premature infants are capable of nursing if much younger than 28 or 29 weeks of menstrual age at birth.

In the foregoing review of human fetal reflexes, whether of the trunk or entirely local, for which one or another of the divisions of the trigeminal nerve has served as the receptor part of the arc, it is evident that the fifth cranial nerve makes connections, via various internuncial neurons, with six of the cranial nerves (V, VII, IX, X, XI, XII) and with a series of cervical spinal nerves.

The fibers of V, given off by the cells in the Gasserian

ganglion, enter the central nervous system to synapse with intermediate neurons which lie wholly within the medulla and spinal cord. The effector nerves of all these reflex arcs originate within the central nervous system, though their fibers leave it to be distributed to the muscles concerned. Thus, evidence has been afforded to demonstrate that the central nervous system in human fetuses is capable of functioning, not only prenatally, but very early in gestation.

TABLE 3

SPINAL NERVE REFLEXES IN THE HUMAN FETUS: LOCAL REFLEXES OF THE UPPER EXTREMITY

Menstrual Age in Weeks	Region of Stimulation	Nature of Response
10½	Shoulder	Rare independent extension of brachium
10½	Palm	Occasional partial finger closure, rarely with pollex flexion
11	Palm	Constant partial finger closure, usually with wrist flexion, sometimes with elbow flexion, medial rotation of brachium, or forearm pronation
11½	Shoulder	Occasional abduction of brachium
13	Palm	Occasional nearly complete finger closure, rarely with pollex opposition
13½–14	Palm	Occasional complete finger closure
15–15½	Palm	Maintained finger closure
18½	Palm	Weak, true grasp
27	Palm	Sufficient grasp almost to support body weight momentarily

There is, however, additional evidence still to be adduced for functioning of the central nervous system in fetal life.

After both trunk and local reflexes have been elicited by trigeminal stimulation, but before either type has completed its repertoire, local reflexes can be evoked in both the upper and lower extremities (tables 3 and 4). Whereas both upper and lower limbs begin their movements as components of the trunk activities, at about 10½ weeks independent limb movements are exhibited. These local reflexes are mediated by reflex arcs through the spinal cord, consisting of spinal ganglion cells, internuncial neurons, and motor neurons. Consequently, these reflexes, as well as those involving cranial nerves, are indicative of functioning of the central nervous system.

At 10½ weeks, stimulation of the shoulder with hairs having sufficiently low "pressure values" to insure that the resulting movement is a reflex, not caused by direct mechanical stimulation of the muscles involved, has in a few cases elicited extension of the brachium. At about this age, possibly a little before, light stimulation in the palm may cause a quick, partial closure of the fingers, except the thumb. The pollex has been observed to flex as well, but this is rare at almost any fetal age. A few days later (11 weeks), nearly every fetus exhibits partial finger closure on palmar stimulation. Usually, at this age, the wrist also flexes. At times, elbow flexion, medial rotation of the brachium, forearm pronation, or all three movements may accompany the finger flexion.

By 11½ weeks, occasional abduction of the brachium may occur as part of the local reflex of the upper extremity. This is always followed by brachial adduction, as part of the return to its resting position. It so happens that abduction or adduction of the brachium at the shoulder has not been recorded as an independent movement before 27 weeks.

Halverson (1937) has concluded from his studies that prehension in children involves two elements, finger closure and grasp, appearing in that order. These two components of postnatal prehension have a reflex background in fetal life, and in the same sequence. The appearance of partial finger closure at about 10½ weeks and its development into a constant response at 11 weeks are described above. Finger closure remains only partial until 14 weeks, when a few fetuses exhibit almost complete flexion of the fingers. The number of fetuses showing complete finger closure increases by 14 weeks, but the reflex is still quick, with almost immediate opening of the hand. It is not until 15 to 15½ weeks that the immediate return of the fingers to the resting position ceases in a few fetuses. By 18½ weeks, the first evidence of true grasp occurs when a glass rod or a hair may be retained inside the closed fist. Grasp at this time is weak, and any object held by the fingers may easily be withdrawn. However, grasp becomes steadily stronger and by 27 weeks will nearly support the body weight momentarily. As yet, no case of simultaneous bimanual grasp has been observed. In each case tested, a true grasp with one hand is immediately released when a similar object is placed in the palm of the other, and it has proved impossible to secure grasp when both hands are simultaneously presented with any object.

Prechtl (1953) has mentioned the difficulty of securing the grasping reflex in premature infants of 1200 to 2500 grams except while the babies were suckling quietly. He further states that neonates at term, before suckling, exhibit only weak grasp which becomes stronger during feeding. However, a few weeks after the neonatal period, strong grasp may be elicited without simultaneous sucking activity. In our observations, there is no question of the effectiveness of the grasp exhibited by at least one 27-week fetus in which

this reflex was sought within 15 minutes after birth. It has proved difficult to elicit grasp from many fetuses in this general age range, and we have been unable to test the grasp reflex during feeding in any premature infant.

Up to this point in our discussion we have been concerned only with exteroceptive reflexes, those elicited by external stimulation. Another type of reflex is manifest early in fetal life. This is the proprioceptive reflex. Whenever the length of a muscle is altered as a result of mechanical stretching, proprioceptive sensory endings within the muscle are stimulated. The reflexes set up through these arcs have to do primarily with postural effects or with adjusting the action of the muscle concerned to its activity (see Herrick, 1947). In general these reflexes are mediated by two-neuron arcs, though intermediate neurons may be present in some cases. If a muscle is stretched by even an infinitesimal amount, a stretch or myotatic reflex is induced. In the Pittsburgh studies, the first clearly demonstrable stretch reflexes occur at 9½ weeks. Windle (1944) believes that they may occur much earlier. He has ascribed the upper extremity movements reported by him at 7½ to 8 weeks, and elicited by tapping on the amnion or by "flipping" the limb, to the group of stretch reflexes. As stretch reflexes are always highly localized and affect only the part stimulated, they might give the appearance of being "simple movements." It would thus appear that the "simple movements" of Swenson and Windle might be of this nature, although we have never observed them at so early an age. It may well be that such reflexes do occur earlier than we have seen them. If the "simple movements" of Swenson and Windle are of this nature, they play but a minor role in the development of fetal behavior, because stretch reflexes remain localized in nature even in the adult (see Humphrey, 1953). Their chief significance would probably lie in the realm of postural rela-

TABLE 4

SPINAL NERVE REFLEXES IN THE HUMAN FETUS: LOCAL REFLEXES OF THE LOWER EXTREMITY

Menstrual Age in Weeks	Region of Stimulation	Nature of Response
10–10½	Sole of foot	Plantar flexion of all toes
11½	Sole of foot	Either plantar flexion of all toes or dorsiflexion of hallux and fanning of other toes, sometimes with knee flexion, then extension (as a kick) and with hip flexion, rotation, or abduction
12½	Sole of foot	Principally dorsiflexion of hallux and toe fanning, dorsiflexion of foot at ankle, flexion at knee and hip
13½	Sole of foot	Occasional dorsiflexion of all toes
32 or before	Inside thigh	Cremasteric reflex

tions. At 9½ weeks, in the Pittsburgh studies, stretching of the biceps muscle or repeated stretching of the fingers has given some evidence of the presence of stretch reflexes.

Although the first reflex elicited by stimulation of the sole of the foot (table 4) has been seen in the same age group (10 to 10½ weeks) as the first appearance of partial finger closure on palmar stimulation, in any individual fetus exhibiting a plantar response the finger-closure reflex is already established. Observations by Angulo (1935) and others have demonstrated that the most recently established reflex is the first to be extinguished by progressive anoxia (see also Humphrey, 1953). Double simultaneous stimulation tests of palm and sole (see Hooker, 1954) have also shown that anoxia extinguishes the plantar reflex before the palmar reflex disappears. This earlier suppression of the plantar reflex, as

anoxia progresses, offers added evidence for its later appearance developmentally.

In the human fetuses tested in the Pittsburgh studies, the earliest response observed on stimulation of the sole of the foot was plantar flexion of all toes at 10 to 10½ weeks. This is in agreement with the extensive plantar reflex studies of Minkowski (1923). However, in a later communication, Minkowski (1928) revised his opinion on the basis of further observations, then stating that the earliest plantar reflex might be either plantar flexion of all toes or dorsiflexion of the big toe (hallux) and fanning of the other toes. It has proved difficult to set exact ages for the fetuses examined by Minkowski, but it is our belief that the age of the youngest fetus observed by him was also about 10 weeks. In the Pittsburgh studies the earliest mixed responses to plantar stimulation were not found until about 11½ weeks. At this time, the same fetus may exhibit both types of response interchangeably. Whichever type of response is exhibited, it is often accompanied by flexion at the knee, then quick extension of the leg in a kick. At the same time, the thigh may flex, rotate in either direction, or abduct, with subsequent return to resting position.

From about 12½ weeks until birth (and for a time thereafter, for that matter), the plantar reflex takes the form chiefly of a dorsiflexion of the hallux and fanning of the other toes. This is a Babinski-like response. Plantar flexion of all toes may occur at any age, but it is an isolated type of response after 12½ weeks. Furthermore, from 13½ weeks, or possibly earlier, dorsiflexion of all toes may at times be observed as a response to plantar stimulation. In general, this type of response is more rare than plantar flexion of all toes.

It is fully realized that the foregoing account of the se-

quential appearance of exteroceptive reflexes in the human fetus is not a complete statement of all that is known on the subject. Space does not permit a more detailed review of the Pittsburgh studies here. Much remains to be done along several lines, and these studies are not yet completed. Before a few additional comments are made, it seems desirable to place the activities given in their proper relationship to the problem of the development of embryonic behavior in vertebrates.

It may be recalled that the early reflex movements elicited by exteroceptive stimulation of the human fetus begin as a contralateral flexion of the neck at about 7½ weeks. The amount of trunk musculature that participates in the response spreads caudally in accordance with the recognized principle of cervico-caudal differentiation of the neuromuscular mechanism. As the trunk musculature capable of contraction passes the upper extremities and finally reaches the pelvic region, the brachia and the lower extremities move with the trunk. This is clearly an expanding total pattern in the sense in which the term was used by Coghill.

As the nervous system continues its differentiation and new neuromuscular connections are established, specific local reflexes appear, first in the face, then in the upper and the lower extremities and in the trunk (table 5). Such reflexes are not exhibited earlier than 9½ weeks. This appearance of local reflexes after the establishment of the total pattern corresponds to Coghill's description of the individuation of partial patterns from the total pattern.

In consequence, the development of human fetal reflex behavior appears definitely to substantiate Coghill's (1929b) dictum that "the same law prevails in the development of behavior of human beings as that which has been observed in *Amblystoma.*" Note that it is the "law" or principle that behavior develops first as a total pattern, from which partial

TABLE 5

SPINAL NERVE REFLEXES IN THE HUMAN FETUS: LOCAL TRUNK REFLEXES

Menstrual Age in Weeks	Region of Stimulation	Nature of Response
13	Chest	Isolated respiratory chest contractions
15	Abdomen	Abdominal muscle contractions
22	Chest	Temporary diaphragmatic contractions
23½	Chest	Temporary effective respiratory chest contractions and phonation
27	On delivery	Permanent respiration established

patterns are later individuated, that constitutes the important consideration here. There is no implication that more than this basic principle holds good between man and *Amblystoma* in the development of the behavior of either.

In the human embryo and young fetus, both the reflexes evoked by stimulation of the integument supplied by the trigeminal nerve and the early reflexes of the extremities mediated through spinal nerves are stereotyped in character. Within very narrow limits, each response secured from a given reflexogenous area is, in amplitude, character, and duration, almost exactly like every other elicited by like stimulation of that site in any individual or, indeed, in any fetus of the same response age. The stereotyped character of these early reflexes does not disappear until the fetus reaches 13 or 14 weeks of age. Furthermore, all reflexes that appear later during fetal life are also stereotyped when they are first elicitable and remain so for a period thereafter before they lose this quality.

In the development of postnatal behavior there is fre-

quently, at least, a repetition of the sequence of events seen in the development of fetal reflexes. This is well illustrated, for example, in a comparison of the development of the fetal grasping reflex (Hooker, 1938) with the development of voluntary grasping postnatally (Halverson, 1937). The cortically controlled voluntary act, however, becomes smoothly coordinated and may have great variability.

It has already been indicated that much has been omitted from this review. In some instances, as is the case with the organs of special sense, omission is due to the fact that no significant tests have as yet been made in the course of these studies. The whole problem of spontaneous movements has been ignored. Emphasis has been placed upon early reflex activity to the exclusion of most of the later behavior of the fetus. These, and other, omissions are regretted, but space for their consideration is lacking.

It is hoped, however, that this account of human fetal reflex behavior has demonstrated that the fetal nervous system is able to function at a very early age. If such function occurs *in utero,* human behavior becomes a continuum from about 7½ weeks of menstrual age to death. Whether or not the earliest activities elicited by tactile stimulation ordinarily occur *in utero* during an uninterrupted gestation is beside the point. That the capacity for such movements exists has been demonstrated, and these earliest responses, even though they may not first appear at the same age *in utero,* are part of the continuum of human behavioral development.

The exteroceptive reflex arcs utilized by the fetus are not isolated units. They are components of a primarily integrated nervous system having innumerable connections with other areas of the central nervous system. As the developing organism grows, its nervous system grows with it, making new connections within the brain and spinal cord, as well as with structures outside the central nervous system.

During the earlier part of fetal life, the behavior that develops is purely reflex in nature. The intricate nervous mechanisms which make possible the continuing patterns of reflex behavior lay the foundation for future voluntary acts by the postnatal child. The receptors, the internuncial neurons, and the neuromuscular connections used in early fetal reflex behavior are the structural basis on which later action patterns are built. This is retained and utilized in the development of postnatal behavior.

Not even the reflex arcs are discarded as such. They continue to serve the organism throughout its life. As Sir Charles Sherrington (1950) has pointed out, "Reflex action has contributed much to the integration of the individual. It would seem to be reflex action and not mind which primarily integrated the motor individual." And again, "motor behavior in the individual has two components. One is reflex. . . . The other is superstructure and is not reflex." The superstructure here mentioned is the cerebral cortex. The cortex probably plays no role in early fetal activity, and it is uncertain when it begins to assume its functions. However, as it differentiates and gradually takes over in infancy and childhood, it transforms the patterned activity of late fetal life into the infinitely varied behavior of the child and the adult.

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David P. C. Lloyd, *The Discrete and the Diffuse in Nervous Action;* May 8, 1958

THE DISCRETE AND THE DIFFUSE IN NERVOUS ACTION

Nearly 70 years ago the eminent Spanish histologist Cajal announced a series of physiological inductions concerning the fundamental structure of the spinal cord. Among these were schemata, reproduced here in figure 1, of what have by virtue of the French edition of his monumental work (1909, 1911) come to be called *"les réflexes unilatéraux circonscrits"* and *"les réflexes unilatéraux diffus."* To the left of figure 1 one sees the circumscribed mechanism in which afferent nerve fibers entering the spinal cord make direct connection with motor nerve cells over a limited or localized region of the spinal cord. To the right one finds the diffuse mechanism represented with an internuncial nerve cell intercalated between afferent and motor nerve cells, it extending up and down the spinal cord to bring the afferent influence to a much-extended field of motor nerve cells. Fifty-three years passed before the actual physiological significance of these schemata became apparent, and, in fact, it would seem that they were largely ignored in the interim. In a way it was not too surprising that this should have been so, for the physiological constants of nerve fibers and of nerve cell junctions were insufficiently known, and the apparatus of the physiologist was strained to and beyond its power of resolution in the attempt at analysis of the central machinery of reflex action.

The new era began when Gasser and Erlanger (1922) successfully employed the Braun tube as an inertialess instrument for the recording of nerve impulses. With its use the conduction velocities of various types of nerve fibers have been learned, as has the time consumed in the transmission

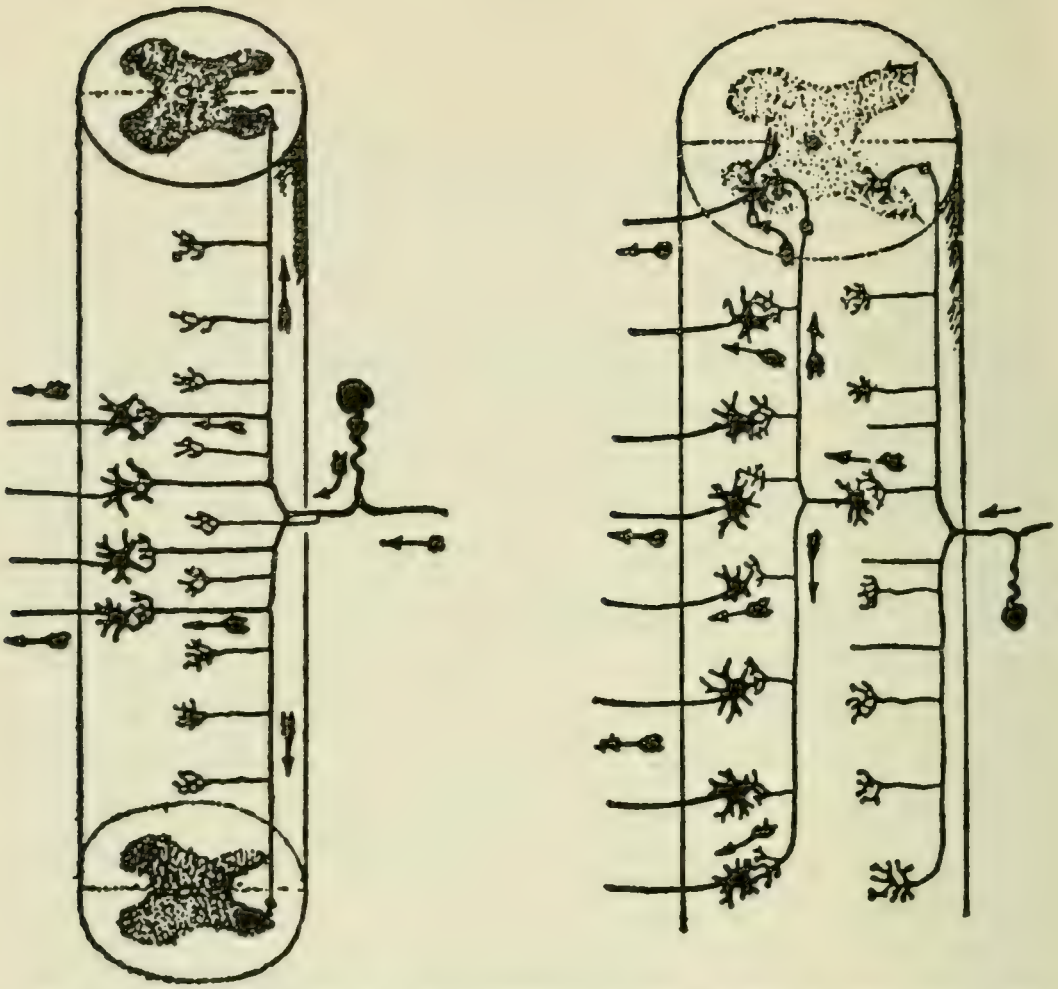

FIG. 1. Diagrams by Cajal, first published in 1890, in which he represented the concepts of the circumscribed and diffuse reflex mechanisms. Arrows indicate the direction of conduction from afferent fibers entering the spinal cord directly to motoneurons and so out again (left diagram), or from afferent fibers to an interneuron and thence up and down the spinal cord to a wide field of motoneurons which in turn conduct outwards (right diagram). Modified from Cajal, 1909.

of excitation from one nerve cell to another. In essence the cathode ray oscilloscope and associated paraphernalia have permitted the physiologist to say not only "where" but "when" with sufficient accuracy to establish the functional significance of the Cajal schemata. And there can be no doubt as to their functional significance.

Today one would refer to the two schemata of Cajal as the monosynaptic reflex arcs and the polysynaptic reflex arcs, respectively—terms that do not contain built into their meaning the notions of discreteness and diffuseness. This, historically, perhaps was unfortunate, for in the end the

qualities of discreteness and diffuseness rather than those of monosynapticity and polysynapticity provided the essential clue to the functional meaning of Cajal's schemata. It was this notion that led to the selection of my title for the present James Arthur Lecture and that prompted the thoughts, musings, reflections, and speculations that comprise a goodly measure of its content. In bringing these before you, I hope that I shall not in any way do injustice to the honor conferred on me by invitation to deliver one in this distinguished series of lectures.

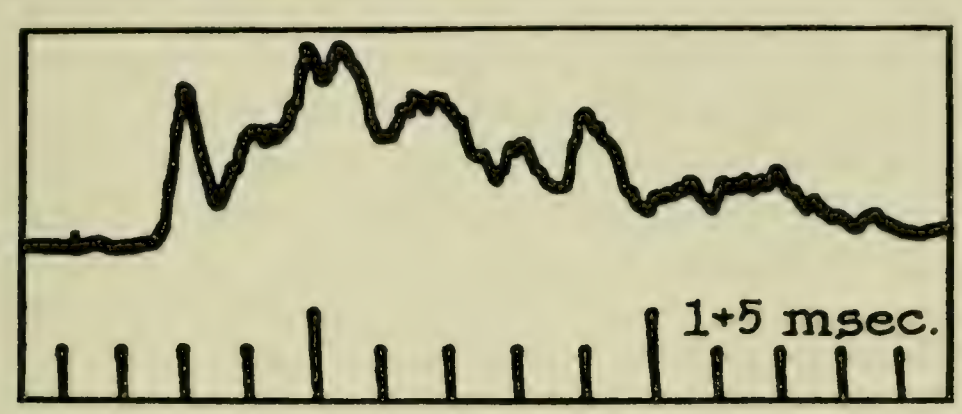

FIG. 2. Segmental spinal reflex discharge evoked by single shock stimulation of a dorsal root and recorded by cathode ray oscilloscope from the ventral root of the same segment. The initial upward "spike potential" denotes transmission of impulses through reflex arcs of two neurons in series: the afferent neuron and the motoneuron. The remaining irregular deflections denote transmission through more complicated (polysynaptic) reflex arcs. From Lloyd, 1955.

Let us consider now a functional picture of the circumscribed and diffuse mechanisms. Figure 2 contains an oscillographic tracing of the reflex output of a segment of the spinal cord thrown into action by a single stimulus to its dorsal or afferent root. The output is recorded from the corresponding ventral or motor root. There is, first of all, a small deflection signaling the instant of stimulation. Next there is a "spike-like" action potential indicating the discharge of a well-synchronized volley of nerve impulses, and finally an enduring irregular wave indicative of a shower of nerve impulses rather than of a volley. Following upon the precise determinations by Lorente de Nó (1935) of the

time required for the transmission of excitation from one nerve cell to another (so-called synaptic transmission), one can state with confidence that the initial spike-like action relates to reflex transmission through an arc of but two neurons in series length (Renshaw, 1939). Employing the same constant of time, one concludes that the remainder consists of discharge through reflex arcs containing more than two neurons in series.

Figure 2 is a functional picture in one sense, but an anatomical one in another. It demonstrates that transmission through the spinal cord of actual nerve impulses does, indeed, occur in the manner predicted by Cajal's diagrams, and in this sense it is functional. On the other hand, from the point of view of reflex physiology it is anatomical, for the dorsal root is an anatomical collection of afferent fibers subserving a variety of reflex functions, and the reflex result from stimulation of it accordingly must be an incoordinate mingling of divers actions. What is more, it says nothing concerning the essence of Cajal's inductions, which lies in the words *"circonscrit"* and *"diffus."*

Some type reflexes

The problem now is to make a functional dissection of the segmental reflex to isolate its components. But before such an analysis is undertaken, it is germane to consider briefly a few of the ipsilateral reflexes that might be represented in the result of dorsal root stimulation as it appears in the recording illustrated in figure 2.

If a limb be flexed passively, it is found to resist the externally applied force by means of extensor muscle contraction that is reflex in origin. This was called by Sherrington the stretch reflex. It was analyzed in terms of muscle contraction by Liddell and Sherrington (1924, 1924) in two papers that are models of scientific thought, execution, and presentation. Pertinent for the present purpose among the findings were that the reflex contraction was confined to the

muscle stretched; that the reflex was "dead-beat," contraction ceasing abruptly with relief from the imposed stretch; and that the stretch contraction was inhibited by traction on the antagonist of the muscle under examination. Liddell and Sherrington concluded that the central pathway must be simple, but the degree of simplicity could not be assessed, nor did they attempt so to do.

If, now, the flexion imposed upon the limb be increased from that which evokes reflex opposition to reach a degree potentially harmful to the stretched muscle fibers, the "overstretched" muscle, an instant before engaged in strong contraction, suddenly gives way. The giving way is of reflex origin; the stretched muscle is inhibited, its antagonist ofttimes displaying, coincident with its relaxation, a brief contraction. This "inhibitory" reflex is called the lengthening reaction; it is stretch-originated, as is the stretch, or myotatic reflex, it countermands.

If, finally, the limb comes into contact with some source of hurt, it is withdrawn, the action, reflex in nature, being a generalized contraction of the flexor musculature of the limb. This, briefly, is the flexor reflex.

What I have just said concerning these three reflexes, so well seen in the decerebrate preparation, was well known years ago, and it seems at first glance surprising that the rather obvious correlation between the qualities of these reflexes and the anatomical qualities of Cajal's reflex pathways seemingly was not made. What more appropriate mechanism for the stretch reflex than Cajal's *"réflexe circonscrit"*? What more approprite for the flexor reflex than the *"réflexe diffus"*? But things that may seem so obvious to one generation are not infrequently far from being so to its predecessors. Also, there were road blocks in the way to confuse the issue. I mention but two. Prior to 1939, when physiological experiment confirmed the existence of monosynaptic reflex pathways in the spinal cord, anatomical study had not always done so, and the weight of opinion appears

to have been against the existence of *"collaterales réflexo-motrice"* extending from the dorsal root fibers to form direct connection with motoneurons. On the other hand, the most painstaking and careful analysis of the flexor reflex then possible, that by Eccles and Sherrington in 1931, had suggested that its latency, when facilitated, was so short as to indicate transmission by monosynaptic as well as polysynaptic reflex paths. Is it any wonder, then, that the significance of Cajal's inductions was lost? Not until the early 1940's were the road blocks cleared so that the high road to discovery could be resumed.

The spinal mechanisms of elementary reflexes

The first step in dissecting the anatomical segmental reflex into its functional components was to shift one's stimulating electrodes from the dorsal root to peripheral nerves, where the afferent supply from muscle and from skin could be stimulated in isolation, one from the other. When this was done (Lloyd, 1943a) the monosynaptic reflex discharge into a ventral root was found only on the occasion of stimulating muscular afferent fibers, the character of response being exemplified in record A of figure 3. Absent when the cutaneous nerves were stimulated, there was nevertheless a copious polysynaptic reflex discharge, as seen in record B of figure 3.

Once the monosynaptic and polysynaptic reflex discharges had been segregated one from the other, and the former demonstrated clearly to be muscular in afferent origin, the latter largely cutaneous, the major road block was removed and the way open to further experimentation. It was then that a logical hypothesis could be constructed and put to test. If the monosynaptic reflex pathway was indeed that of the stretch reflex, then monosynaptic reflex discharge should, because of the circumscribed nature of the stretch reflex, be found confined to the motor fibers of the muscle nerve subjected to stimulation, and not in the nerves to

FIG. 3. Reflex discharges recorded in a ventral root following single shock stimulation of afferent nerve fibers from muscle (record A) and from skin (record B). The monosynaptic reflex discharge, yielding a sharply synchronized "spike potential," is seen only in record A. A small polysynaptic reflex results also from stimulation of the muscle afferent fibers, but is much more prominent following stimulation of the cutaneous afferent. After Lloyd, 1943a.

other neighboring muscles. This proved to be the fact (Lloyd, 1943b), as illustrated by figure 4 wherein one sees, indicated by the break in the tracing, a recording of the afferent volley conducted directly in the nerve from stimulating to recording electrodes, followed after a brief interval by the monosynaptic reflex volley, the reflex nature of which is proved (fig. 4B) by the fact of its disappearance following interruption of the central reflex pathway.

But this was not enough really to establish the monosynaptic reflex pathway as that of the stretch reflex. It was necessary to show that the adequate stimulus (muscle stretch itself) provokes a discharge demonstrably monosynaptic in character. Experiments such as that exemplified in figure 5 provided the requisite demonstration. The uppermost re-

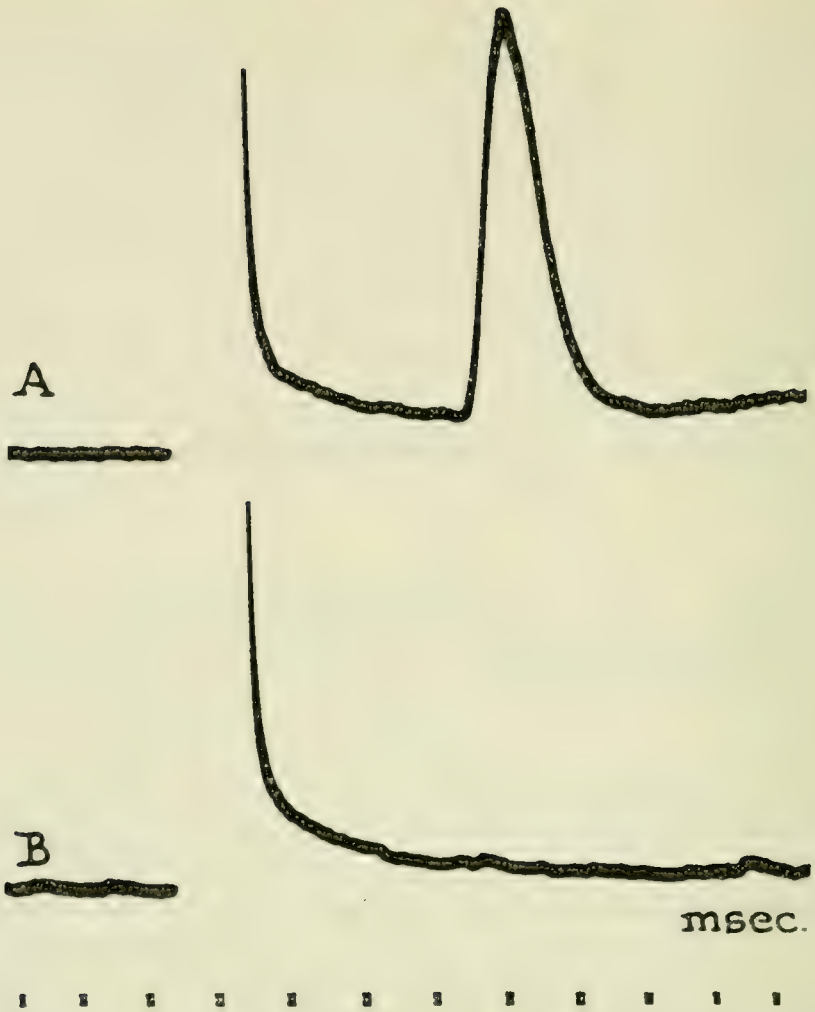

FIG. 4. Reflex result of stimulating and recording from the same muscle nerve. In record A the directly conducted volley is followed, after 4 milliseconds, by a monosynaptic reflex volley. In record B the monosynaptic reflex volley has been abolished following severance of the dorsal roots. After Lloyd, 1943b, 1952.

cording (fig. 5A) contains the afferent response to a brief sudden stretch, comparable to, yet even more restricted in time than, the blow of the physician's reflex hammer upon one's unsuspecting knee-tendon. The next record (fig. 5B) contains a known monosynaptic reflex as it appeared in a ventral motor root in response to electrical stimulation of the afferent path at the exact point from which the afferent response to stretch was recorded. The lowermost record (fig. 5C) contains the stretch-evoked reflex identically recorded. Because the sum of the latencies in the upper two recordings equals the latency in the third, monosynapticity of the stretch-evoked response is proved.

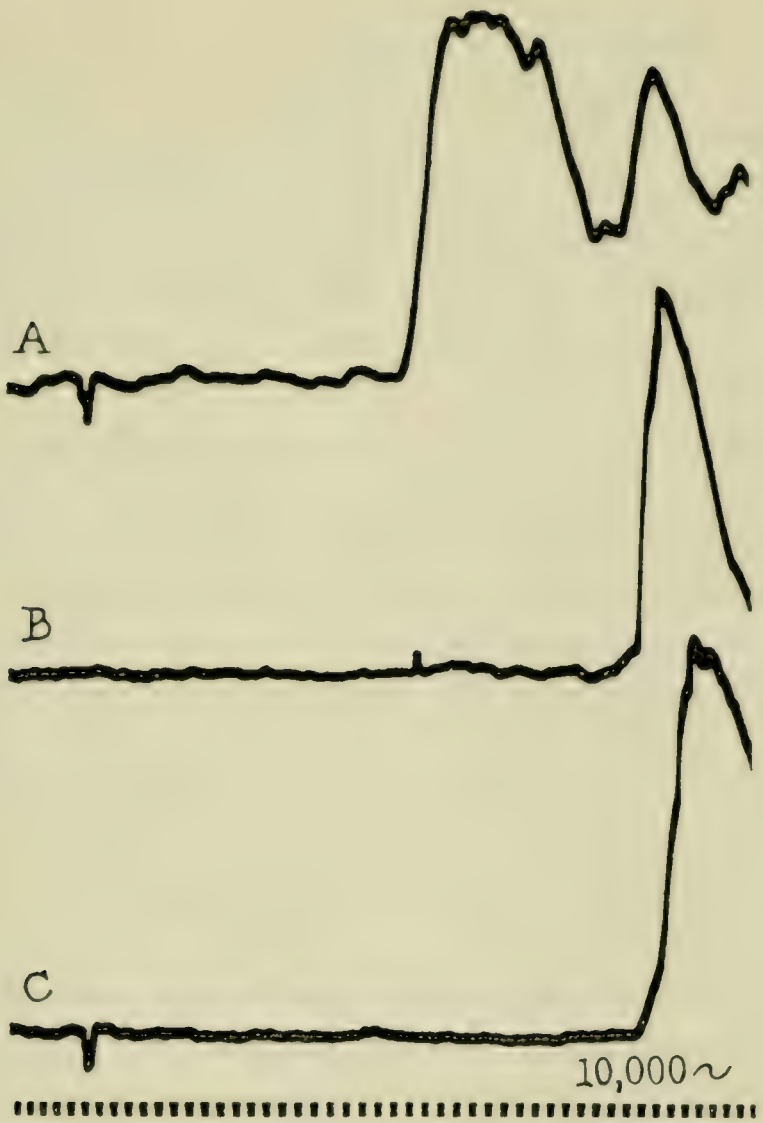

FIG. 5. Proof that the adequate stimulus (stretch) evokes a monosynaptic reflex. Record A, afferent repsonses to stretch of m. gastrocnemius. Record B, known segmental monosynaptic reflex. Record C, monosynaptic reflex response to stretch. The latencies of A and B equal the latency of C, constituting the proof. After Lloyd, 1943c, 1952.

The myotatic unit

Much action takes place within the nervous system that is, in a manner of speaking, "silent" with respect to the external world. Subliminal excitation and inhibition occur at the motor nerve cell, to be revealed externally only by a change in magnitude of some test of the motor nerve cell's excitability. A monosynaptic reflex can be employed to provide just such a test. Being of a certain amplitude when

elicited in isolation, it is increased if subliminal excitation be present, decreased if inhibition be the influence. As Granit wrote in 1950, "The full theoretical significance of the analysis by means of the monosynaptic volley should not be missed. If, for instance, the test shock finds the motoneurons inhibited, then. . . . This inhibition has ultimately by some central mechanism been applied on to the motoneuron itself."

If one searches through the monosynaptic paths of a variety of limb muscles, as, in fact, was done some 12 years ago (Lloyd, 1946a, 1946b), with the use of them in pairs, one to test what change the other might, or might not, have wrought upon the motoneurons it commands, a pattern emerges. Briefly put, if the pairs are derived from two fractions of a muscle, or are full synergists at a given joint, the action of one upon the response of the other is in the direction of increase. There is facilitation of response indicative of excitatory convergence, by time relations demonstrably monosynaptic. The course of facilitation at the motoneuron level is presented in figure 6, plotted in terms of reflex amplitude on the ordinates and time on the abscissae, zero time being set at coincidence of the convergent volleys. Facilitation is greatest when conditioner and test are coincident at the motor nucleus; it diminishes with time in a characteristic manner.

If, on the contrary, the pairs are derived from antagonists at a given joint, the influence, similarly monosynaptic according to the dictates of time (Lloyd, 1941, 1946a, 1946b; Wilson and Lloyd, 1956), is inhibitory. The temporal course of that inhibition is illustrated in figure 7, reflex amplitude again being plotted on the ordinates as a function of time plotted on the abscissae.

Finally, if the pairs have any other relation than those described, their routes through the spinal cord are independent, and no change is wrought by the one upon the other.

The description of these interconnections I have given is

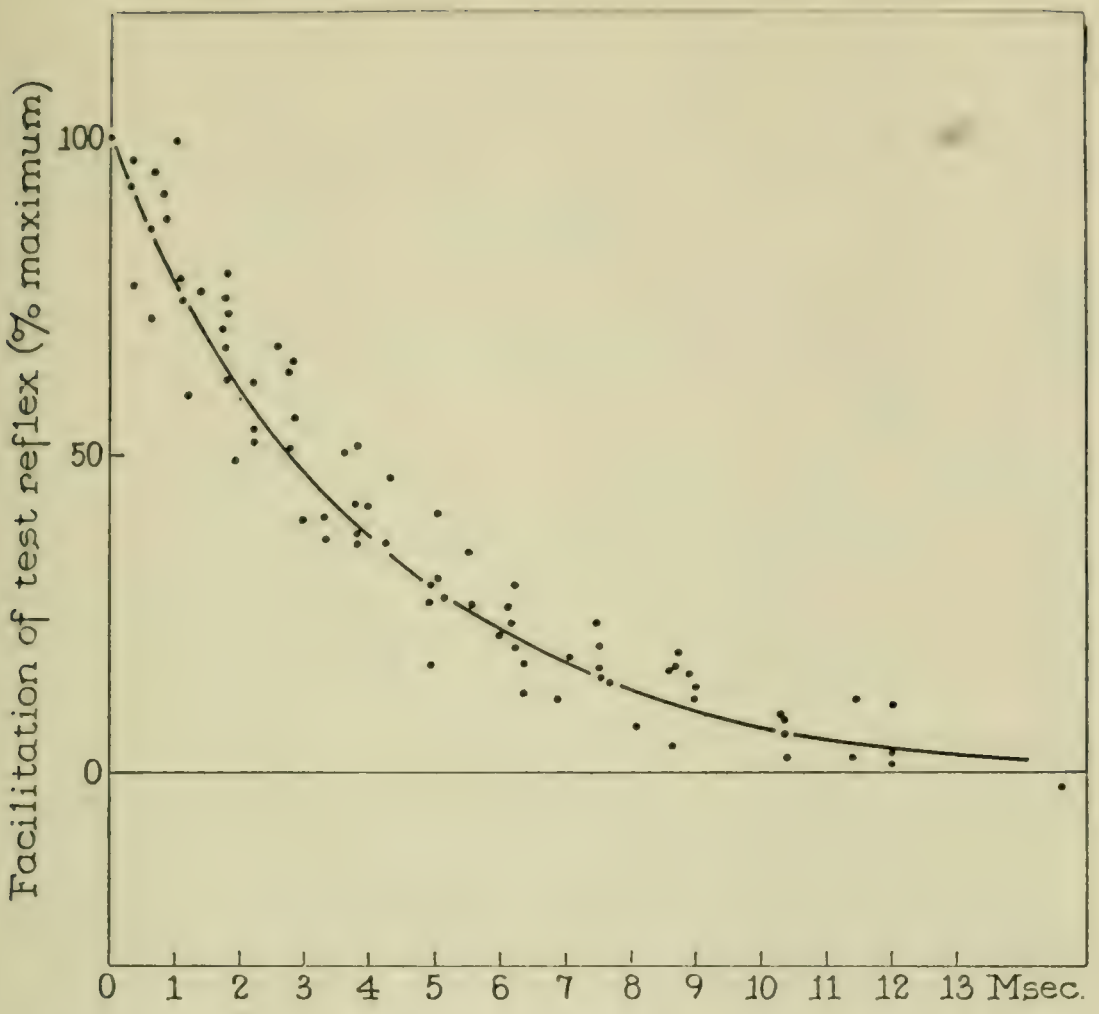

FIG. 6. Temporal course of excitability change (facilitation) caused in a motor nucleus by a synchronous monosynaptic reflex afferent volley as tested by a convergent synergic monosynaptic reflex. From Lloyd, 1946a.

operational; it reveals the facts as experiment discloses them. However, the greater meaning emerges in bolder outline if the facts be restated in different form. A muscle, through its stretch-activated monosynaptic reflex connections, is controlled by itself, by its immediate synergists, and by its immediate antagonists. In turn, through like central connections, that muscle influences its neighbors, synergists, and antagonists. Thus the muscles of a given joint are mutually dependent; nothing in the way of mechanical change can happen to one without influencing the control over the others. In short the muscles of a given joint, together with the monosynaptic reflex connections that bind them, con-

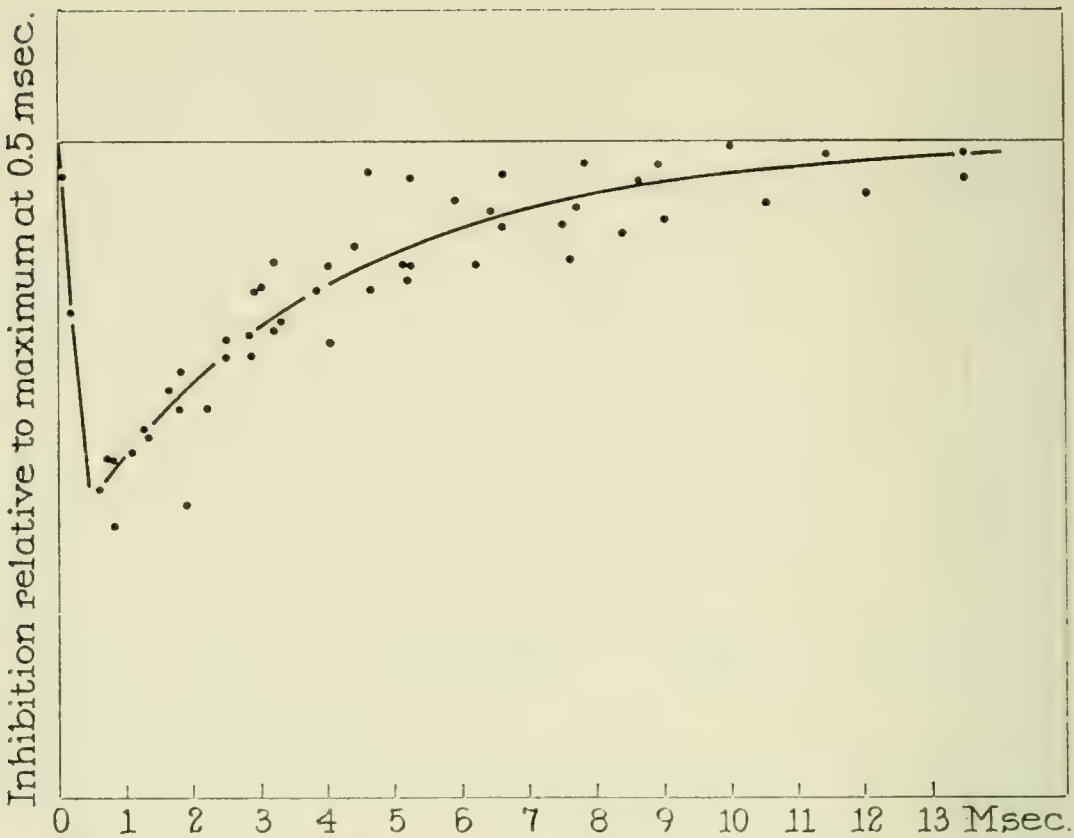

FIG. 7. Temporal course of excitability change (inhibition) caused in a motor nucleus by a synchronous monosynaptic reflex volley as tested by a convergent antagonist monosynaptic reflex. From Lloyd, 1946a.

stitute a unit. This, called the myotatic unit (Lloyd, 1946b), is the elementary unit of postural control.

Mechanism of the lengthening reaction

Mention has been made of the lengthening reaction that in severe stretch comes into opposition to the stretch reflex itself. It too is stretch-activated and in the autocthonous sense is inhibitory. In the intact preparation it finds external expression only because there exists, by the very nature of its origin, an excitatory action, the stretch reflex, upon which it can be written. So in the search after its mechanism, one resorts to the use of monosynaptic reflexes, so useful in revealing the otherwise externally silent actions.

Without entering into great detail concerning the lengthening reaction, one may state that the action upon the motoneuron is exerted disynaptically, which is to say that inter-

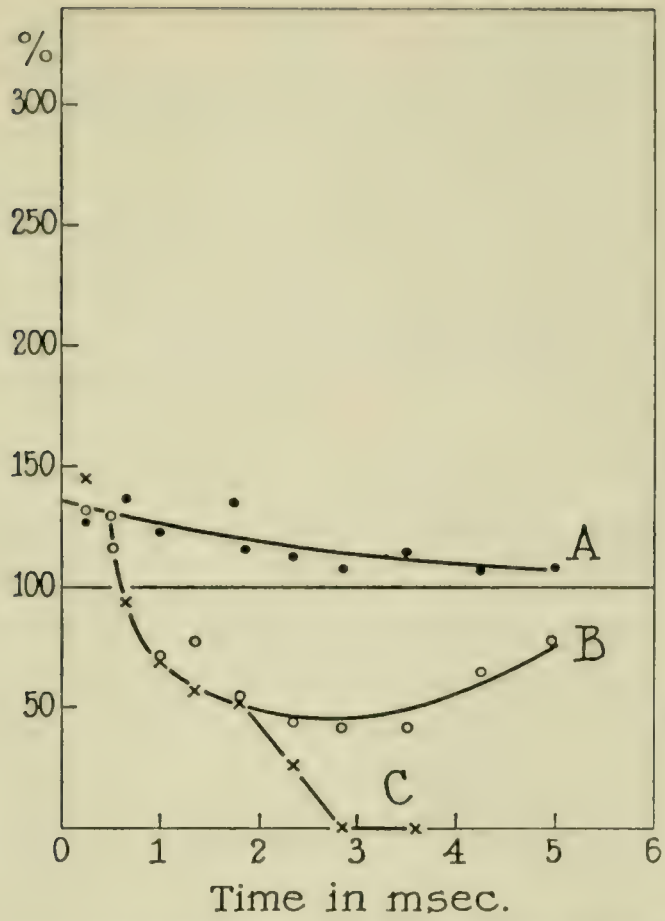

FIG. 8. Excitability changes caused in a motor nucleus by synchronous afferent volleys in incrementing strength. Curve A plots the monosynaptic reflex facilitatory change similar to that seen in figure 6. Curve B shows the disynaptic inhibitory action that is superimposed on the facilitatory change after slight increase in strength. Curve C shows the occurrence of a further inhibitory change after considerable strengthening of the stimulation. This last is, in fact, the inhibitory concomitant of a flexor reflex. From Laporte and Lloyd, 1952.

nuncial neurons, or connector cells as they are sometimes called, are placed between the afferent fibers and the motoneurons (Laporte and Lloyd, 1952). Figure 8 exemplifies the sort of evidence upon which this conclusion is based. Curve A of figure 8 plots the course of monosynaptic stretch reflex conditioning of a synergist test reflex recapitulating, in effect, the experiments illustrated in figure 6. Curve B, obtained with the use of conditioning volleys but slightly enhanced, shows the stretch reflex facilitatory action to be cut off abruptly after approximately one two-thousandth of a second (the time required to pass through an internuncial relay; Lorente de Nó, 1935), there being subsequently a

net inhibition of the motoneurons. The third curve, C, does not concern us at the moment. It is, in effect, a control showing the result dependent upon still further enhancement of the conditioning action. A similar result is to be found whenever action in a pair of synergist muscular afferent channels is combined, and not infrequently the two actions, monosynaptic excitatory and disynaptic inhibitory, cannot be segregated one from the other in the type of experiment under discussion.

Throughout the myotatic unit the action of lengthening reaction afferent fibers is precisely the opposite of the stretch reflex afferent fibers and in all instances equally delayed in time. The lengthening reaction, then, is in reality one part of an integrated pattern of action the totality of which might well be called, according to its nature, the inverse stretch reflex. Intercalation of an interneuron in the inverse myotatic reflex mechanism I believe to be highly significant from a functional point of view, although its functional role in this instance is not one of diffusion of action. I shall return to this question below, but first let us consider the mechanism of flexor reflexes.

Mechanism of the flexor reflex

When, with one's recording electrodes placed upon the nerve to a flexor muscle, one stimulates any other nerve in the vicinity, there appear action potentials indicative of a shower of reflex discharges. Figure 9 illustrates a typical flexor reflex discharge, the afferent limb of the reflex pathway being a cutaneous nerve (the sural, to be specific), the motor limb being the nerve to semitendinosus (a flexor of the knee-joint). The successive records were obtained with the use of stimuli incrementing in strength. Little mensuration is needed to convince one that the discharge was mediated in the spinal cord by polysynaptic connections, or that the multiple, and even the closed, chains of interneurons described by Lorente de Nó (1933), and illustrated diagrammatically here in figure 10, were involved. To the left

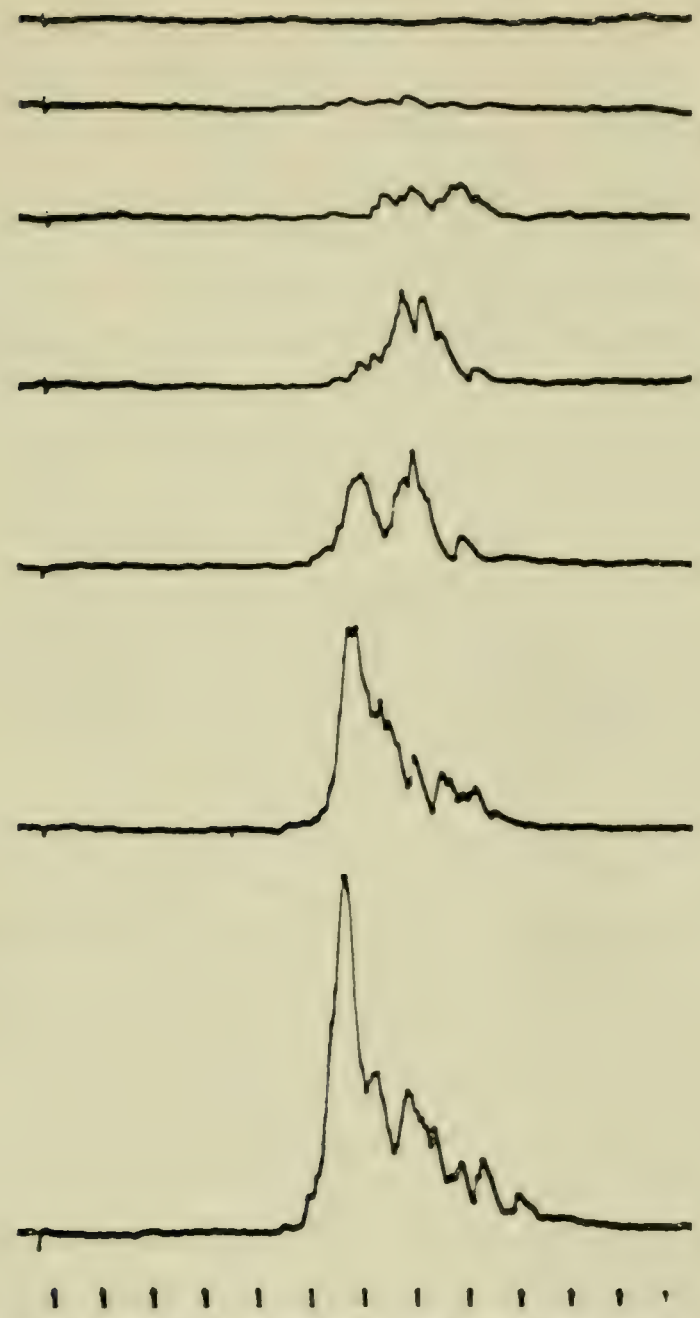

FIG. 9. Typical flexor reflex discharges evoked by afferent volleys of graded intensity. The responses were recorded from semitendinosus nerve following single shock excitations of the cutaneous sural nerve. The topmost record resulted from stimulation at strength below reflex threshold, the bottommost from maximal stimulation for the reflex in question. From Lloyd, 1957.

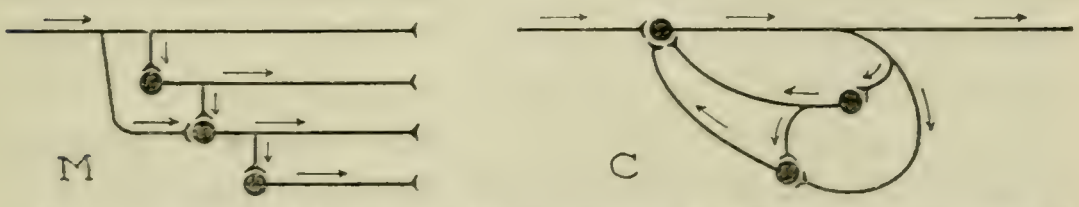

FIG. 10. Diagrams of Lorente de Nó to illustrate the two fundamental types of internuncial circuit. On the left is the multiple chain; on the right, the closed, self-reëxciting chain. After Lorente de Nó, 1938, from Lloyd, 1955.

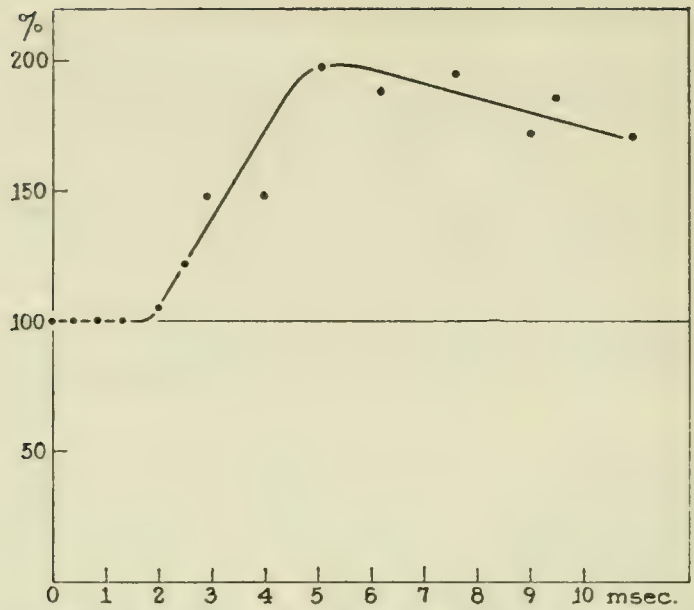

FIG. 11. Excitability change in a flexor nucleus during the course of a flexor reflex evoked by single shock stimulation of a cutaneous nerve. The latent period of some 2 milliseconds proves the minimum flexor reflex pathway to be one of three neurons in series. Modified from Lloyd, 1946b.

of figure 10 is depicted a multiple chain by means of which an action initially synchronous becomes dispersed in time by virtue of passing through neuron chains of different lengths. To the right is depicted the closed self-reëxciting chain. But such a discharge as is seen in figure 9 does not reveal the minimum pathway available to flexor reflex action. To determine this one resorts again to use of monosynaptic reflex tests for change at the motoneuron level. When this is done in a variety of situations, the result in one of which is seen in figure 11, there is always a period in which no change is seen, in duration something less than one five-hundredth of a second, before flexor reflex action is signaled by increase in excitability in the flexor motor nucleus. When an accounting is made of time for conduction and for delay at nerve cell junctions, one cannot avoid the conclusion that the minimum flexor reflex pathway is one of three neurons in series.

If one places recording electrodes upon a number of flexor nerves in the limb, confining the stimulation to a single cutaneous nerve, then discharge is found in greater

or lesser degree in all. The flexor reflex is diffuse, indeed, in its field of action.

In this brief account of several spinal mechanisms I have hoped to show the justification for equating monosynapticity with circumscription of action and polsynapticity with diffusion of action. If it required more than 50 years to validate the physiological inductions of Cajal, it is perhaps not so very surprising that more than 30 years were required to stamp "valid" upon this sentence written in 1911 by Jolly, which I quote: "The relation between the synapse times suggests that the knee-jerk mechanism involves one spinal synapse or set of synapses, while the flexion reflex involves two." And those "synapse times" of Jolly's were off only by a factor of two, which is not by much when one considers the small magnitudes involved, and yet enough, once the synapse time had been measured accurately, to suggest that Jolly's conclusion might not have been correct.

Mass action, giant fiber systems, and internuncial pools

We turn now to more general considerations of neural organization, moving, as it were, from solid ground to shifting sand—from the realm of relative certainty and a measure of proof into one of speculation, uncertainty, and purposivism.

Although some animals may curl up in defiance, presenting a forbidding aspect to some potential marauder, while others adopt protective coloring to prevent detection, it is in general true that animals are equipped for sudden withdrawal and flight away from a source of harm, and in a sense the withdrawal and flight are mass actions. The mechanisms for withdrawal and flight are of interest from an evolutionary point of view. Withdrawal is the more primitive reaction and certainly all that is available to the sessile forms, for example, the sea anemone. Among the free-moving invertebrates there may be localized withdrawal, but the striking action is one of flight. It is among these free-moving forms

that a special system of giant nerve fibers has evolved and, apparently, evolved several times over to serve the purpose of mass action. As one moves up the scale, it does seem rather unlikely that the fish, properly speaking, withdraws from potential danger. Its mechanism, too, is one of flight, but some difference may exist between the squid and the fish, for the fish in flight very clearly uses his ordinary means of locomotion, thrown, as it were, into high gear. But among the higher vertebrates, quadruped and biped, withdrawal and flight are both possible; they are integrated functions and yet separate. Whereas the lobster, or the squid, removes himself forcibly and as a whole, and the fish swims vigorously away, the higher vertebrate need not do likewise. A part may be withdrawn when hurt, with the organism as a whole maintaining its ground. On the other hand it may take to flight, then using, as does the fish, its normal means of locomotion. Two patterns of action are present: one for withdrawal, one for flight. The reflex capabilities of the decapitated cat in this respect were described in a delightful manner by Sir Charles Sherrington (1910) whom I quote, "Under these stimuli and in these forms the flexion-reflex is evidently protective. It is often accompanied by stepping of the crossed hind-limb and, though less commonly, of the other limbs as well, but not of the limb itself stimulated. The irritated foot is withdrawn from harm and the other legs run away."

The flexion reflex of the mammal is often considered to be primitive, for it is in a sense a mass action, and because of its nociceptive character. But it may not be so primitive as it seems at first glance despite these apparent evidences. The truly primitive withdrawal would be the spreading reaction seen in coelenterates dependent in its degree of involvement upon the degree of facilitation in the nerve net. In this withdrawal the extent to which "local sign" is in evidence varies roughly inversely with the stimulation, ultimately to disappear altogether with maximal withdrawal.

This is a fact observable by any small boy who has watched and played with anemones along the rocky shore. The anemone, of course, cannot take flight. A flight mechanism based upon a giant fiber system is an evolutionary development grafted upon the primitive withdrawal system. In it there is no local sign. The central giant fibers of the lobster, for instance, connect at each segment directly with motor giant fibers. If a central giant fiber is active, all the motor fibers become so, and a resulting mass flexion of the tail serves for rapid escape. Interestingly enough, and I suppose to confound the argument, the lobster's close relative, the crab, has lost its motile tail, has no giant fiber system, and must scurry off on eight of his 10 legs, which, to judge by the ghost crabs, he does very successfully.

The giant fiber system is carried over into the chordates. *Amphioxus* apparently has no localized movements. The axons of its giant fibers course backward from the anterior part of the body and forward from the posterior part. Young (1950) suggests that stimulation at the oral end would cause *Amphioxus* to retreat into the sand, and at the caudal end to emerge and escape. This may represent local sign of a sort, although it is in fact nothing more than what the squid achieves by altering the angle of its funnel.

As a generalization, the giant fiber system begins to disappear as more elaborate mechanisms of locomotion develop that can, among other things, take over the functions of flight. But then animals are left without a withdrawal mechanism. This latter develops anew, apparently, as legs are developed, and it is unlikely to be the direct descendant of any withdrawal mechanism that went before.

The main features of the withdrawal mechanism of higher vertebrates, in particular mammals, that makes use of the highly organized internuncial systems are the fixity of pattern and the degree of local sign that are exhibited. Presumably the entire flexor-directed internuncial system of the region is reached by afferent action consequent upon

hurtful stimulation, but the action is distributed throughout the system according to patterns, rather than spread through it, as occurs in the coelenterate. All parts are not equally affected even by the strongest afferent influx. The point is nicely exemplified by table 1, which is taken from

TABLE 1

(After Creed and Sherrington, 1926, from Creed *et al.*, 1932.)

AFFERENT NERVE	HIP FLEXOR (TENS. FASCIAE FEM.)	KNEE FLEXOR (SEMITENDINOSUS)	ANKLE FLEXOR (TIBIALIS ANT.)
Internal saphenous..	100	56	87
Popliteal (Tibial)...	3 or less	42	100
Peroneal (distal to Tib. Ant. N.).....	14	100	69

the classical work of Creed and Sherrington (1926) on concurrent contraction in flexor muscles. One sees that stimulation of the saphenous nerve produced its greatest flexor reflex response in the hip flexor, whereas stimulation of the tibial nerve was almost, but not quite, ineffective at the hip while producing its greatest effect at the ankle. Finally, stimulation of the peroneal was most effective at the knee-joint. From this one can appreciate the fact that hurtful stimulation at various loci on the limb will cause the limb to assume different final positions. Fixity of pattern and local sign, then, are the key distinctions between the primitive withdrawal mechanism that was lost in evolutionary advance and that which was gained at a later stage. From the point of view of mass action in reflex performance it is the fact of local sign that differentiates the primitive mass action system of the giant fibers and the finely integrated mass action of an internuncial system.

Other functional roles of interneurons

In addition to their well-established roles as distributors of action in the nervous system, the interneurons may serve other important needs of an integrative mechanism. The

surface of the motoneuron is limited (Eccles, 1957, estimates it at 5×10^{-4} cm^2), and the motoneuron is the final common path upon which all the myriad influences ultimately must play, either directly or indirectly, if they are to find any expression in the external world. In this vein I digress, but only slightly, to express this thought in the words of Sir Charles Sherrington (1924), "These, the skeletal muscles, are the motor machinery for all that life of the animal which the older physiologists were wont to call the 'life of external relation.' Of the importance of that life of external relation the moralist has written that even in man the crown of life is an action, not a thought. Should we demur to this distinction, we can still endorse the old adage that to move things is all mankind can do, and that for such the sole executant is muscle, whether in whispering a syllable or in felling a forest." I would add to this only that muscle awaits the command of the motoneuron, and faithfully executes that command when given.

As the nervous system has advanced along the road of evolution, the influences multiply, as do the tracts that mediate them, all aiming at the motoneuron already encrusted with synaptic knobs—those points of contact for the delivery of excitatory and inhibitory direction. How can all these new influences be accommodated? On the one hand the old order could break down, leaving room for the new. This would imply that the nerve cell origins of the synaptic knobs covering the motoneurons might differ, for instance, in cat and in monkey, which in fact they do. On the other hand influences of like sort, in terms of their ultimate action upon the motoneuron, could converge upon an interneuron, making of it a common path of communication to the motoneuron and greatly alleviating the space problem on the motoneuron surface. The notion that is advanced is depicted diagrammatically in figure 12, in which a large number of sources of influence is represented by fibers convergent upon an interneuron which in turn connects to the motoneuron at

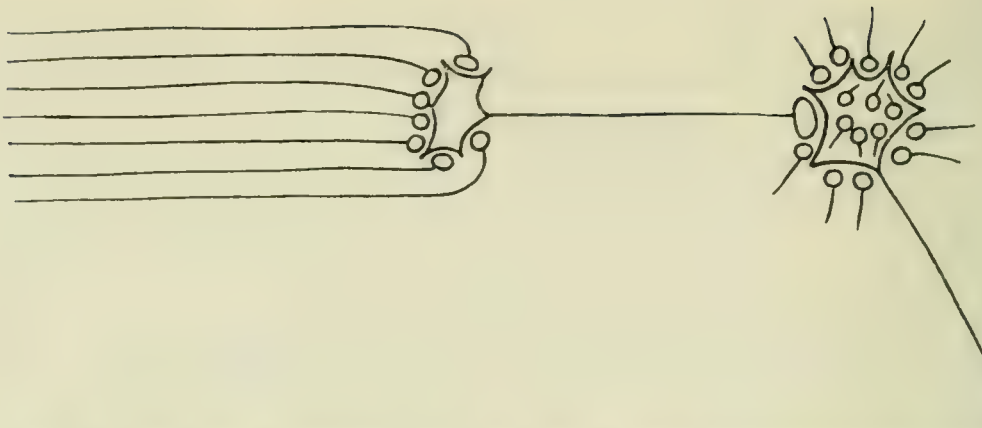

FIG. 12. Diagram to indicate the manner in which interneurons serve as a focus of convergence and, by acting as a common path for a variety of influences, reduce the spatial requirements on the soma surface of motoneurons.

the right already heavily encrusted with fibers from yet other sources. The pyramidal system, from one point of view, might exemplify this function of interneurons, for in its development it serves as the common path to the motoneuron for willed movement. Convergent upon it are those influences that culminate in its direction to the motoneurons to execute the desired movement.

Another function with which interneurons have been endowed is that of changing the nature of chemical transmitter at a given step of a neural pathway. In its original form the hypothesis was proposed by Feldberg (1950) who, noting that the pyramidal tract and dorsal roots were low in choline acetylase, while the enzyme was abundant in motoneurons and other cell masses in which these paths terminate, suggested that cholinergic and non-cholinergic neurons alternate in series.

More recently Eccles (1957), mindful of Sir Henry Dale's suggestion that it is unlikely that different branches of one and the same neuron would elaborate different chemical transmitters, and supposing that a single transmitter substance could not have both excitatory and inhibitory functions at different loci, has proposed that an interneuron should be intercalated into the monosynaptic inhibitory path, the interneuron having no function other than that of

switching from an excitatory transmitter to an inhibitory transmitter. This is not the occasion to follow all the finely spun argument advanced to support Eccles' assumption or the chain of evidence against it. Sufficient to say that it is not a necessary assumption (Grundfest, 1957) and that the most careful study of time relations precludes the possibility that there is an intercalated interneuron in at least some of the inhibitory connections. So, at best, this proposed function of interneurons is highly controversial.

One final function for interneurons is deserving of mention. It is what might be called "the valve action." To illustrate this, one returns to consideration of the stretch reflex and the lengthening reaction, with their respective monosynaptic and disynaptic pathways shown in figure 13. Not enough difference exists between the stretch threshold of

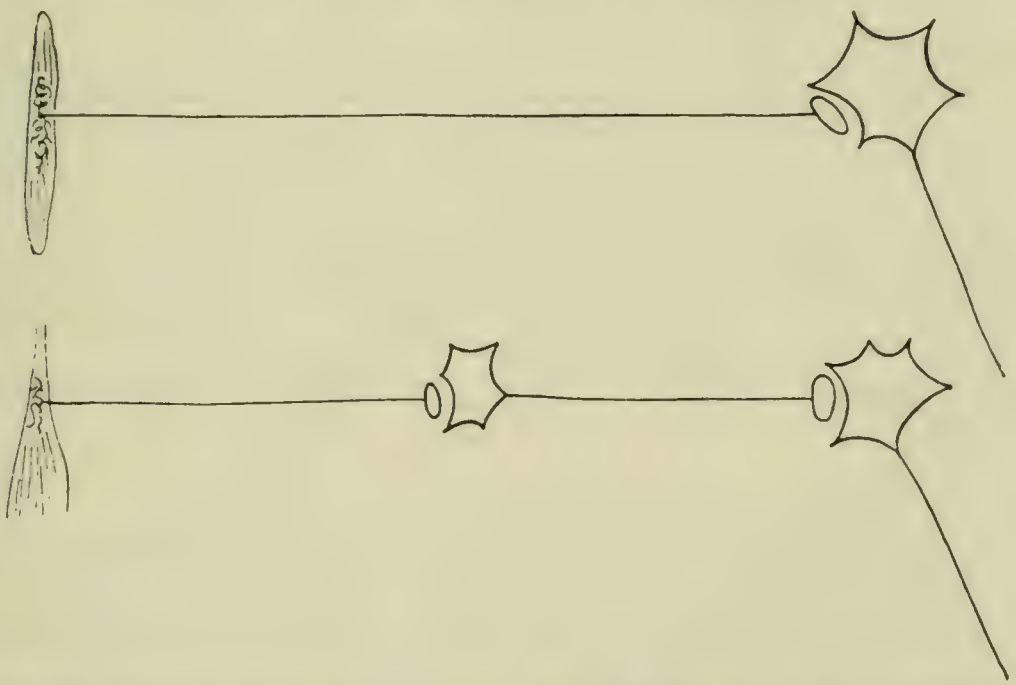

FIG. 13. Diagram of the monosynaptic reflex pathway from muscle spindle afferent fiber to motoneuron (above) and of the disynaptic reflex pathway from Golgi tendon organ through an interneuron to motoneuron (below). Somatic reflex action inevitably involves tension changes in muscle, which means that myotatic afferent impulses inevitably arise, and, because of the direct connection to motoneurons, these last inevitably are influenced. Thus myotatic reflex activity plays a part in all reflexes of the intact animal. On the contrary, inaction of the interneuron, as by inhibition, leaves the motoneuron free from influence. The interneuron thus can act as a valve.

the muscle spindle, afferent end-organ for the stretch reflex, and that of the tendon organ, afferent for the lengthening reaction, to account for the great difference in reflex threshold of the two reflex effects in the decerebrate animal. Furthermore, in the spinal animal, it is the inhibition of the lengthening reaction rather than the excitation of the stretch reflex that is the presenting feature (Henneman, 1951), unless one is dealing with highly synchronized brief stretch, in which case the excitatory impulses, so to speak, beat out the inhibitory impulses in point of time.

That stretch excitation of autocthonous motoneurons is present at all degrees of stretch follows from the fact that monosynapticity of action implies inevitability of action. That the inhibition may dominate in the spinal animal and yet be held in check in the decerebrate means that the internuncial link of the disynaptic path is open in the former and closed in the latter. This, indeed, is the action of a valve. It would seem that there is, collateral to the stretch reflex pathway, a connection, inhibitory in character, to the internuncial relay of the lengthening reaction, which holds the latter in abeyance until such time as the input from tendon organs becomes overwhelming. For these responses to be coördinated in appropriate manner, it is essential that an interneuron be present in the pathway for the lengthening reaction.

Monosynapticity as an evolutionary development

Because all that is neural in the central nervous system, save the primary afferent projections and the motoneurons, is internuncial in character, it is self-evident that proliferation of the interuncial system is a cardinal feature in evolution of the human brain. This means that there has been an enormous increase in complexity of the liaison between perception of, and action in, the external world. Coupled with this is the suggestion by implication that directness of connection is therefore primitive. If we compare the giant fiber

systems for flight (paradigms of directness) with the elaborate flight mechanism of higher animals, the point would, indeed, seem well taken. But if we were to explore a less obvious facet of evolutionary development we might find just the opposite to be true. Indeed, there is some evidence to suggest that short-latency, direct connection to motoneurons stands at the very pinnacle of evolutionary development of the nervous system.

The monosynaptic reflex pathways so highly developed in the cat (Lloyd, 1943a) and in man (Hoffman, 1918; Magladery and others, 1952) are present only in a rudimentary form in the frog, and have not been seen to be capable of transmission even with the most massive afferent input, although many have observed the slow potential change, a post-synaptic potential so-called, indicative of monosynaptic connection. An example of this is presented in figure 14. In recording from a ventral root of the frog while stimulating the dorsal root of the same segment, one finds a blaze of late

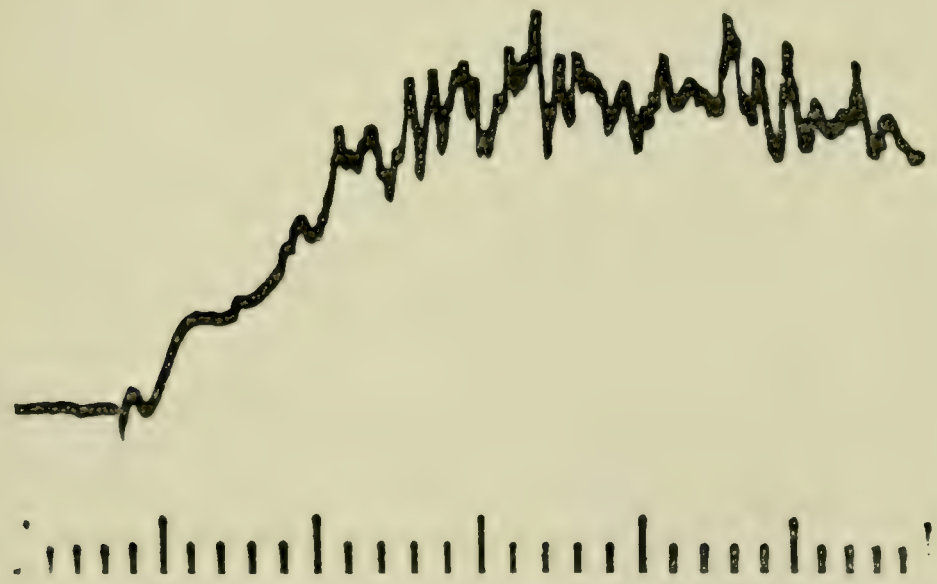

FIG. 14. Synaptic potential and reflex discharge of bullfrog motoneurons in a segmental reflex. The potential change beginning 1 millisecond after stimulation bespeaks the presence of monosynaptic reflex connections of a sort, however, that do not give rise to reflex response. It is probable that this results from the fact that the primary afferent connections are located on the motoneuron dendrites rather than on the cell body. Time 1 and 5 milliseconds. From an unpublished experiment of D. P. C. Lloyd and A. K. McIntyre, University of Otago, Dunedin, New Zealand.

reflex discharge (proof that stimulation has engaged all the myelinated afferent fibers), and yet in the monosynaptic reflex position, at the beginning of electrical change, there is no reflex, the only indication of connection being the above-mentioned subthreshold excitatory potential.

But it is in consideration of the pyramidal system that we find the strongest evidences of the preëminent role of direct connection. The cat possesses a pyramidal tract for encephalized control of its musculature, all the fibers of which end not upon motoneurons, but rather in the internuncial pools from which activity is relayed to the motoneurons (Lloyd, 1941b). When watching a cat in action, one may see it fanning the toes, extending the claws to scratch, flexing the paw, and so on, all mass movements of the sort to be expected, in the light of present-day knowledge, of action mediated through an internuncial pool.

The monkey, on the other hand, has the ability to move its fingers in a discrete manner, and it is in this animal that we find, in the studies of Bernhard, Bohm, and Petersen (1953), for the first time physiological evidence for the existence of direct connection from pyramidal tract to the motoneuron.

Thus in both stretch reflex pathway and in the primate pyramidal system the emergence of a short-latency, direct connection seems to be correlated with the emergence of a discrete, finely localized control over motor performance. Interesting it is, indeed, that in its first evolution the direct connection from ganglionic mass to motoneuron should be a mechanism for superimposing a massive diffuse action upon actions of a more or less local nature, whereas in its second evolution it should be precisely the reverse, a mechanism for superimposing discreteness of action upon a nervous system geared to mass actions. In assessing the importance of this recurrence in a new form of a system of direct impingement upon the motoneuron, let us not forget that it is the possession of discrete control of his fingers and op-

posable thumb that has made man the forger of tools to forward his own destiny and the player of musical instruments for the soothing of his soul.

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THE HERITAGE OF THE HUMAN BRAIN

Heritage means inheritance. In this sense the present discussion pertains to the heritage of the human brain. However, the term "heritage" has another, more pertinent definition in phylogeny. It takes me back to the days when I was exposed to the dramatic world of evolution and the paleontology of the vertebrates here at the American Museum of Natural History by Professor William K. Gregory. To this master (1951), the heritage characters are the older, basic, conservative, and deep-seated traits in an organism. The heritage characters reveal the true place of an animal within the orders, classes, and families of the animal kingdom.

The human brain is the product of a long phylogenetic history. The past resides in the fabric of its structural and functional components. In this presentation I would like to discuss the possible evolution of some of these components. The elements selected include some with "long" phylogenetic histories and others with relatively "short" phylogenetic histories. Because many of these examples also apply to other units of the brain, some specific points will illustrate principles with a broader scope and significance. In addition a glimpse into this history will indicate that the human brain is a product of both "old" and "new" elements.

Background statement

The vertebrates have a recorded history of over four hundred million years (fig. 1), back into the Ordovician period when the oldest vertebrates, fish of the Class Agnatha (lampreys and hagfish are living examples), first ap-

peared in the fossil record. The Class Placodermi of fish appeared during the Silurian period and became extinct by the end of the Paleozoic era. The Class Chondrichthyes (cartilage fishes, including sharks and rays) and the Class Osteichthyes (bony fishes, including carp, trout, and flounder) were first found in the fossil record in the Devonian period. The fish that left the water gave rise to the Class Amphibia (living frogs and salamanders) during the late Devonian. The Class Reptilia appeared later in the Carboniferous period. During the first half of the Mesozoic era is found the first fossil evidence of the Class Aves (birds) and the Class Mammalia (warm-blooded, hairy animals). The orders of mammals were all established by the Paleocene period approximately 60,000,000 years ago. The evolution of all eight classes of vertebrates took place over a

Eras	Periods or Epochs	Approximate Time Since Beginning, in Millions of Years
Cenozoic	Recent	[About 20,000 years]
	Pleistocene	1
	Pliocene	10
	Miocene	25
	Oligocene	35
	Eocene	50
	Paleocene	60
Mesozoic	Cretaceous	120
	Jurassic	150
	Triassic	180
Paleozoic	Permian	210
	Carboniferous	270
	Devonian	300
	Silurian	330
	Ordovician	420
	Cambrian	510

FIG. 1. The geologic time scale.

tremendous span of time, during which the brain and the other organs had the opportunity to undergo a multitude of changes.

A characteristic of phylogeny is the persistence of change that continuously takes place in the successions of living organisms. The alterations result in change of complexity and modification of the subsequent and surviving forms which replace their antecedents. The procession of families, genera, and species within each of the eight classes throughout geologic time persisted until today's living vertebrates represent the culmination of prior evolution. Many forms became extinct. Some living fossils persist, such as the reptilian *Sphenodon*, a relic of the Permian, and the mammalian hedgehog and opossum, survivors of the Paleocene. Other living fossils also exist.

One of the grand expressions of the complexity and diversity of animal forms is the concept of adaptive radiation expressed by Henry F. Osborn, a former President of the American Museum. This concept implies the exploitation of the ways of life by organisms that utilize the opportunities that occur. Accompanying this invasion into the many ecological niches are the changes that occur within the organisms themselves. The source of this expression within the organism are genetic mutations, while many of those that persist have survival value. The interactions between the species and their environment express themselves in change and diversity. I am utilizing this concept to interpret the phylogeny of the brain, although this concept is usually applied to organisms.

Why stress these established concepts, which are obvious to any student of evolution? The fact is that these concepts are overlooked by some unwary biologists, including neuroanatomists. A list of living mammals arranged in order of a sequence of structural differences has been interpreted as having phylogenetic significance, although it may have no

relation to the true phylogenetic position of the mammals. The "sequence" may in reality be an expression of adaptive radiation. For example, the number of uncrossed nerve fibers in the mammalian optic chiasma is correlated primarily with the location of the eyes (adaptive radiation) rather than with the phylogenetic position of the animal (see The Visual System, below). A mistaken notion of the relation between two mammals may be indicated by a statement such as, the cow and horse are closely related, when, in fact, these species are in two distinct orders (the former in the Artiodactyla and the latter in the Perissodactyla) the common ancestry of which is probably in the Paleocene when the orders of mammals were established.

The basic outlines of the phylogenetic tree have been worked out by the astute analyses of the fossil record by paleontologists. For obvious reasons it is difficult (impossible in most cases) to interpret the evolution of soft tissues from the direct fossil record. In a remarkable study, Tilly Edinger (1948) reconstructed the outlines of the evolution of the horse's brain from fossil brain casts and was able to draw a number of penetrating conclusions from this study. One such conclusion was that the surface anatomy of the brain of *Eohippus* (dawn horse) was similar to that of the common opossum—a living fossil.

However, for interpretations of the phylogeny of the brain, great reliance must be placed on a judicious selection of living forms and the utilization of living fossils. It is really a game of selecting controls out of nature's vast experimental design. In essence the successful reconstruction of the evolution of the brain requires the selection of animals that represent critical stages. One complication is that a "living fossil" may retain a multitude of primitive characters, but the one in question may be modified. For example, although the insectivores are living representatives of basic mammalian stock, the poor sight in many con-

temporary insectivores (mole and shrew) may be a regression. After this warning, I may fall into this trap.

Units under discussion

To illustrate the heritage of the human brain, I have selected several functional units of the nervous system. These include (1) the visual system, (2) the pyramidal system, (3) the reticular system and the lemniscal systems, and (4) the cortex of the cerebrum (fig. 2).

The visual system is a structurally compact sensory system with a long phylogenetic history. The pyramidal (corticospinal) system is a structurally compact motor system with a relatively short phylogenetic history. The reticular system is a diffuse, yet organized afferent and efferent system with a long phylogenetic history, and the lemniscal systems are structurally compact systems with phylogenetically new additions. The cortex of the cerebrum is the gray mantle of the cerebrum, of which portions have long phylogenetic histories and other portions, short phylogenetic histories.

The prefossil vertebrates

The vertebrates that preceded those in the fossil record developed or evolved from forms that possessed a cephalocaudal (head-tail) orientation and a bilateral symmetry. How this occurred is a matter of speculation, but the results are a matter of record. A constellation of general receptors (pain and so forth) and specialized receptors (smell, sight) were grouped at the head end. Along with this the brain differentiated in the central nervous system. A series of decussations and commissures (nerve cells with their cell bodies on one side and axons that cross the midline to the opposite half) apparently developed in the central nervous system as a mechanism for correlating the activities of the two halves of the body.

Two other fundamental morphologic features were ap-

parently established early in vertebrate evolution: (1) Blood vessels invaded the central nervous system and became intimately related to the neural elements of the brain and spinal cord. This feature is present only in chordates of all the animal phyla (von Bonin, 1950). (2) Three fundamental divisions are present in the brain of all vertebrates; prosencephalon (telencephalon and diencephalon), mesencephalon, and rhombencephalon (metencephalon and myelencephalon). Within these structures are the substrates from which the brains of all the vertebrates evolved throughout the more than four hundred million years of vertebrate phylogeny.

THE VISUAL SYSTEM

Man is a member of the primate order—an order which is difficult to characterize because of its many primitive features. However, two basic primate characters are the coordination of a well-developed visual sense and varying degrees of manual dexterity (Simpson, 1949).

Let us turn our attention to a consideration first of the visual system.

In most vertebrates, sight is the dominant sensation. The visual system is a window to a narrow band of radiation which creates a sensory awareness and a mental reaction. To the biologist, the sensory response is the crucial point. The significance of vision in man can be gauged from the fact that, of all the nerve fibers entering or leaving the central nervous system, more than one-third are in the optic nerves. Whereas the fibers of the optic nerve number over a million, those of the auditory nerve, in contrast, contain approximately thirty thousand fibers.

Let us examine the optic chiasma (figs. 2 and 4), the site of decussation of the fibers of the optic system. Walls (1942) claims that there is "no discernible reason for any [type of crossing, including the optic chiasma]—they apparently just

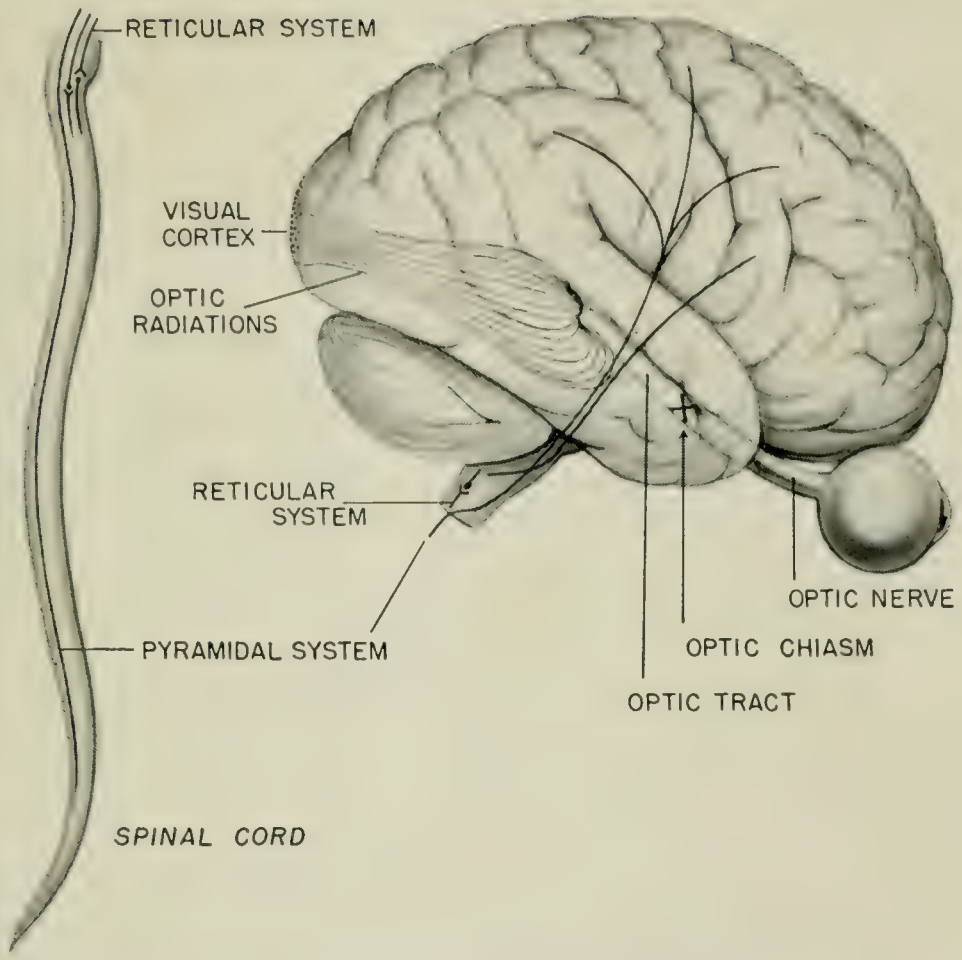

FIG. 2. The brain and spinal cord of man. Among the functional units of the nervous system discussed in the text are: (1) the visual system, represented by optic nerve, optic chiasma, optic tract, optic radiations, and visual cortex; (2) the pyramidal system—a motor system with a widespread cortical origin; (3) the reticular system, present throughout the central nervous system, represented by synaptic symbols indicating its multineuronal and multisynaptic nature; and (4) the cortex of the cerebrum which in man is folded into sulci and gyri.

happened . . . and became genetically fixed. . . ." Because chiasmas and commissures are frequent in the central nervous system of all vertebrates, they must have more than just chance significance. Possibly in primitive forms they may have been a chance affair associated with genetic mutations. Viewed pragmatically the crossing over was retained because it had biological and survival value to the organism. Ramón y Cajal's (1911) explanation is as brilliant and effective a hypothesis (Polyak, 1957) as has been advanced.

In reality there is no way of proving why crossing over occurred. In essence Cajal felt that the reaction to light, acting as a noxious stimulus to a prevertebrate, resulted in a withdrawal of the rostral end away from this stimulus. Hence the visual impulses were most effectively utilized in the economy of the organism by crossing to the opposite side. By the time the brain evolved, the decussation of the visual fibers was complete. In order to execute coordinated avoidance responses in a bilaterally symmetrical body it was necessary for the organism to relay the visual impulses to the musculature of the same and opposite side—hence the recrossing of the motor system. As a result, decussations have been retained.

Another explanation by Cajal for the optic decussation is indicated in figure 3. The fields of vision, which are represented by the arrows, are reversed by the lens of the eye. The result is that the projection on the retina is inverted. If each eye is stimulated by only part of the field, then the panorama of the field in the brain will not be reproduced accurately if the optic pathways do not decussate (fig. 3A) and will if the optic pathways do decussate (fig. 3B). Ovio (1927), who disagrees with Cajal's interpretation, claims that the entire field is projected to each eye and hence the presence or absence of a decussation is immaterial (fig. 3C and D). However, in laterally directed eyes Cajal's figures are probably correct. Because the early forms in which the

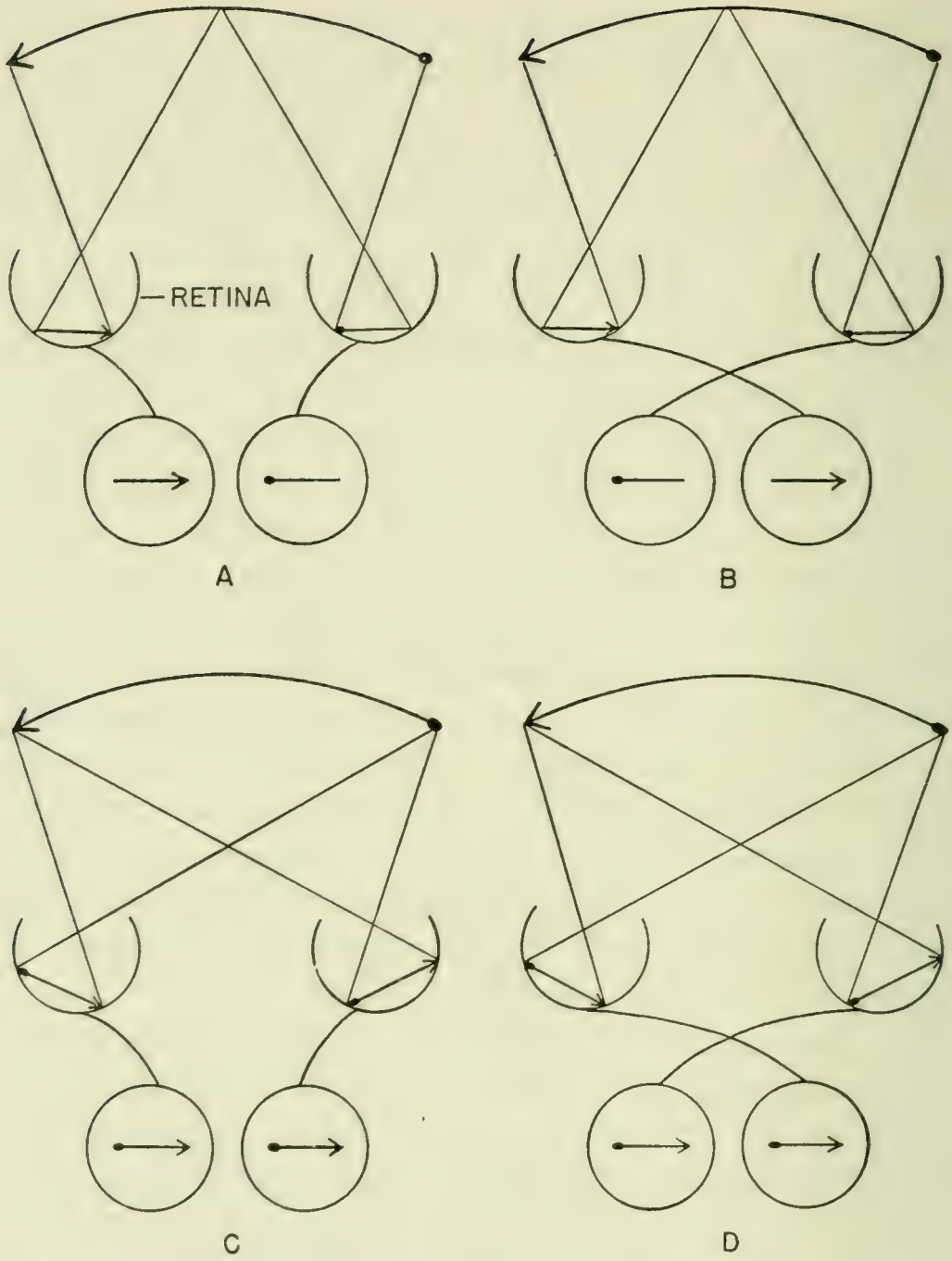

FIG. 3. Explanations for the original role of the optic chiasma in lower vertebrates. The arrow above each eye represents the field of vision (the panorama of the environment), and the arrow on the retina is the projection of the field inverted by the lens. A disparity of the projection of the panorama to the central nervous system exists if the optic pathways do not cross over (A) and no disparity exists if they cross over (B), according to Ramón y Cajal (1911). There is no disparity of the projections to the central nervous system, according to Ovio (1927), whether the optic pathways decussate (C) or not (D).

decussation arose are lost in antiquity, the experimental testing of these theories is impossible.

In all non-mammalian vertebrates (fishes, amphibians, reptiles, and birds) all the fibers of the optic nerve cross over in the optic chiasma. On this basis we may conclude that the total decussation of optic fibers in the optic chiasma is a heritage character that was probably established in the early vertebrates and has persisted in all non-mammals.

In most mammals some of the visual nerve fibers passing through the optic chiasma are uncrossed (Polyak, 1957). The number of uncrossed fibers varies from none in the primitive primate *Tupaia* (a tree shrew) to almost one-half of all optic fibers in man and higher primates. There are only a few, if any, uncrossed optic fibers in the Cetacea, insectivores, and rodents. Approximately one-twentieth of the fibers are uncrossed in the rat, one-sixth to one-eighth uncrossed in the horse, one-fifth uncrossed in the common opossum, one-fourth uncrossed in the dog and Australian bushy tailed opossum, one-third uncrossed in the cat, and one-half uncrossed in the higher primates and man (fig. 4). This character of having both crossed and uncrossed fibers in the optic chiasma resides exclusively in mammals and is called the Law of Newton, Müller, and Gudden (Walls, 1942). The uncrossed components are the axones of retinal ganglionic cells on the temporal (lateral) side of the retina (fig. 4). This is the area of the retina that receives its photic stimulation from the environment in front of the animal. Further analysis indicates that a close relation exists between the degree of frontality of the eyes and the proportion of uncrossed fibers. The animals with the most laterally placed eyes have from none to a few uncrossed fibers, and the animals with frontally directed eyes have the greatest proportion of uncrossed fibers. In brief, the number of uncrossed fibers is related to the size of the field of vision where there is overlap between the two eyes. The conclu-

sion is that the uncrossed components are an expression of adaptive radiation correlated to the degree of frontality of the eyes. It is highly possible that no uncrossed components were present in the optic chiasma of the basic mammalian stock. Hence the uncrossed components arose independently in the different mammalian orders.

The presence of both crossed and uncrossed fibers in the optic chiasma and optic tract (fig. 4) has parallels in other afferent (sensory) systems in man—for example, the auditory system and the vestibular system. In the auditory pathways, the crossing over occurs in the trapezoid body, which is in a way the equivalent to the optic chiasma, while the crossed (predominant number) and uncrossed fibers form

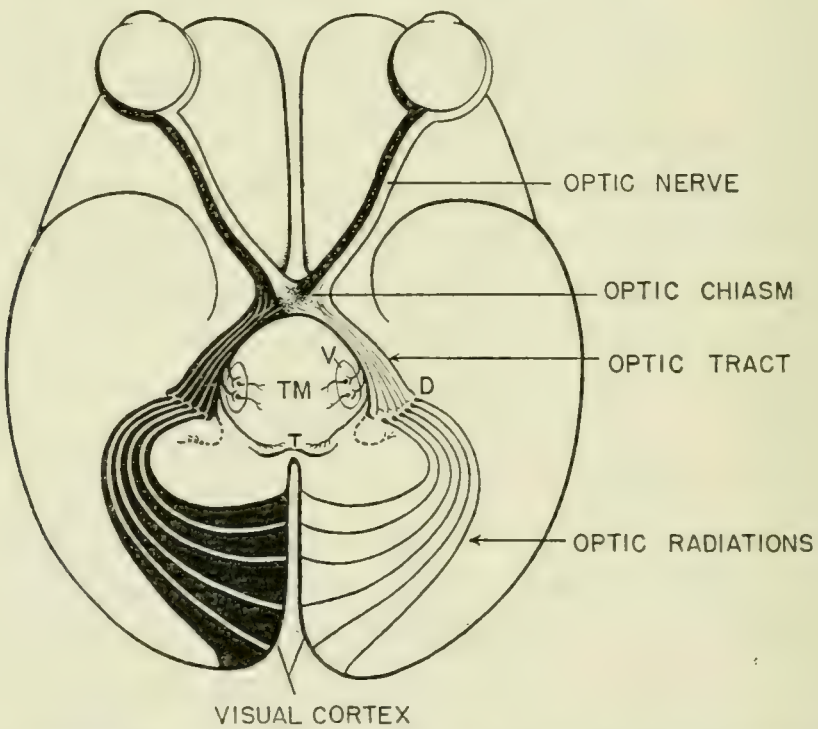

FIG. 4. Diagram of human visual system. Note that the fibers originating from the lateral (outer) half of each eye do not cross over in the optic chiasma, whereas the fibers originating from the medial (inner) half of each eye cross over in the optic chiasma. Because the lens inverts the fields of vision, the image that projects to the lateral halves of the eye comes from the fields in front of the eye. *Abbreviations:* D, dorsal division of lateral geniculate body; T, tectum of midbrain (specifically, superior colliculus); TM, tegmentum of midbrain; V, ventral division of lateral geniculate body. See text for explanation; figure adapted from Polyak (1957).

the lateral lemniscus, the equivalent to the optic tract. The data on the relative number of crossed and uncrossed fibers of the lateral lemniscus in other animals are virtually unknown (owing to inherent technical difficulties), so that it is not possible to make even a tentative statement of the phylogenetic history of the relative proportions of crossed and uncrossed components. The vestibular pathways within the central nervous system are also composed of both crossed and uncrossed components.

Regeneration of the optic nerve

The quality of the regeneration of the optic nerve is of comparative neurological interest. When a nerve of the peripheral nervous system of an adult vertebrate is transected, regeneration of the severed fibers may occur, with good function recovery. This does not apply to the severed nerve fibers of the central nervous system of some vertebrates. With the optic nerve as an example of a fiber tract of the central nervous system, let us take a synoptic view of its regenerative potential in some vertebrates. Among the technical reasons why the optic nerve is classified as a central nervous system tract are the absence of neurilemma (Schwann) cells, the presence of meningeal sheaths (pia-arachnoid sheath and dura mater) investing the nerve, and the fact that its nerve fibers are of the second order.

The optic system in teleost fishes (five marine and two fresh-water species from five different families) has the capacity to regenerate and to restore vision after the optic nerve is completely transected (Sperry, 1955). Data on the quality of regeneration of the optic nerve in any cyclostomate and cartilaginous fishes are not available.

When the optic nerves of frogs and salamanders are severed, excellent regeneration and visual recovery occur—possibly exceeding those in the teleosts. The plasticity of regeneration of the optic system in the frog is illustrated

by an experiment by Sperry (1951). A normal frog or a frog with regenerated optic nerves (following transection) was able to capture a flying fly with the tongue by the visuomotor coordination of body, head, and tongue. A frog with regenerated optic nerves in which the eyes were rotated through 180 degrees at the time of transection was unable to capture a flying fly. Its visuomotor coordination was directed to the right instead of the left (or vice versa).

The paucity of data on the regeneration of the optic nerve in birds and reptiles is such that no preliminary statement can be made concerning the regenerative potential in these two classes of vertebrates.

If the optic nerve of man and other mammals is transected, its fibers degenerate and do not regenerate, even if the blood supply remains intact (Polyak, 1957). Some fibers of the central nervous system of adult mammals will regenerate following their transection and will regain their electrophysiological properties (several papers *in* Windle, 1955), but unequivocal functional return has not been demonstrated.

The phylogenetic implications of the regeneration of the central nervous system are speculative, as the problem has been investigated in only three of the seven living vertebrate classes. A cautious conclusion can be made that in the mammals the potentiality for regeneration is present in at least some fibers of the central nervous system. It is possible that the poor regeneration in the mammalian central nervous system is not due primarily to the lack of an inherent regenerative capacity of its nerve cells, an old heritage, but rather to other factors that prevent, inhibit, or block regeneration.

Tectum of the midbrain

In the midbrain is located the tectum, an important central station of the visual system (fig. 4). This structure is

the chief central end station for "psychic" vision and visual reflexes in the inframammalian classes of vertebrates and in some "lower" mammals.

In man and "higher" mammals, the "visual" tectum (superior colliculus) is associated mainly with the light reflex (pupillary constriction) and accommodation (figs. 4 and 5). The phylogenetic path taken by the primates and man is essentially one in which the psychic aspects of visualization shift from the tectum to the cerebral hemispheres by what is known as encephalization (migration of functions to higher levels). The result is that (1) the tectum becomes smaller and retains the centers for light and accommodation reflexes, (2) a shift occurs in the relative sizes of the dorsal division and ventral division of the lateral geniculate body of the thalamus (fig. 4), and (3) the cerebral cortex assumes paramount significance (figs. 2, 4).

Encephalization

A living animal that in its way stands near the start of the road of encephalization is *Tupaia,* a Malayan tree shrew that is classifiable as an intermediate form between the insectivores and the lemurs. *Tupaia* may be considered to represent a key form at the base of the primate stock—a living fossil.

Tupaia resembles the inframammals by having (1) an optic chiasma that contains only crossed fibers, (2) a tectum that is the dominating mechanism in the optic reflex arcs and in the visual psychic perception, and (3) a large ventral division of the lateral geniculate body. *Tupaia* foreshadows the higher primates by having (1) a dorsal division of the lateral geniculate body and (2) a visual cerebral cortex which is but slightly differentiated.

Encephalization has two anatomical aspects because in evolution the thalamic nuclei and the cerebral cortex are functionally closely related, especially as the lateral genicu-

late body relays the optic impulses to the primary projection areas of the cerebral cortex. Hence encephalization can be subdivided into diencephalization (lateral geniculate body is a nucleus of the thalamus which is a division of the diencephalon) and into corticalization (refers to cerebral cortex). Although we are discussing the optic system at this time, this concept also applies to other sensory systems such as the auditory system and the general sensations of pain, temperature, and touch in their various manifestations. These systems during phylogeny are also associated with an increasing functional role of the thalamus and the cerebral cortex.

The ventral division (pregeniculate nucleus) of the lateral geniculate body is relatively large in inframammals and in "lower" mammals, including *Tupaia.* In the higher primates this ventral division is quite small. This division is concerned with motor reflexes, for it relays impulses to the midbrain tegmentum (fig. 4). This mechanism predates the thalamo-cortical connections (Herrick, 1948).

The dorsal division of the lateral geniculate body (fig. 6) is not only small in *Tupaia* but has only three laminae of cells. In the lemurs the division is larger and has the typical "higher" primate pattern of six laminae. This stratification of the geniculate body is associated with the perfection of the primate visual system.

A concept that may have phylogenetic validity was suggested by Herrick (1948) on the basis of some comparative neurological data. In the "lower" forms such as urodeles, the optic terminals are widely dispersed to many structures of the brain stem and the explanation of this spread "is to be sought on motor side of arc." In the "higher" forms there is segregation of the optic terminals until in the primates the psychic visual pathways (retina to lateral geniculate body to cerebral cortex) relay in a point to point projection, and, as stated by Clark (1943), "there is no possibility

that these impulses can be disturbed and modified 'en route.'. . . The cerebral cortex receives retinal impulses in a remarkably pure and unadulterated form."

Corticalization is associated with the acuity and higher faculties of sight in the mammals. The primitive mammalian soricid shrews have no visual cortex, while *Tupaia* has a cortical area that is not the typical visual (striated) cortex. The lemurs and true monkeys have a cyto-architecturally definable striated cortex which is located mainly on the lateral surface of the occipital lobe. In the "higher" monkeys, great apes, and man, this striated cortex gradually becomes located primarily on the medial surface of the occipital lobe (figs. 4 and 6). This medial "migration" is actually an accommodation to the increasing size of the cerebral hemispheres in the primates and is not a true migration.

From a functional viewpoint, corticalization is associated with the transference of visual perception from the tectum to the cerebrum. In the rabbit and rat encephalization has proceeded so that lesions of the tectum give no visual defects (Ghiselli, 1937), but the transference is not completely corticalized, for a rat with the visual cortex ablated loses pattern vision but is not blind. The ablation of the striated area in the cat, dog, or monkey results in an animal that has no object vision but can still perceive light and dark (Marquis, 1935; Klüver, 1941). They are aware of shadows passed over the eyes. The chimpanzee and man have no light perception when the striated cortex is totally lost.

The principle of encephalization also applies to other sensory systems as well. In man corticalization has not progressed so far in the general senses as in the visual sense. Cortical loss does not completely abolish pain sensation, for example. The crude general senses (pain, temperature) are largely subcortical sensations, and acute senses (weight discrimination, stereognostic capacity) are cortical sensations.

An increase in corticalization has taken place in the phylogenetic sequence of monkey, great apes, and man.

THE PYRAMIDAL SYSTEM

The pyramidal (corticospinal) system is a motor tract that projects from a large area of the cerebral cortex, passes through the pyramid of the medulla, and terminates in the spinal cord (fig. 2). It has a role in the performance of skilled movements. As the tract is present only in mammals, it is phylogenetically a new tract.

In this discussion, I am omitting any reference to the relation of the pyramidal tracts to the supplemental motor areas, to the secondary motor areas, and to afferent input. Instead I wish to concentrate on only one point—an interpretation that explains the variability in the extent and location of this motor tract as an expression of adaptive radiation.

The following information is reviewed by Lassek (1954). There are wide anatomical variations in different mammals as to the position, length, cross sectional area, and fiber count of this tract. A constant feature is its identical course in the brain stem (fig. 5).

Short pyramidal tracts are presumed to be present (Marchi technique) in such diverse mammals as the opossum (Order Marsupialia), rabbit (Order Lagomorpha), guinea pig (Order Rodentia), pangolin (Order Photidota), bat Order Chiroptera), mole, hedgehog (Order Insectivora), sheep (Order Artiodactyla), and mule (Order Perissodactyla). The tract extends the entire length of the cord in the rat and mouse (Order Rodentia), cat and dog (Order Carnivora), and monkeys, apes, and man (Order Primates). The tract is located in the posterior funiculus in most rodents, in the anterior funiculus in the mole and hedgehog, and primarily in the lateral funiculi in carnivores and primates (fig. 5).

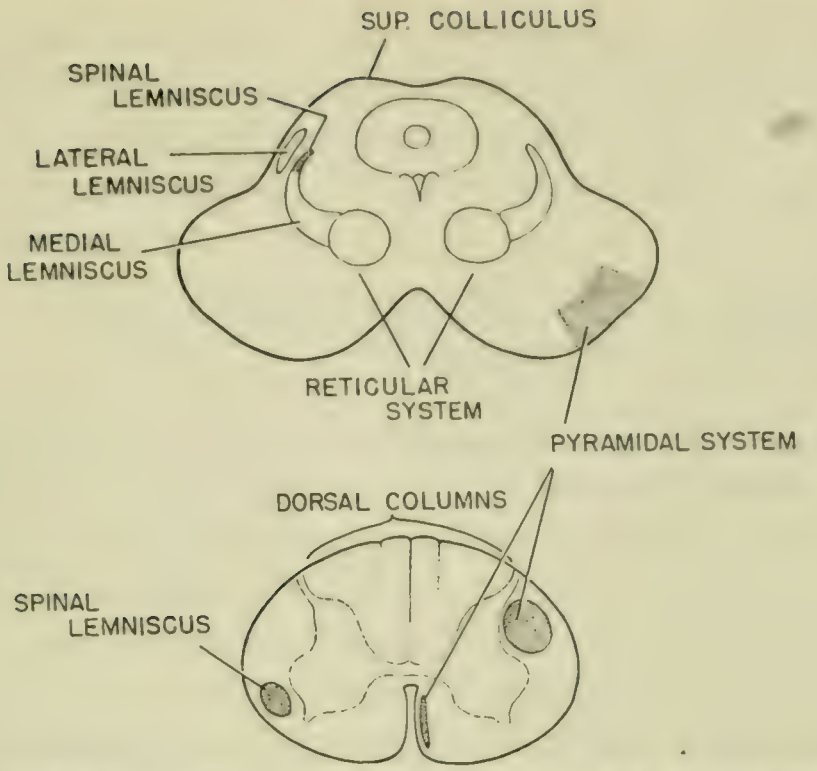

FIG. 5. Cross sections of the human mesencephalon and the spinal cord (lower figure) to illustrate the location of several structures. The upper part of each figure is the dorsal aspect. The lemniscal systems include the spinal lemniscus (pain, temperature, and light touch, also called spinothalamic tracts), the medial lemniscus and dorsal columns (touch and proprioception), and the lateral lemniscus (audition). Part of the reticular system is located in the midbrain. The superior colliculus is associated with the light reflex.

According to Lassek (1954) no correlation exists between the number of fibers present in this system with the size or the weight of an animal or to the ability of mammals to perform skilled movements. It is likely that more data will be forthcoming on various anatomical aspects of this system in many mammals when some of the newer experimental techniques, such as the Nauta-Gygax method, are applied.

To find a phylogenetic interpretation for these and other data on this diverse series of living mammals, Lassek uses phrases such as "as we go up the phylogenetic scale."

A more logical interpretation is that its variability in extent and location in the spinal cord of different mammals is another expression of the principle of adaptive radiation. In view of the fact that each mammalian order has an inde-

pendent origin in the Paleocene, it is likely that from a common location in the brain stem of the early mammals the pyramidal system expressed itself independently in the various orders of mammals during their subsequent evolution.

THE RETICULAR SYSTEM AND THE LEMNISCAL SYSTEMS

The phylogenetically old integrator of the central nervous system is known as the reticular system (figs. 2 and 5). It is present throughout the neuraxis—spinal cord, brain stem, and cerebral cortex. Some parts of it are called the reticular formation or the central reticular core.

The lemniscal systems include some of the long tracts of the central nervous system (fig. 5). A lemniscus is generally considered to be an ascending tract, with its nucleus of origin in the spinal cord or lower brain stem and its terminus in the brain stem and thalamus, and as transmitting a sensory modality or several related sensory modalities (Herrick and Bishop, 1958). A case could be made for broadening the definition and concept of the lemniscal systems to include all long tracts that are now excluded, including those to and from the cerebellum and motor tracts such as the pyramidal tract.

The reticular system may be characterized as the multineuronal, multisynaptic, diffuse, non-specific, and phylogenetically old system. The lemniscal systems may be characterized as the oligoneuronal, oligosynaptic, compactly organized, specific, and phylogenetically relatively new systems.

Let us quickly interpret these terms. A multineuronal, multisynaptic, and diffuse system implies that relatively many nerve cells (neurones) and synapses are diffusely organized and interposed between the site of the initial stimulus and the site of terminus. Although the neuro-anatom-

ical organization appears as a reticular network under the microscope, the reticular system has well-organized patterns (Scheibel and Scheibel, 1958). An oligoneuronal, oligosynaptic, and compactly organized system implies that relatively few nerve cells, relatively few synapses, and a compact bundle organization are present in each unit of these systems. The lemniscal systems are specific in that their ascending pathways conduct impulses of specific modalities of the senses—pain, temperature, touch, vibratory sense, audition, and so forth (fig. 5). The non-specific character of the reticular system is associated with the concept that the ascending portion of the system is important in exerting a generalized influence on the cortex, with the resulting arousal or wakefulness (Magoun, 1958). The stimulus is not of a specific modality, although the specific pathways do send collateral fibers into the reticular system.

The reticular system is old phylogenetically in that it is present in all the living vertebrates, while the lemniscal systems are more prominent in the higher vertebrates (Herrick and Bishop, 1958).

In a broad sense the afferent pathways of the reticular system include the ascending reticular pathways (Nauta and Kuypers, 1958) and the efferent (motor) pathways, including the extrapyramidal system (reticulospinal tracts). In the salamander (Herrick, 1948; Herrick and Bishop, 1958; Kappers, Huber, and Crosby, 1936) are found several lemniscal systems in which the segregation of the functional systems is incipient. They are associated with cutaneous sensibility, low-grade auditory and vestibular proprioceptive fibers, and proprioceptive function (dorsal spinal lemniscus, lateral lemniscus, visceral-gustatory lemniscus, and others).

In the mammals, especially primates, the lemnisci are prominent and compact. These mammalian lemnisci are probably derivatives of lemnisci similar to those present in the salamander and have been modified by the addition of

more fibers and more refined modalities. In man these tracts include the spinal lemniscus (pain and temperature), dorsal columns (tractus gracilis, tractus cuneatus), medial lemniscus (touch, proprioception), and lateral lemniscus (audition). (See fig. 5.) These tracts as well as the pyramidal tract in a sense bypass the reticular core (Bishop, 1958).

The relation of the reticular system and lemniscal systems to the heritage of the human brain is significant. In 1934 Herrick summarized the significance of the neuropil in the evolution of cerebral structure. The neuropil is the dense felt-work of fibers in the central nervous system—in other words, the network of the reticular formation. "The neuropil is the mother tissue from which have been derived both the specialized centers and tracts which execute the refined movements of the local reflexes and the more general web which binds these local activities together and integrates the behavior." A plausible concept is that the diffuse neuropil (reticular formation) is probably the primordial network, while the long compact tracts have been formed by a concentration and functional modification of neuropil fibers during evolution. The nuclear patterns (cell bodies of nerve cells) of the brain-stem reticular formation have phylogenetic implications. The small reticular cells are more numerous in the mammals than in lower forms. This morphological evidence supports a concept of the "greater" functional significance of the reticular system in mammals as compared to lower forms. Special nuclear groupings of the reticular cells are found in all vertebrate classes, with the possible exception of the Amphibia. These nuclei are formed as a response to the influence of various stimuli (neurobiotaxis), for during phylogeny and ontogeny these cells frequently migrate to and concentrate in other portions of the brain stem (Kappers, Huber, and Crosby, 1936). This suggests that the nuclear patterns of the larger cells express an adaptive radiation related to functional

requirements. The general patterns of nuclear organization are discussed by Kappers, Huber, and Crosby (1936), Olszewski and Baxter (1954), and Noback (1959).

Another indication of an ancient heritage in the human brain is found in the descending tract of the trigeminal nerve (pain and temperature from head), the tractus solitarius (taste and visceral senses), and the descending vestibular tracts. These tracts, which are formed by the root axons of some cranial nerves, descend in the brain stem of mammals. After synapsing many of these systems ascend to higher levels. In the salamander, for example, the root fibers of the afferent cranial nerves bifurcate into ascending branches and descending branches (Herrick, 1948). In mammals and man the descending tracts just noted are probably the retention of the descending branches found in the ancestral vertebrates. Incidentally, the intrinsic neurones of the reticular system in mammals have axons that bifurcate into long ascending branches and long descending branches (Scheibel and Scheibel, 1958).

Although the lemniscal systems are well developed in man and the primates, the large extent of the reticular system in these forms indicates that the integrative function of the latter system is probably not subordinated during evolution. The prominent lemniscal systems in man and the primates are associated functionally with more refined modalities and anatomically by some myelination (Herrick and Bishop, 1958). One consequence of phylogeny of the primates especially has been the shift from the generalized stereotyped activity of the "lower" vertebrates to more emphasis on skilled non-stereotyped activities. The lemniscal systems play a role in this phylogenetic trend in the primates.

THE CEREBRAL CORTEX

The human cerebral cortex is probably the most intricate and complex structure in the animal kingdom. It is respon-

sible for our biased anthropomorphic thinking. I can discuss here a few facets of this structure.

The cerebral cortex of mammals is divisible into the paleocortex, archicortex, and neocortex (figs. 2 and 6). A discussion of synonymous and subsidiary terminology, which abounds in the literature, is beyond the scope of the present paper.

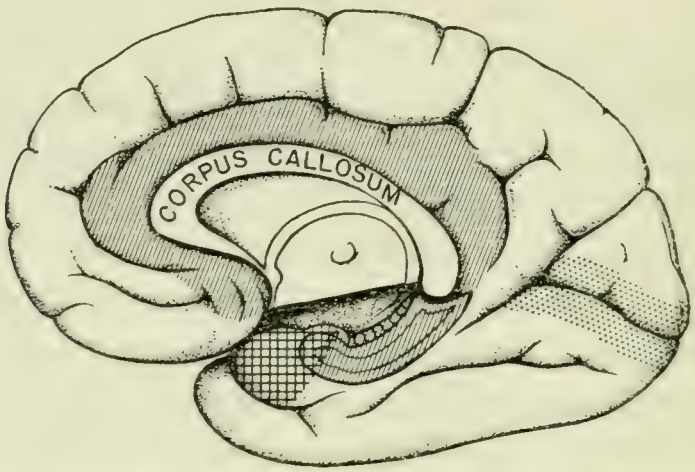

FIG. 6. Medial surface of human cerebral hemisphere. Outlines of the archicortex (parallel lines), the paleocortex (cross hatched), and the neocortex (unstippled) are suggested. The archicortex above the corpus callosum is called the mesocortex. A portion of the archicortex is exposed by a partial dissection. The visual fibers from the lateral geniculate body are projected to the visual cortex (stippled).

The paleocortex and the archicortex are present to a greater or lesser degree in all living vertebrates. In the primates, they form a ring around the diencephalon and corpus callosum. Together they are referred to as the rhinencephalon (smell brain), the limbic lobe of Broca, visceral brain, or the allocortex. In a word, it is the old cortex with a history of over 400,000,000 years. It persists in man, and although it is overshadowed by the large neocortex, the allocortex has considerable size, especially the archicortex. Its basic function, which is only superficially understood today, is in the realm of smell, emotion, and visceral autonomic activity.

The paleocortex is associated with smell, and its stimula-

tion in the intact cat evokes actions related to feeding, sniffing, chewing, and salivation. The archicortex (specifically hippocampus) is not related to smell, as is indicated by the fact that it is present in such mammals as the anosmic dolphin and whale. In 1937 Papez implicated this structure and others in this region as the central mechanism for emotional expression. On the basis of stimulation and ablation experiments by Klüver and Bucy (1939) and others in cats and monkeys, the relation of these regions to some phases of emotion is on a firm footing. When the hippocampus was stimulated an animal showed signs of fear, anger, or fury, and its facial expression was transformed to one of attention, surprise, anxiety, or bewilderment. When the temporal lobe and hippocampus were ablated bilaterally in monkeys and cats (Klüver-Bucy syndrome), wild and vicious animals were transformed into tame and fearless animals. Such monkeys would touch snakes that would normally have produced intense fright and terror. The heritage of this old cortex persists in man and affects our daily lives.

The neocortex makes its initial appearance in the reptiles (Crosby, 1917; Kappers, Huber, and Crosby, 1936), but it is in the mammals that the neocortex blossoms out as a dominant structure of the brain. Small-brained mammals have smooth cortices (lissencephalic brains) and large-brained mammals have cortices with gyri and sulci (gyrencephalic brains). The presence of gyri and sulci, fissuration, is explained by Baillarger's law of folding compensation. Fissuration is a method by which a large brain retains the balance between the volume of the cerebral cortex and that of the subcortical cerebral structures. To increase its volume, the cortex expands in area as the square (not by greater thickness), while the subcortical structures expand as the cube. The differences in the linearity of the sulci are, in part, related to the size of the brain. As the brains in a "phylogenetic" series increase in size, the linear contours

of the sulci on the cerebral surface change. Within the primate order the small-brained lemurs have a series of longitudinally oriented sulci, and the medium-sized brains of the monkeys have a series of transverse and arcuate-shaped sulci (Tilney and Riley, 1928). The large brains of the great apes and man have a complex fissural pattern.

Many orders have animals with cerebral sulci and gyri—all large-brained animals including elephant, horse, cow, whale, cat, and man. No completely gyrencephalic order of mammals exists, as all orders arose from small-brained lissencephalic animals (Edinger, 1948). The early fossil horse (*Eohippus*) and the primitive living primates have smooth cortices. The implication is that the game of trying to compare fissures in different orders such as the ansate coronal sulcus in the cat with the central sulcus in primates has doubtful significance. Comparing functional cortical areas in animals of different orders is defensible. There is a general relation between body size and brain size, especially in related mammals. The brain size in turn has a relation to degree of fissuration. Although this relation holds, it is not absolute. Edinger (1948) has demonstrated that, in the Eocene horses, a slight increase in body size was accompanied by a large increase in brain size. In the Oligocene horses, on the other hand, the increase in body size was accompanied by only a slight increase in brain size.

During phylogeny the new parts of the brain, such as the neocortex, have become more prominent as compared to the older parts, such as the small allocortex. "However, such phylogenetic changes as have been analyzed appear to follow simple laws of relative growth so far as rates are concerned and can usually be correlated, by rather elementary mathematical procedures [small allometric growth curves], with the over-all size of the brain" (Harman, 1957). Ontogenetically this also applies to the growth of parts of the human brain (Noback and Moss, 1956).

In the phylogeny of the human brain from the insectivores (the basic mammalian order), a number of trends are apparent. The living insectivores are characterized as small-brained mammals with a relatively large allocortex, a relatively small neocortex, a visual integrating mechanism in the tectum, and a stereotyped motor response. As we progress "up the scale" of primates (lemurs, monkeys, anthropoid apes, and man) there is a progression of changes. The allocortex becomes relatively smaller and the neocortex relatively larger. In neocortical evolution, psychic perception and interpretation of vision are encephalized. This is correlated with the importance of vision, for in the primates visual discrimination is associated with the lively exploratory drives and its associated coordination with the useful hand. At the other end of the cerebrum is the prefrontal lobe cortex. Primates are socially inclined and have family bands and bonds. The prefrontal lobe plays its role in this area, for, in man, many of our social values and drives hinge on this area. It is here that a balance is struck between caution and uninhibited expression and the fact that ultimate goals are fabricated. It is the region of the day of the prefrontal lobotomy (Mettler, 1955).

In the phylogeny of the primate cortex, there is a progressive shift as the stereotyped motor activities of the more primitive mammals are modified by the ascendancy in the neocortex of influences that result in some release from stereotyped movements. The relative freedom of the hand with its opposable thumb is but one example. The pyramidal system is one mechanism in this release.

The nerve cell is the morphological substrate of the cortex or any other structure. A significant fact is that the cerebral cortex of mammals has a characteristic cellular pattern despite variations in cell number, cell form, and size. "What remains constant is the arrangement of the plexuses of dendritic and axonal branches, i.e. of the synaptic articulations

through which nerve impulses are transmitted" (Lorente de Nó, 1949). The cellular elements added, in the "higher" mammals, especially man, are tremendous numbers of cells with short axons (intracortical cells). Quoting again from Lorente de Nó, "Cajal assumed that the large number of cells with short axons was the anatomical expression of the delicacy of function of the brain of man. At present this assumption is almost a statement of fact."

SUMMARY

1. The brains of the vertebrates display a remarkable diversity of structure and of function. It is probably the most plastic structure in the animal kingdom.

2. The heritage of the long phylogenetic history of the vertebrate brain resides in the fabric of the structural and functional components of the human brain. (a) The nerve fibers that cross over in the optic chiasma have their counterparts in all the vertebrates. This old heritage goes back over 400,000,000 years. (b) The uncrossed nerve fibers in the optic chiasma are found only in the mammals. This new heritage goes back probably less than 60,000,000 years. (c) The coordinating mechanisms associated with the reflex patterns of the eye persist in the tectum of the human midbrain—an old heritage. On the other hand, the substrates for visual perception have shifted to the lateral geniculate body and cerebral cortex (encephalization)—a newer heritage. (d) The pyramidal system, which plays a significant role in the motor activity of the human hand with its opposable thumb, is found only in mammals—a newer heritage.

3. The integrating mechanisms of our basic drives such as sleep and emotion reside in the reticular system and the allocortex of man. These mainsprings have a long phylogenetic history—an old heritage.

4. The cellular substrates of the long lemniscal systems,

concerned with specific sensory modalities, and the neocortex—newer heritages—are probably derived from the older multineuronal reticular system.

5. An expression of the interaction between the "old" cortex and the "new" cortex occurs in certain epileptic seizures in a man who passes through a state of confusion (paleocortex) and has a moment of speech difficulty (neocortex).

6. The concept of adaptive radiation is demonstrated by diversity of certain structures in the nervous system. Three examples in the mammalian brain include: (a) The number of uncrossed fibers in the optic chiasma is not related to the phylogenetic position of the animal but rather to the degree of frontality of the eyes. (b) The variability in the location and extent of the pyramidal system in the spinal cord in different forms can be readily explained as a system evolving from a common base but expressing itself in a different way in each order. (c) The fissural patterns in the cortex of different orders of mammals arose independently of one another because all orders arose from smooth-brained (lissencephalic) animals.

7. Nature is not static. Although man's evolution of the past 200,000 or so years has been due primarily to the aids of civilization (Shapiro, 1957), the human brain, if man survives, will probably continually change over the millions of years to come. This past seems to attest to this concept.

8. The stanza of William King Gregory (1951) in his book "Evolution Emerging" is apropos:

> "But who can tell the span or know the limits
> In Time's equation of the Past and Future?
> What! will the players quit, with coin in hand,
> Tipping the cosmic table in their anger?
> 'Tis idle to imagine, they'll stay in,
> 'Law' against 'chance,' so spin the wheel again!"

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JAMES ARTHUR LECTURES ON THE EVOLUTION OF THE HUMAN BRAIN

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Ernst Scharrer, *Brain Function and the Evolution of Cerebral Vascularization;* May 26, 1960

BRAIN FUNCTION AND THE EVOLUTION OF CEREBRAL VASCULARIZATION

"KNOWLEDGE OF THE ONTOGENY AND PHYLOGENY OF THE VESSELS WITHIN THE BRAIN SUBSTANCE IS STILL SOMEWHAT MEAGER" (E. HORNE CRAIGIE, 1938).

The quoted statement is as valid today as it was in 1938. During the past century a vast amount of effort has been directed toward the study of the evolution of the brain from the lowest forms to the primates. However, little attention has been paid to the phylogeny of the vascular system, without which the human brain could not have attained its present level of differentiation. This neglect of cerebral vascularization as a subject for study is surprising in view of its importance to clinical medicine. "According to reports of the epidemiologic and demographic sections of the World Health Organization, mortality rate from vascular disease of the nervous system holds third place (following heart disease and cancer). This problem has social significance because vascular diseases of the brain frequently disable and make invalids of people who, on the basis of their age, should still be working and still be valuable members of society" (Anonymous, 1959; see also Wright and Luckey, 1955). One of the reasons for the prominent role of the cerebral vascular system in human pathology is the high degree of sensitivity of nervous tissue to lack of oxygen and nutrients. Dysfunction of the central nervous system may result, therefore, from trivial causes such as prolonged erect posture. In this condition the heart may have trouble overcoming gravity and consequently pump an inadequate supply of blood into the brain. Fainting is the well-known result of such

temporary anemia of the brain. More serious interference with the flow of blood in the cerebral vessels for even a short time, the time being measured in minutes (Dennis and Kabat, 1939; Bronk, Larrabee, and Gaylor, 1948; Gänshirt and Zylka, 1952; Ten Cate and Horsten, 1954), will cause irreparable damage to nerve cells. Similarly, when at birth the transition from intra-uterine oxygen supply via the maternal circulation to oxygenation of the newborn's blood by his own active respiration does not occur promptly, permanent brain damage and even death may result. Clearly, the human brain could not have reached its complex organization and could not function at the high level it does, if there had not occurred a parallel evolution of its system of supply, namely, the cerebral blood vessels.

The study of this evolution cannot be approached by tracing it through the phyla of the animal kingdom in the order of their taxonomic position beginning with the lower multicellular forms. We shall find instead corresponding levels of morphological and functional differentiation of cerebral vessels in unrelated groups of invertebrates and vertebrates. Consequently we shall consider various types of cerebral vascular systems from the point of view of functional competence, using whatever examples serve best to illustrate consecutive steps in the evolution of cerebral blood supply, irrespective of the level of the phylogenetic order at which they occur.

Extracerebral Blood Supply

As long as the central nervous system is small and primitive, as in many invertebrates, in cephalochordates (*Branchiostoma*), and in cyclostomes (spinal cord of *Petromyzon*), diffusion of oxygen and nutrients from surface vessels is adequate to keep the nerve cells alive and functioning. Also the insect brain, which in some orders reaches a high degree of structural differentiation and functional

competence, possesses no intracerebral vessels. However, the insect brain does not depend for its oxygen supply on the hemolymph which surrounds it. The tracheae, fine tubes kept permanently open by chitinous spirals supporting their walls, conduct air into the tissues and even into single cells (Hilton, 1909). The nerve cells are thus aerated by pipes open to the air outside the body. This system is highly efficient, as anyone can attest who has experienced the effects of low oxygen pressure at high altitudes, where insects fly around without signs of discomfort. Also, the mode of providing nutritive materials to the insect brain may not be so inadequate as it would seem if diffusion from extracerebral blood were the only means of supply. There is evidence that glia cells may play an active role in the transport of nutrients to neurons in insects (B. Scharrer, 1939; Pipa, 1961) in a way similar to that which has been suggested for vertebrates (Farquhar and Hartman, 1957; Hartman, 1958). Glia cells as intermediaries between hemolymph and nerve cells may be particularly important in such a case as that of the honeybee which is subject to wide fluctuations of its blood sugar level, the effects of which could well be disastrous if blood came in direct contact with nerve cells. Extracerebral blood supply need not indicate, therefore, a low level of vascular differentiation in all instances; it may, for example, represent one way of maintaining an effective blood-brain barrier.[1] However, the absence of intracerebral blood vessels may have prevented the evolution of insects beyond their present level, since there is a limit to the size that a brain which is nourished from its surface may attain. This may be just as well, because smarter, larger, and more effective insects would probably cause more trouble than man could endure.

[1] The problem of the blood-brain barrier has been extensively studied in vertebrates, particularly man (for references, see Bakay, 1956). Little, if anything, is known about it in invertebrates.

One cannot be sure whether primitive vertebrates the central nervous systems of which do not possess internal vessels remained what they are because their cerebral circulation is poorly developed, or whether the vascular pattern persisted in an underdeveloped stage because it is adequate for the primitive central nervous system of these forms. All vertebrates, except the few cases mentioned, and some invertebrate phyla have "invented" intracerebral vessels which permit growth of the central nervous system. In the course of evolution, an increasingly complex vascular system attempted to keep up with the progressive differentiation of the vertebrate brain and its growing demands. In the most highly developed forms, such as man, the circulatory system of the brain appears to have reached its limits.

Cerebral Arteries and Veins

With the appearance of intracerebral vessels, those on the surface of the brain become trunk lines maintaining a continuous flow of blood which keeps the capillary system supplied at all times. They are divided into arteries which conduct the blood to the intracerebral smaller vessels, and veins which drain the capillary bed. In view of the high degree of sensitivity of nerve cells to lack of oxygen, we are particularly interested in those emergency provisions that assure collateral circulation in case of occlusion of an artery. In the primate brain the internal carotid and the vertebral arteries form a system of anastomoses at the base of the brain (arterial circle of Willis) from which the major arteries originate. These in turn branch out over the surface of the brain, anastomosing and forming a rich network (figs. 1 and 2). It is these surface vessels that have been frequently studied in living animals, either in the exposed brain or through plastic windows inserted into the skull. Many useful and interesting observations have been made in this way, but it must be

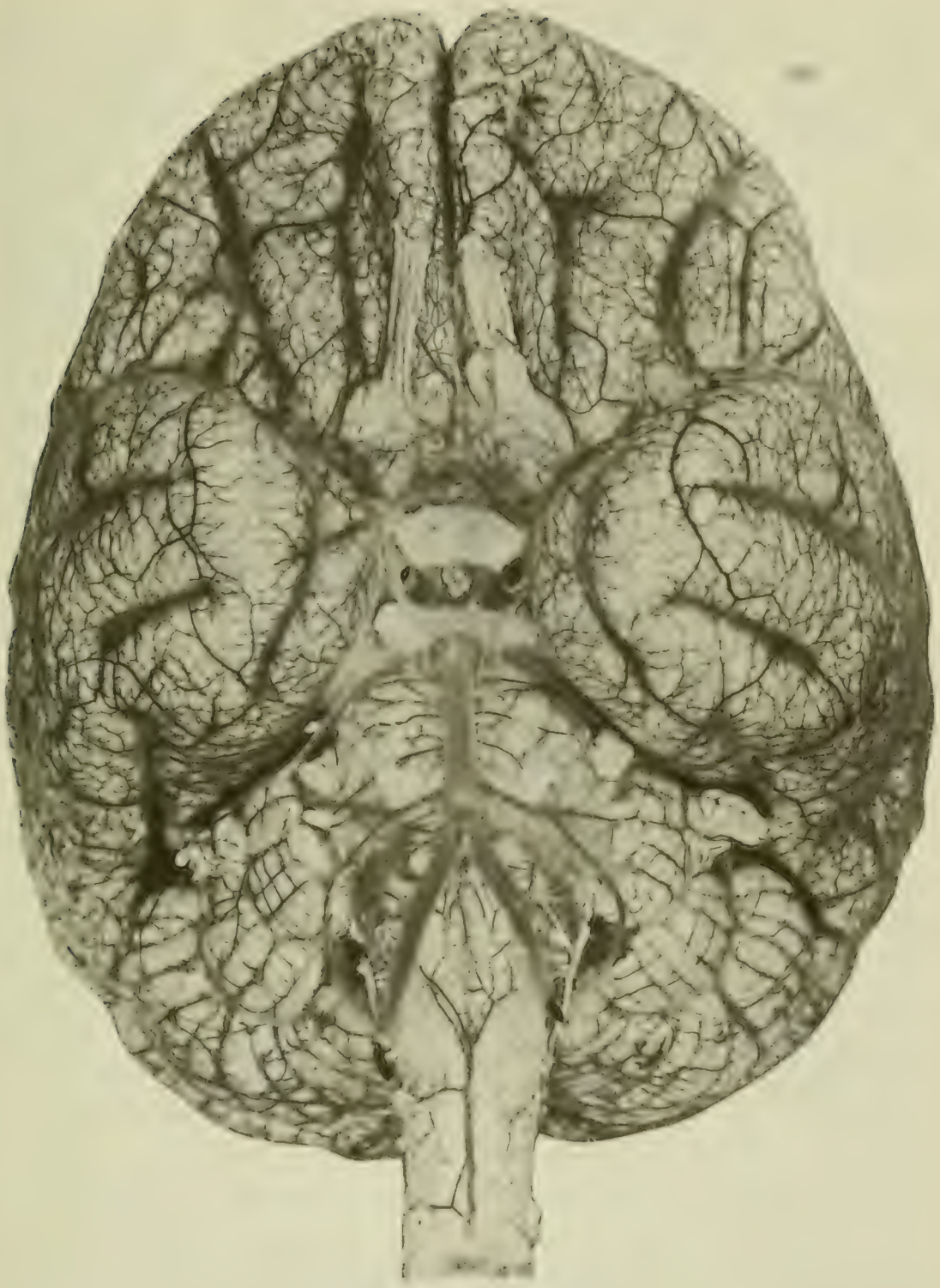

FIG. 1. Ventral view of the brain of a rhesus monkey. The surface vessels are injected with colored gelatine. For explanation, see figure 2.

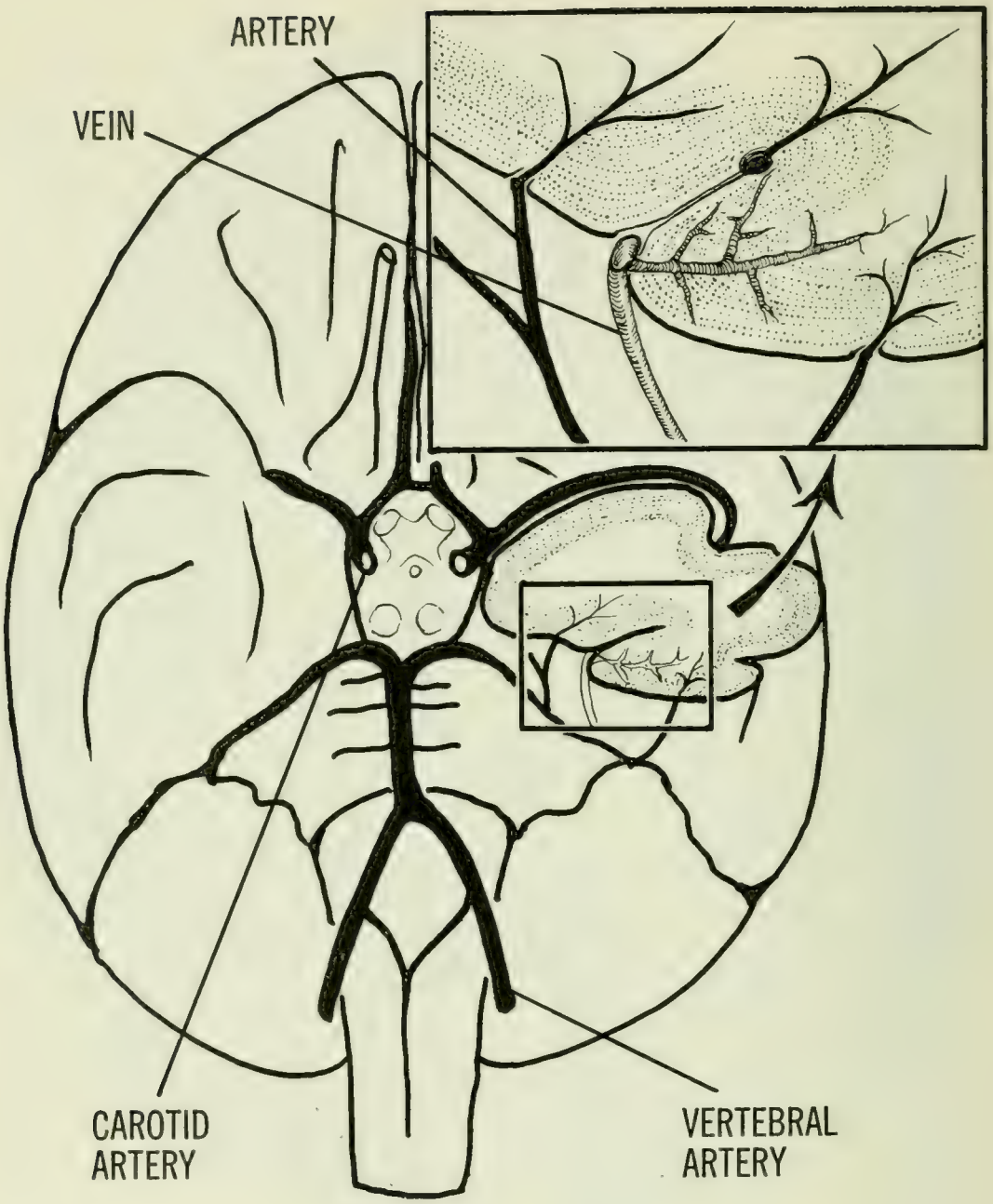

FIG. 2. Same view of monkey brain as is illustrated in figure 1. The anterior pole of the left temporal lobe has been cut off in order to show how blood vessels enter the brain substance. The arrow points to the enlarged picture of the rectangular area of the cut surface.

remembered that they provide only partial information about cerebral circulation. This information is akin to the readings that a public utilities company obtains from measuring the amounts of water, gas, and electricity delivered to a building. Such "data" convey only a general idea of the activities inside a house; what goes on in each room remains unknown.

Once arterial branches enter the nervous tissue, we can no longer observe them in the living animal but must depend on the study of dead tissue and on indirect evidence obtained by a variety of experimental methods. The pitfalls implicit in this approach are well illustrated by the erroneous identification of arteries and veins by Pfeifer (1928, 1930) who, in a series of papers, described the arteries as veins and the veins as arteries in sections of injected brains of various mammals. This error, although it was pointed out (Campbell, 1938; E. Scharrer, 1938), has produced all sorts of wrong conclusions. The correct identification is illustrated in figure 3 of the present paper. The anatomical differences between arteries and veins are probably related to hemodynamic conditions. The blood is injected by the arteries into the capillary bed under high pressure; the smooth curves and mode of branching of the arteries presumably facilitate the flow of blood. By contrast, the blood drains from the capillary bed under low pressure; the smaller venous channels join the larger veins at right angles, like drainage ditches in which the water flows slowly toward larger canals. In lower vertebrates, cerebral vessels have not been studied with respect to their mode of branching, and it is, therefore, not clear whether this feature constitutes merely a functional adaptation in the placental mammals or has evolutionary significance. In marsupials paired arteries and veins branch in like manner (see below).

Abbie (1934) formulated two principles governing the

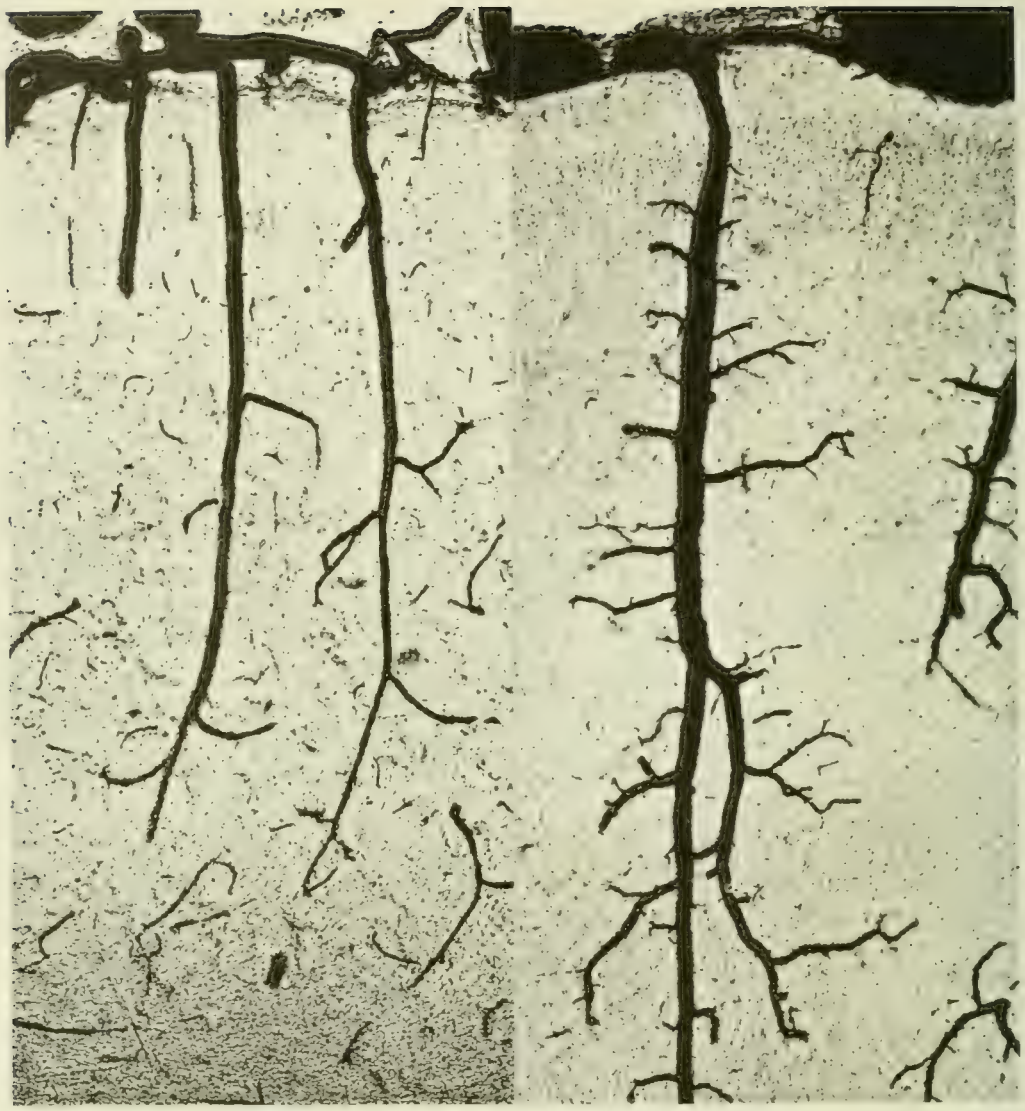

FIG. 3. Injected cat's brain. A. Intracerebral arteries. B. Intracerebral vein. Note the difference in the ramification of the two kinds of blood vessels.

relationship of arteries and cerebral tissue of vertebrates, namely, functional constancy and economy of distribution. Whenever a neural mechanism develops, an artery develops for its supply, and this relationship remains constant throughout evolution. As to the economy of distribution, we shall have more to say in some of the following sections of this paper.

The Ontogenetic Development of the Cerebral Vascular System

Consecutive stages in the differentiation of the cerebral vascular system during embryonic development of higher forms have their parallels in adult patterns of animals of lower phylogenetic order. These may be noted with interest, but conclusions should be drawn cautiously or not at all.

In the early period of development, "*le système vasculaire paraît n'avoir qu'un rapport égal et uniforme avec toutes les parties de la masse nerveuse centrale.*" In later stages, "*on commence à voir sur certains points, aux tubercules quadrijumaux, par exemple, une quantité plus considérable qu'ailleurs de ces vaisseaux,*" as Guyot observed as early as 1829. Since then the development of the cerebral vascular system has been studied by relatively few investigators (see Craigie, 1955; Strong, 1961). It is not only difficult to inject small embryos, but even in successful specimens one cannot be sure of the completeness of the injection. Vessels grow into the nervous tissue as solid strands of cells, becoming patent tubes later when they join up with other vessels. Here procedures of histochemistry may be applied to advantage. For example, the blood vessels of the developing rat brain are (and the fact is uniquely true of them but not of vessels of other organs) rich in alkaline phosphatase, the presence of which may be demonstrated by the method of Gomori (1939). Irrespective of whether or not the vessels are open, they can be traced in their entirety in sections from which the vascular system may be reconstructed as it appears at various stages of its ontogenetic development. As might be expected, the vessels form relatively simple networks in young embryos, similar to those found in more primitive vertebrates, e.g., urodeles. With increasing age, adult patterns begin to emerge, i.e., as nuclei and fiber tracts become more clearly defined, capillary density begins to show differences

that reflect progressively the anatomical maturation of the brain (E. Scharrer, 1950).

It has been noted by Klosovskii (1956; see Simonson, 1960, under Bibliographies and Reviews) that the cerebral vessels of placental mammals grow into the embryonic brain tissue in the shape of loops. These are eventually absorbed into the general network, with a few remainders of paired vessels here and there in the adult central nervous system as, for instance, in the cat (Fleischhauer, 1961). The observation of loops in the early development of cerebral blood vessels is of interest in view of the fact that all vessels in the adult brain of marsupial mammals and of a variety of other vertebrates are of the loop type. These are of considerable interest and are discussed, therefore, in some detail in the following sections.

Loops and Networks

Whenever, in the course of evolution, blood vessels started to grow into the central nervous system they had two possibilities of joining up, as illustrated in figure 4. They can fold on themselves, so that each artery becomes paired with a vein and the capillaries end in hairpin-like loops. In this way systems of terminal vessels come about that do not communicate with one another. The brain of the earthworm (*Lumbricus*), the lamprey (*Petromyzon*), and many higher vertebrates shows this kind of vessel. A different type results when they join to form networks which also occur in both invertebrates and vertebrates. Finally, there are some animals that show intermediate types, i.e., networks with terminal loops. Although the difference between the network type and the loop type appears striking to the observer who compares sections of injected brain tissue obtained from animals showing the two types, e.g., opossum and rat, it is not difficult to visualize how the loop type can be converted into a two-

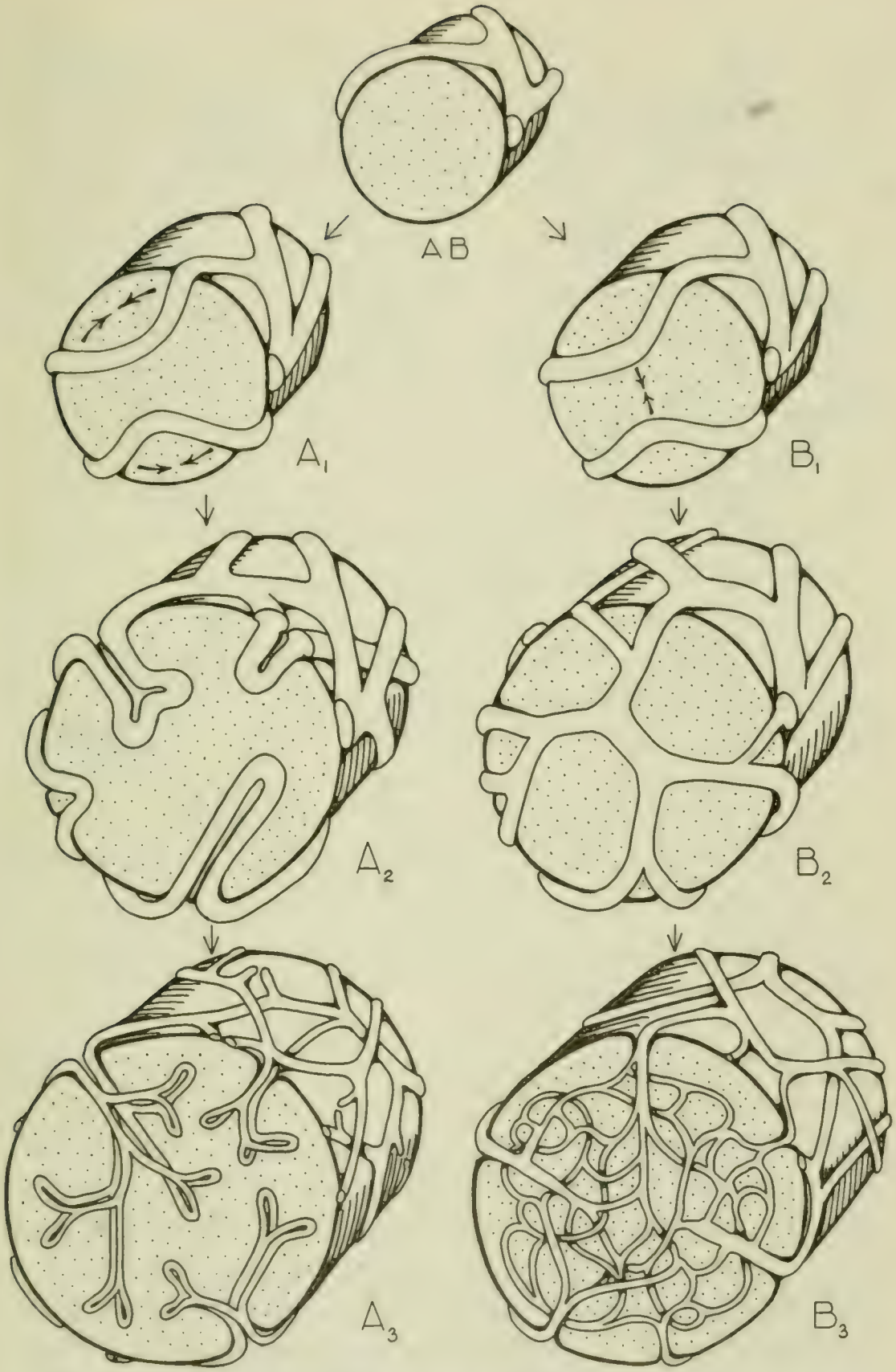

FIG. 4. Blood vessels growing into the nervous tissue may give rise to either terminal loops (A_1, A_2, A_3) or networks (B_1, B_2, B_3).

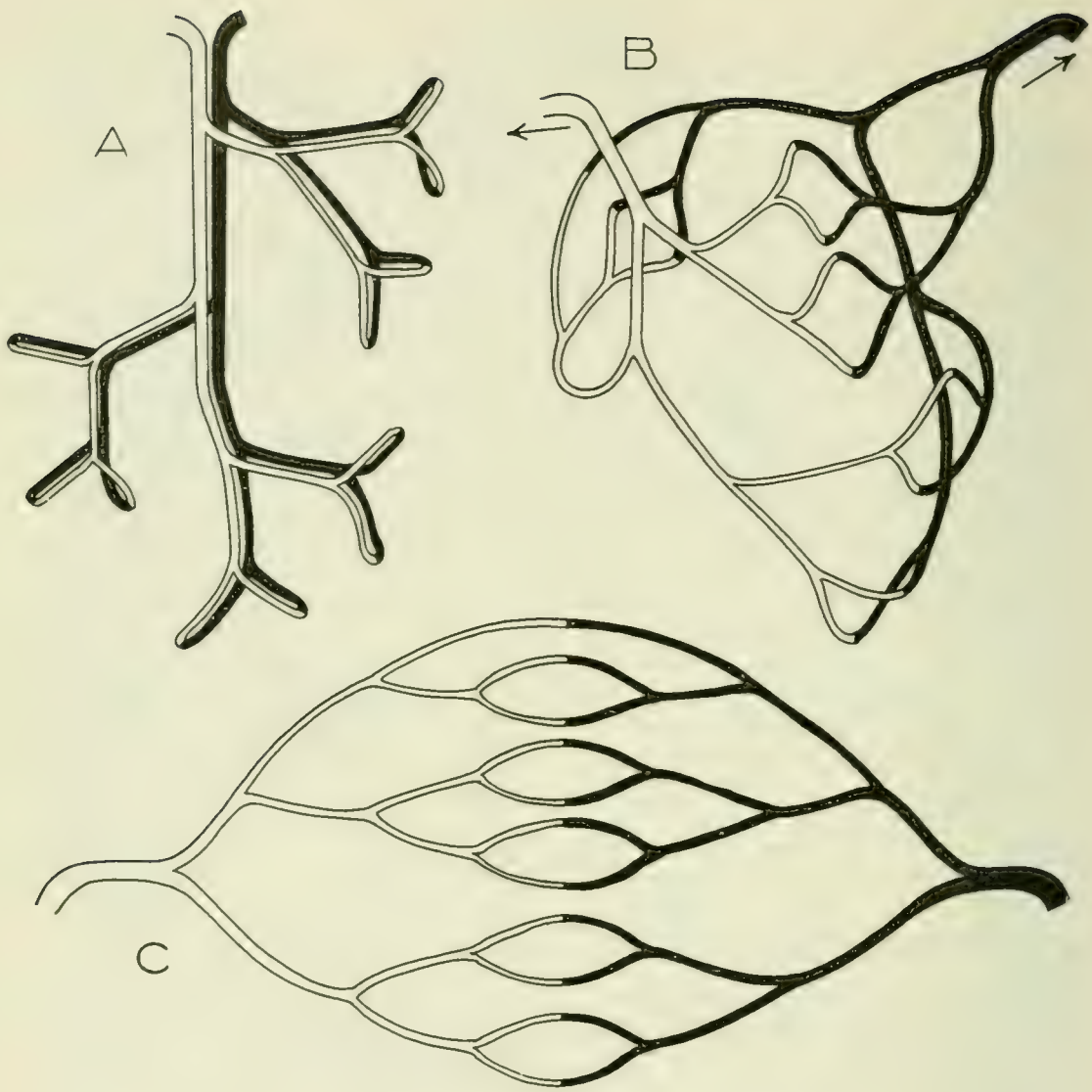

FIG. 5. Diagrams to show the relationship between a system of terminal loops (A) and a network of blood vessels (C).

dimensional network, by pulling artery and vein apart (fig. 5).

The question arises whether, in the course of evolution, loops preceded networks, and the latter therefore represent a more advanced type. It is true that the cerebral vessels of the marsupials, which are more primitive than the placental mammals, are of the loop type and that corresponding relationships obtain in reptiles and amphibians, but in general the occurrence of either type in unrelated groups of invertebrates and vertebrates does not support this concept (E.

Scharrer, 1944c). Before a superior rank to one of the two types is assigned, it might be well to examine their functional potentialities and to define more precisely in which sense the type of cerebral vessel might indicate levels of evolutionary progress.

The Loop Type: The occurrence of vascular loops was first described by Schöbl in the central nervous systems of reptiles (1878) and urodeles (1882). The findings were confirmed by Sterzi (1904) but aroused little interest until Wislocki and Campbell (1937) described the loop type of blood vessels in the brain of the opossum (*Didelphys virginiana*). In addition to further studies by Wislocki (1939), a number of investigators explored the cerebral vascular system of marsupials (E. Scharrer, 1938, 1939a, 1939b, 1940a, 1940b; Craigie, 1938c; Sunderland, 1941) and reexamined a variety of invertebrate and vertebrate brains for the occurrence of these peculiar vessels (Craigie, 1938a, 1938b, 1939, 1940a, 1940b, 1941a, 1941b, 1943; E. Scharrer, 1944b, 1944c).

The brain of the earthworm (*Lumbricus terrestris*) is supplied by paired vessels ending in hairpin loops (fig. 6A). A search among additional representatives of annelids and of invertebrates in general is likely to turn up a number of other groups possessing this type of vessel. Among the most primitive vertebrates, the cyclostomes, *Petromyzon* (Sterzi, 1904; Craigie, 1938a, 1938b, 1955) shows the same type of brain vessels as the earthworm. Actually, the vessels of the lamprey brain are more primitive than those of the earthworm in that they are simple, long, hairpin-shaped loops, which occasionally form a side loop but never branch. The vessels of the earthworm brain are more complex in that they branch as do those of the marsupial brain. Among the amphibians, the urodeles (salamanders, newts, and others), among the reptiles, the lizards, and among the mammals, the marsupials (opossum, kangaroo, and others), belong to

FIG. 6. Terminal capillary loops. A. Brain of the earthworm (*Lumbricus terrestris*). B. Brain of the opossum (*Didelphys virginiana*).

the category of animals with paired cerebral vessels ending in hairpin loops (fig. 6B).

The discovery by Wislocki and Campbell (1937) of the peculiar blood vessels of the opossum brain proved highly rewarding. The availability of a mammal whose brain is supplied by true end-arteries permitted the experimental investigation of a number of problems that had been raised by Cohnheim as early as 1872 in conjunction with observa-

tions on the vascular origin of neuropathological lesions. Thus, for instance, the selective vulnerability of the hippocampus, a phylogenetically ancient part of the mammalian brain, in carbon monoxide poisoning which had been related to end-arterial supply (Uchimura, 1928a, 1928b) was shown to have a different etiology (E. Scharrer, 1940b).

The Network Type: The human brain, which is supplied by a capillary network, shares this kind of vascularization with the brains of the squid, the hagfish, the ganoid and teleost fishes, the amphibians (except the urodeles), the reptiles (except the lizards), the birds, and the mammals (except the marsupials). Thus the great majority of the animals, the central nervous systems of which have been examined with respect to vascularity, exhibit the network type. In this arrangement all cerebral and spinal vessels are interconnected with one another by a vast bed of capillaries. It has been said that a red blood cell could enter at the olfactory bulb and thread its way through this type of capillary system to the end of the spinal cord without ever having to emerge and enter a vein. Such a voyage would be impossible in the brain of a marsupial in which an erythrocyte can pass through one vascular tree only, which it must leave via the companion vein of the artery, i.e., at the point where it entered the brain.

Determination of Vessel Type

The phylogenetic development of the cerebral vascular system could have taken place in two ways. Extracerebral vessels could have given rise to intracerebral vessels of the loop type which in higher forms became transformed into vessels of the network type. The alternative is a parallel development of loop and network systems from extracerebral blood vessels (see fig. 4), with the result that either system may be found in representatives of invertebrates and vertebrates unrelated to phylogenetic levels. The latter is what

actually happened. The question arises as to what determines the type of blood vessel: Is it a property of the brain tissue which induces the ingrowth of the one or the other type, or are the determining factors inherent in the blood vascular system itself?

The question is difficult to decide by experimental methods in the early stages of development when the central nervous system becomes vascularized. However, one may draw some conclusions from the behavior of regenerating brain vessels which are given an opportunity to grow into brain tissue other than the kind that they normally supply. In experiments in which pieces of dead brain were exchanged between opossums having the loop type of vessels and guinea pigs in which the brain vessels are of the network type, the vessels of the host brain made an attempt to grow into the alien implant. These newly growing vessels were of the host type. Capillary loops, typical for the opossum, grew into implanted guinea pig brain tissue. Capillary networks characteristic of the brain of a placental mammal such as the guinea pig grew into opossum brain implants (E. Scharrer, 1940a). The experiment falls short of proving the thesis that the two existing types of cerebral vessels are the result of factors intrinsic in the vascular system and do not depend on any structural or chemical characteristics of the nervous tissue that they supply. However, the result agrees with the corresponding conclusion one must draw from the comparative survey. If one assumes a determining role of the nervous tissue, one must accept the proposition that the brains of the earthworm, the lamprey, the urodeles, the lizards, and the marsupials have something in common which causes blood vessels to form terminal loops, whereas the brains of all other animals, known to be supplied by networks, would have to have another common denominator on the presence of which depends the differentiation of the network type of vessels. This is most unlikely, and it seems

safe to conclude that either one of the two inherent potentialities may be realized. The choice may be more or less accidental. How else could one interpret the fact that, within the cyclostomes, the brain of *Petromyzon* is vascularized by loop vessels, that of *Myxine* by a network?

If this view is correct, it was by chance that among the mammals the marsupial brain acquired loops and that of the placentals networks. Had it happened the other way around and the marsupials chosen the network type, would they have brought forth a *Homo sapiens* and would Dali's "Marsupial Centaurs" depict orthodox mythology? On the other hand, would the placental mammals, in spite of all their other potentialities for higher differentiation, never have developed a brain capable of abstract thought if its blood vessels were of the loop type? Or would the human brain have reached the same level of differentiation, irrespective of the type of vessels supplying it? How do the two types compare in terms of functional competence?

Comparison of Loop and Network Vessels

One look at the terminal vessels of a marsupial brain reveals what appears to be a major defect of this type: if an embolus occludes an artery, the brain area supplied by this particular vessel will be without nourishment and oxygen, because there are no connections with neighboring arteries that could take over by establishing a collateral circulation. That such a situation will indeed arise can be shown experimentally. If one injects *Lycopodium* spores into the carotid artery of an opossum, they will become lodged in the small arterioles cutting off the flow of blood. As a result, the nerve cells surrounding the capillary branches supplied by this arteriole will die (E. Scharrer, 1939a). One might expect that a network will be superior in such an emergency in that the anastomoses among the blood vessels will be utilized to supply the ischemic area. Actually such is not the case (Steeg-

mann and Fuente, 1959). Occlusion of an artery in a network system also results in the death of the nervous tissue in the area supplied by the affected vessel. It appears that the capillary anastomoses are not adequate to supply the ischemic area quickly enough to prevent stasis of the blood and get circulation under way before the nerve cells suffer irreparable damage. This inability of vessels in the human brain to establish collateral circulation is so marked that Cohnheim in 1872 pronounced the doctrine of the brain's being supplied by "end-arteries," without confirming his thesis by the actual observation of such vessels in injected material. The frequent autopsy finding of focal softening of brain tissue following vascular accidents convinced Cohnheim that the blood vessels of the human brain are terminal vessels, each of which supplies a territory of its own. This concept dominated the thinking of neuropathologists until Pfeifer (1928, 1930) showed that cerebral "end-arteries" have no anatomical reality. However, the consequences of the occlusion of an artery supplying a network system are the same as those following an embolism of the terminal artery of a loop system. In this respect, then, man could not be worse off if his brain were supplied by the type of paired vessels that characterize the marsupial brain.

The same conclusion may be reached in a different way. If one exposes opossums to carbon monoxide, one of the most vulnerable structures turns out to be an ancient part of the brain, the so-called hippocampus, or Ammon's horn. This is precisely the same area which in man selectively succumbs to carbon monoxide poisoning. The phenomenon is not completely understood, but there is good evidence that it has a vascular basis (E. Scharrer, 1940b; Nilges, 1944). Again the network type does not prove superior to the loop type in a crisis like the one provoked by a toxic substance such as carbon monoxide.

In fact, the loop type would seem to represent an elegant

solution of the problem of uniform and consistent blood supply to nerve cells. If one considers that in a network system blood flowing from the arterial to the venous end of the capillary deteriorates in its content of oxygen and nutrients, one would have to conclude that not all nerve cells lying along a capillary are equally well off. By contrast, in the loop system each pair of capillaries represents a unit operating on the counter current principle which should balance the differences in oxygen and carbon dioxide content at the arterial and venous ends of the two limbs. Such vessels would seem to guarantee the nerve cells a uniform supply throughout their entire length.

All told, the type of vascularization supplying the marsupial brain might have been as adequate as the network type to support the dramatic evolution of the human brain.

Vascular Density and Pattern

Anyone whose attention has not been specifically directed toward capillary types will probably not notice the difference between a section through the medulla oblongata of the injected brain of an opossum and that of a rat. Corresponding cellular areas within the medulla oblongata of the opossum and of the rat will show the same vascular density and pattern, in one case of capillary loops, in the other of networks. Turning now to a discussion of the factors that determine vascular density and patterns in brains of different animals, we shall no longer make separate reference to the two types of blood vessels, because the same principles apply to brains supplied by either type.

The vascular patterns of primitive brains, as, for instance, those of urodeles, are monotonously uniform. In more highly developed types of brains, such as those of teleosts, we find surprisingly variable vascular patterns (fig. 7). Such regional differences presumably evolve in conjunction with cytoarchitectonic differentiation in higher animals. Their study yields

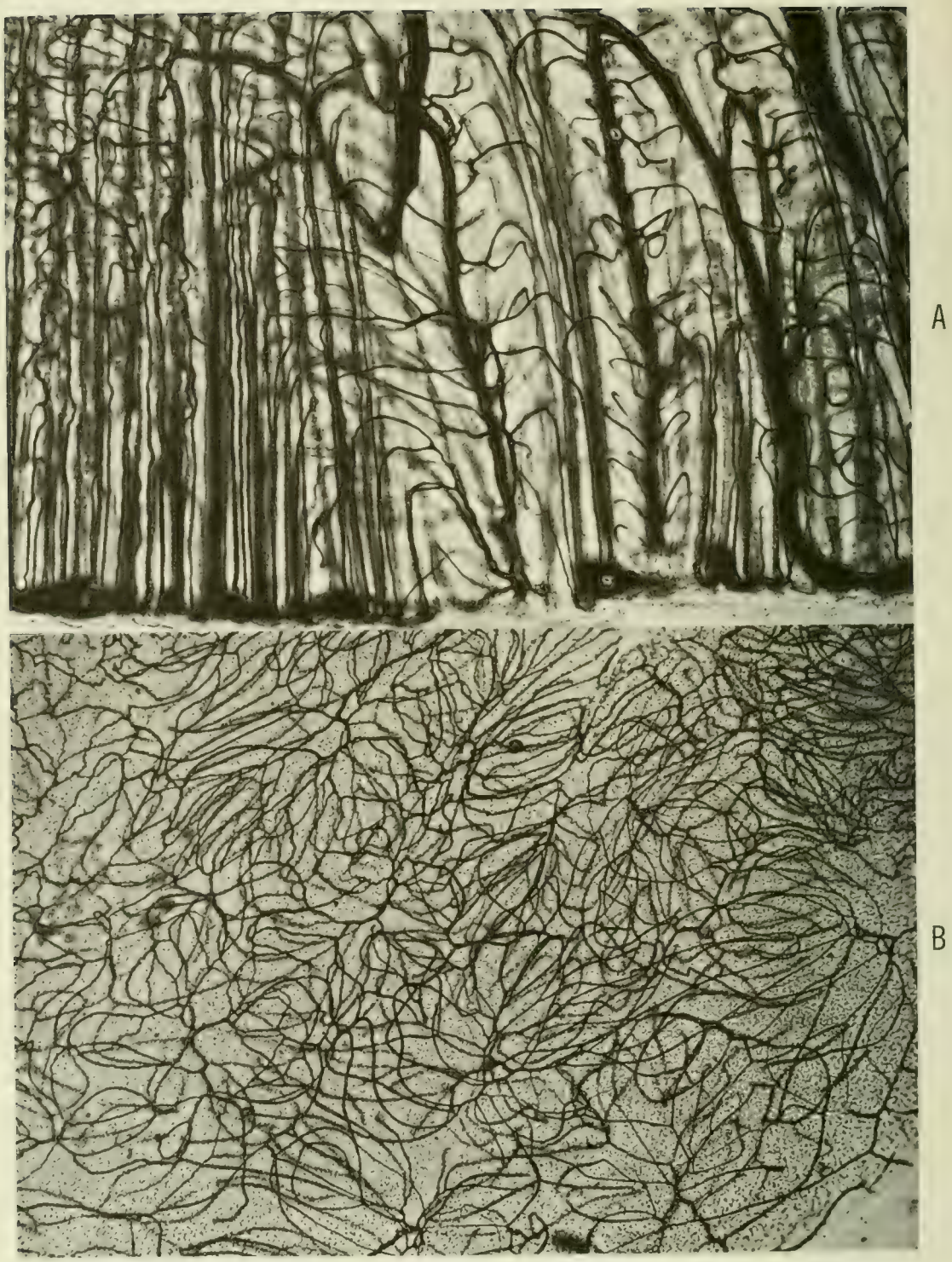

FIG. 7. Examples of the variety of vascular patterns in the brain of a teleost fish (*Tautoga onitis*). A. Lobus inferior. B. Forebrain.

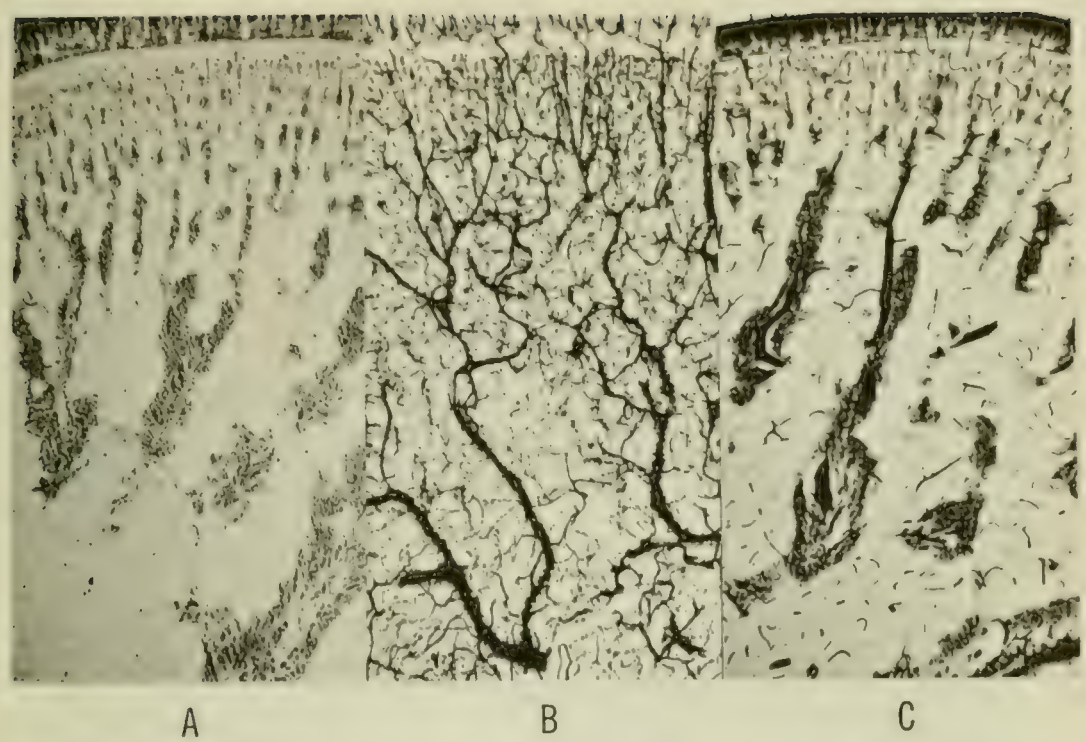

FIG. 8. Optic lobe of brain of squid (*Loligo pelaeii*). A. Pattern of nerve cells (Nissl stain). B. Vascular pattern (India ink-gelatine injection). C. Combination of cell stain and vascular injection.

some useful insights into the functional relationships between blood vessels and nerve cells which are inaccessible to direct methods of analysis (see Billenstien, 1953).

The most striking regional differences concern the density of the blood vessels. It often mirrors the microscopic topography of nuclei and fiber tracts to the extent that they may be accurately identified in sections of brain tissue in which the blood vessels have been injected without the staining of nerve cells or fibers (Pfeifer, 1928, 1930; Altschul, 1939; Dinkhaus, 1942; Craigie, 1920–1943). The question arises, What comes first? Does the cellular arrangement determine the vascular pattern or, conversely, do the cells become so located as to be closest to the vessels from which they receive their sustenance? A comparative survey of vascular versus cellular patterns indicates that either relationship may occur. In the optic lobe of the squid, the nerve cells are arranged along the blood vessels (fig. 8). A similar rela-

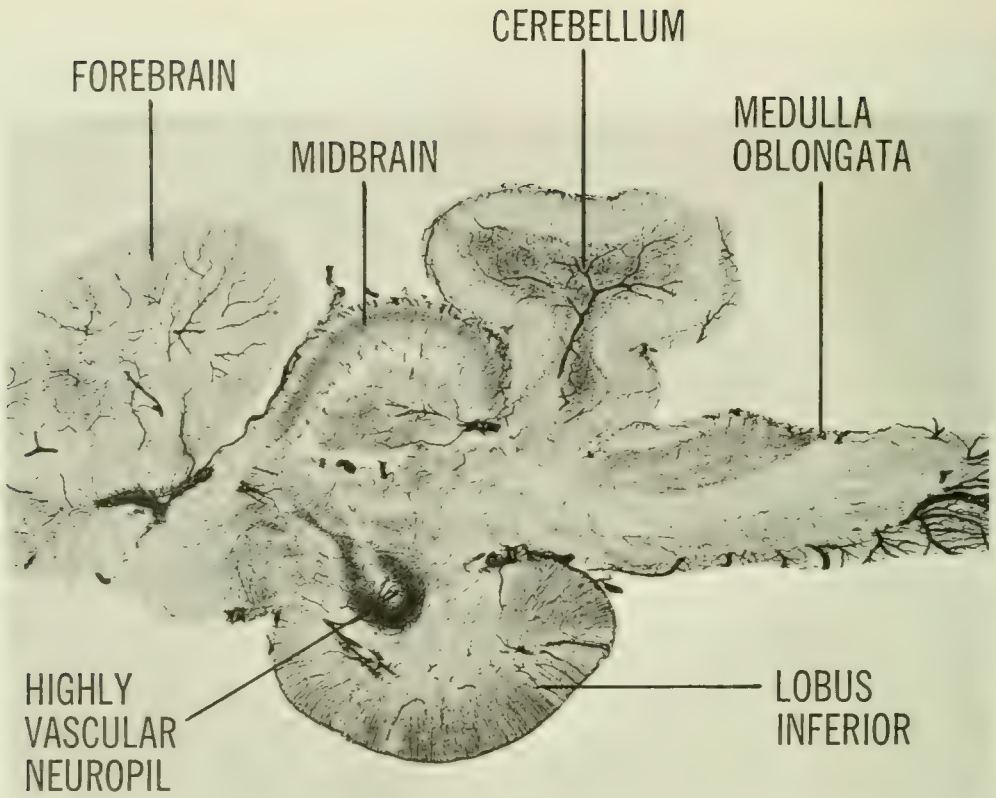

FIG. 9. Sagittal section through the brain of a teleost fish (*Tautoga onitis*) in which the blood vessels had been injected with India ink and gelatine. The varying metabolic requirements of different areas in the brain are reflected in the pattern of vascular density. The most richly supplied area is a neuropil near the center of the brain.

tionship exists in the Nucleus supraopticus accessorius of mammals. However, not many examples can be cited. In general, the organization of the central nervous system in terms of nuclei (i.e., groups of neurons of the same structure, function, and chemistry) and fiber tracts is reflected in corresponding areas of varying vascular density (fig. 9). Areas containing many large cell bodies possess denser capillary beds than those consisting of loosely arranged smaller cells. The latter are better supplied than white matter which consists predominantly of nerve fibers. In terms of metabolic rates these relationships appear reasonable. One would expect that the cell bodies which are centers of protein synthesis would have higher requirements than the fibers, and that areas of crowded large cell bodies will use up more oxy-

gen and nutrients than those in which smaller elements are thinly scattered.

Although this rule holds in a general way, there are exceptions that prove instructive in that they indicate an oversimplification in the explanation stated above. There are occasional areas of densely crowded large nerve cells the vascular bed of which is anything but rich. The Gasserian ganglion of the trigeminal nerve is such an area. The question arises whether factors other than mere size of cell bodies may play a role. It was suggested, and with good reason, that it is not so much the high metabolism of the cell body that requires a rich vascular supply as the turnover at the synapses where impulses are transmitted from one neuron to the next and complex biochemical processes take place (e.g., synthesis and destruction of acetylcholine). This view is supported by the correlation between the presence and absence of synapses on the one hand and the degree of density of the capillary bed on the other. The Gasserian ganglion contains no synapses, and its capillary bed is not so dense as that of the superior cervical ganglion in which cells do synapse. However, even this explanation cannot be generalized without qualifications. If synapses are the decisive factor in determining vascular density, such neuropils as consist largely of synaptic junctions should be highly vascular, even if there are few or no nerve cell bodies included. Such is indeed the case (fig. 9). However, there are exceptions; some neuropils possess relatively few capillaries. Such neuropils have presumably a less active metabolism, as indicated by the smaller number of mitochondria (E. Scharrer, 1944a). The examples may suffice to illustrate the usefulness of quantitative data concerning regional vascularity. They reflect with great sensitivity the differentials in metabolic requirements of adjacent but anatomically distinct areas. We shall presently see how sensitive a measuring device capillary density is.

The Significance of Intercapillary Distance

It has been mentioned above that the central nervous tissue requires a continuous adequate supply of oxygenated blood. Its distribution within the central nervous system seems effectively regulated; each area has its quota of capillaries which is presumably adequate for its normal requirements. Superimposed on the basic anatomical pattern of distribution is a measure of functional control which permits a temporary local increase or decrease of blood flow in accordance with the changing activities of brain centers. However, there are reasons to believe that at no time and in no place can the flow of blood be permitted to cease altogether for even short periods. The thesis is put forward here that it could not stop in a single capillary without consequences to the nerve cells in its immediate neighborhood.

This conclusion is derived from experiments of which the following may serve as an example. The end arteries of the opossum facilitate the experimental occlusion of a small arteriole and its capillaries without interference with those of neighboring vessels, since the capillary loops of different blood vessels do not anastomose with one another. It is easily seen how one can estimate the radius of supply of a single capillary loop, if one determines the extent to which nerve cells die in the neighborhood of a capillary rendered non-functional by the injection of *Lycopodium* spores. The granular layer of the cerebellum of the opossum is particularly favorable for such an experiment on account of its cellular density, because the lines of demarcation between the pericapillary areas in which the cells succumb to anoxemia and those in which they survive are sharp (E. Scharrer, 1939a). The following measurements suggest that there is no margin of safety in the case of such an accident. The distance between capillary loops in the granular layer of the cerebellum averages 50 μ. This is also the width of strips in which the nerve cells have disappeared as a result of experi-

mental emboli. It follows that each capillary supplies the surrounding brain tissue in a radius of about 25 μ, with little if any effective overlap with the area of supply of the neighboring capillaries. Such a marginal ratio of capillaries to nerve cells does not permit the elimination of a single capillary without the loss of nerve cells.

These empirically obtained data were confirmed by different techniques (Opitz and Schneider, 1950; Horstmann, 1960; Thews, 1960; Lierse, 1961) and may well be generally applicable. They have some important applications. There seems to be no reserve of capillaries in the brain as there is, for instance, in muscle. Although it is not clear why marsupials cannot afford such luxury, one may understand why the placental mammals, man in particular, seem to be unable to provide more blood vessels than are absolutely necessary to supply the brain tissue. The human brain, and with it the skull, have about reached the size limit that still permits their passage through the birth canal, although with difficulties for both mother and child. Space within the cranial cavity is at a premium, therefore, and a safer ratio of blood vessels to nerve cells could be accomplished only at the expense of the latter. For the same reason, additional nerve cells would require an expansion of the vascular system for which there is no space in the skull. This circumstance may well set a definite limit to further evolution of the human brain in purely anatomical terms.[1]

Actually, gross anatomical evolution is probably not a

[1] The reasoning of this paragraph does not conflict with the concepts set forth by Hindze (1926) which would indicate, if confirmed, that the gross anatomical study of the circle of Willis, together with the arteries and their branches on the surface of the brain, reveals longer, thicker surface arteries with more branches in human beings of high intelligence than in those of low intelligence. If one accepts the implication that the presumably rich blood supply was related to the high degree of performance of these brains, one must assume, although no data are given by Hindze, that Hrdlička's (1929) finding of a preponderance of large heads among highly intelligent people applied to Hindze's cases, i.e., the heads were probably larger than average and could accommodate a greater number of blood vessels.

conditio sine qua non for further intellectual and ethical evolution. Instead of the installation of additional supply channels, the effective use of existing facilities and the realization of the virtually unlimited potentialities for the progressive differentiation and refinement of intraneuronal connections will be the direction in which the evolution of the human brain can proceed without restraint. Just as the invention of transistors made possible a high degree of electronic performance within limited space and with small expenditure of energy, the miniaturization of synapses and the "invention" of neurohumoral mechanisms with smaller energy requirements than those we know would permit large strides in evolution without a gross anatomical increase of brain mass and, most important, of its supply system. Observations in recent years with electron microscopic techniques indicate that miniaturization exists already in the central nervous system to an unsuspected degree. What was formerly considered as an undifferentiated interstitial matrix filling the assumed spaces between nerve cells, glia cells, and capillaries of the brain ("Nissl's gray") does not exist. Instead there are everywhere richly interdigitating cell processes. Among these are many of very small diameter. We know little about them, but, if they were able to assume functions that are now carried out by larger fibers, the activities of the brain could reach higher levels of complexity and effectiveness without a need for additional space.

Conclusion

This cursory exploration of some aspects of the evolutionary history of cerebral blood supply has afforded us a few unexpected insights in certain areas and has left us unenlightened in others. The discovery of two basic types of cerebral vessels, networks and terminal loops, which appear in invertebrate as well as vertebrate animals irrespective of phylogenetic relationships, has been helpful in the solution of

problems that had been sources of fruitless controversies for a long time. Cerebral vascular systems based on either one of these two types may develop complex patterns. Little more can be stated that would apply generally to cerebral vascular systems of all animals. The evolution of each system can be studied profitably only within phyla, e.g., the mollusks or the vertebrates; the latter have been sufficiently explored to permit a comparative study of cerebrovascular evolution. The capacity of man's present cerebral vascular system may well have reached its limits, and the further evolution of the human brain in terms of mere growth may be impossible for this reason. However, much intracranial space is taken up by ancient circuits that could be and probably are right now in the process of being redesigned for more effective use.

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