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THE CORRELATION BETWEEN STRUCTURE AND FUNCTION IN THE DEVELOPMENT OF THE SPECIAL SENSES OF THE WHITE RAT.

BY

H. H. LANE.

NORMAN, OKLAHOMA
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The Correlation Between Structure and Function in the Development of the Special Senses of the White Rat.

A DISSERTATION

PRESENTED

TO THE

FACULTY OF PRINCETON UNIVERSITY

IN CANDIDACY FOR THE DEGREE

OF DOCTOR OF PHILOSOPHY

BY

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NORMAN

UNIVERSITY OF OKLAHOMA

1917

Accepted by the Department of Biology,
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The Correlation Between Structure and Function in the Development of the Special Senses of the White Rat.

H. H. Lane

Two periods in the ontogenetic development of an organism were recognized more than thirty years ago by Wilhelm Roux, the first that during which the organs are formed, and the second that of the development of function in the organs previously laid down. Within the organism as a whole there is, of course, no sharp line of demarcation between these two periods, for different organs, or even systems, are formed and become functional at different stages in ontogeny; or the two periods may overlap in the development of the same organ, as Harrison has shown to be the case with muscle fibers. The order of appearance of the organs in an embryo is also of significance, since it sometimes happens that the presence and functional activity of one is a necessary precursor to the formation of another organ.

The immediate problem of this investigation is the determination of the nature and amount of the correlation between structure and function in the development of the special senses in the white rat during both prenatal and early postnatal life. The work has been done in the Biological Laboratory of Princeton University. I wish to extend my sincerest thanks for the many courtesies and facilities afforded me, as well as for many helpful suggestions and criticisms, to Professor E. G. Conklin, by whom the problem was suggested to me; to

Doctor Stewart Paton, a pioneer investigator in neurobiology, whose rich experience and knowledge of the field has been constantly at my service; and to Professor C. F. W. McClure, whose deep acquaintance with the facts of comparative anatomy has made it possible for him to offer many valuable suggestions in the course of the investigation. Also I acknowledge my great indebtedness to Professor L. W. Cole, of the University of Colorado, for very material assistance by way of citations to the literature; and finally I am under many obligations to the State University of Oklahoma for a year's leave of absence to pursue this investigation.

The method of attack adopted may be stated in general terms as follows:

To determine by physiological experimentation just when the embryo or young rat first becomes possessed of the senses of touch, taste, smell, equilibrium, hearing and sight, and by a histological examination of the nervous system, both central and peripheral, and of the sense-organs, to discover the structural development exhibited by the parts concerned in each case at the time when the function is first apparent.

Previous Investigations.

No previous investigation along exactly parallel lines is known to me, and only a very few workers have concerned themselves with allied problems and methods of attack; and they have for the most part dealt with the lower vertebrates. An extended review of their papers can therefore be dispensed with here.

WINTREBERT ('04, '05) has published a number of short papers recording the results of his experiments and observations upon a few species

of batrachians, notably the frog and the axolotl. Working on very young embryos of *Rana esculenta,* for instance, at the time when the tail bud had just made its appearance and when the myotomes of the anterior part only of the trunk had become contractile, he made a transverse incision just caudad to the contractile myotomes, of such a depth as to transect the neural tube, the notochord, and a considerable portion of the endodermal tissue. Under these conditions he found that, within a few minutes after the operation, a simple pricking of the end of the tail with a needle results in an immediate contraction of the trunk *anterior* to the incision. The stimulus was transmitted only through the uninjured ectoderm of the ventral body wall. The power of reacting under the conditions of the experiment was present for a period of only four days in the ontogeny; after that the power was lost. He concludes, therefore, that there is a period of "primitive sensitivity," characterized physiologically by its independence of muscular differentiation and of nervous connection between the motor plates and the neural tube.

PATON ('07) undertook to determine the extent to which the heart beat and "the earliest responses to external stimulation . . . . . are dependent upon the functional activity of a nervous system." The forms studied ranged from amphioxus to *Lacerta,* though *Pristiurus* and *Scyllium* gave the clearest results. He found "that the functional activities of the body represented by the beat of the heart and the primitive movements of aband adduction of the body begin at a time when these phenomena may as yet neither be designated as myogenic nor neurogenic in origin" . . . . "That general motility or reactions to stimuli are initiated within the different organs, such as the

myotome or heart, and are at first autochthonous but later fall under the regulating influence of the nervous system." . . . . "The appearance of neurofibrils may generally be considered to be an indication that physiological activity has already actually begun, or will soon begin in the tract in which they have been differentiated." . . . . "One of the chief histological characteristics of the fully differentiated nerve is that it contains neurofibrils, and every bit of evidence so far accumulated points to the appearance of these structures as marking the period of greatest physiological activity in any given nerve." . . . . "It seems to be not at all improbable that impulses, centrifugal as well as centripetal in origin, may play an important part in the differentiation of the neurofibrils."

COGHILL ('14) (and more recently HERRICK and COGHILL ('15)) has made a study of the reflex mechanism concerned in the production of the first swimming movements in the larva of *Amblystoma.* He finds that in the very young larva the Rohon-Beard cells are both extro-and proprio-ceptive elements of a very primitive, but complex, reflex arc through which an extero-ceptive stimulus passes cephalad on one side (the right, for instance) of the cord to commissural neurones near the posterior end of the medulla, and thence to the ventral horn cells of the opposite (left) side, from which in turn the motor impulse travels to the myotomes. By the contraction of the latter a proprio-ceptive stimulus is imparted to the Rohon-Beard cells of the left side of the cord that transmit the impulse by way of secondary neurones to the same commissure and thence to the ventral horn cells of the right side. These then produce a contraction of the myotomes with which they are connected. In this way, as the result of this unique

arrangement, alternate wave-like contractions of the myotomes on the two sides of the body are brought about resulting in swimming movements on the part of the embryo as a whole.

SMALL ('99) has studied experimentally the psychic development of the white rat, during a period extending from the first to the twenty-eighth day after birth. Several references to this paper will be found at various places in this paper.

WATSON ('03) likewise has studied the development of the psychic faculties in the rat by means of a series of "standard problems," and finds that psychic maturity is attained by the twenty-fourth day after birth. Correlated studies were made upon the establishment of medullation in both the peripheral and central nervous systems of this animal, with the result of very conclusively disproving Flechsig's hypothesis. A further account of Watson's results will be found in the appropriate sections of this paper.

Some other papers germane to minor questions raised by my own observations will be considered in connection with the points to which they have relation.

Material and Methods.

The material used in this investigation consists of fifteen different stages in the development of the white rat, ranging from embryos with a crown-rump measurement of 7½ mm. to young sixteen or seventeen days after birth, at which time all the special senses have attained functional activity. In the case of the prenatal stages the mother was first killed by severing the cervical cord by a quick cut with a pair of large bone forceps. The use of anesthetics was avoided for fear of possible deleterious effect upon the embryos or fetuses. The

abdomen of the mother was then immediately opened by a median incision through the ventral body-wall, extending from the public symphysis as far cephalad as necessary. The uterus was removed and placed at once into a dish containing the necessary amount of a solution made up according to the following formula:

Calcium chloride	0.2 gram
Potassium chloride	0.2 gram
Sodium chloride	9.0 gram
Sodium bicarbonate	0.1 gram
Dextrose	1.0 gram
Distilled Water	1000.0 cc.

The dish and its contents had previously been warmed to 38° C., and together with the uterus was transferred to a warm chamber where the embryos were removed and subjected to experiment. The temperature and humidity of the warm chamber were very nearly constant at all times, an effort being made to have conditions as favorable as possible for the success of the experiment. It was found that mammalian embryos are very susceptible to the shock of sudden changes in temperature, frequently only a few moments' exposure to room temperature sufficing to kill them.

Careful records were made at the time of the details of the procedure in each experiment and of the results. For the most part the embryos were preserved in a solution of neutral formol made up as follows: The ordinary 40% formalin was neutralized or made slightly alkaline by an excess of magnesium carbonate. One part of this stock solution was added to nine parts of tapwater, making a 4% solution of neutral formol. The embryos remained in this solution for not less than four days—in several cases much longer, even for several months. They were then subjected to the fol-

lowing procedure which is a slightly modified form of the Bielschowski-Paton ('07) method:

1. Upon removal from the neutral formol the specimen is washed over night in running water, then rinsed three or four times with distilled water and put into a three-fourths of one per cent (0.75%) solution of $AgNO_3$ in the dark. In this it is left for a varying number of days, depending upon the room temperature, until it acquires a light brown color.

2. The specimen is again rinsed in distilled water and put for two hours in the dark into a solution made according to the following formula:

0.75% $AgNO_3$	20 cc.
40% NaOH	4 drops
Concentrated NH_4OH	12 drops

The addition of the NaOH to the silver solution produces a dark brown precipitate which is dissolved by the NH_4OH. In this solution the specimen becomes mahogany colored and more or less translucent.

3. The specimen is again rinsed in distilled water and placed for fifteen minutes in the following solution to dissolve any connective tissue that may be present:

Distilled Water	20 cc.
Glacial Acetic Acid	10 drops

In this it becomes yellowish brown in color.

4. Again the specimen is rinsed in distilled water and put for twelve to twenty-four hours in the dark into a solution composed of:

1% aqueous solution of hydrochinone	20 cc.
4% neutral formol	2 cc.

The time in this solution is determined by the size of the specimen.

5. Once more the specimen is rinsed in dis-distilled water, *gradually* dehydrated in alcohol, cleared in benzol or chloroform (*not* xylol), imbedded in paraffin, and sectioned. Sections five to seven micra in thickness are best for most purposes. The sections are mounted on slides by the usual Mayer's albumen fixative method and after being thoroughly dried are painted over with a 0.5% solution of celloidin, to prevent loss of sections in later processes.

6. After the removal of the paraffin the sections are passed down through the alcohols, rinsed in distilled water, and placed in the dark for two hours in a 0.1% solution of gold chloride neutralized with lithium carbonate. After the gold has been reduced and the sections have a dark grayish blue color, they are quickly rinsed in distilled water and then put for ten minutes in a 5% solution of sodium hyposulphite.

7. The sections are now washed for two hours or longer in running water, passed up through the alcohols to absolute, where they are counterstained in a 1% solution of eosin in absolute alcohol, cleared in xylol, mounted in neutral balsam, and covered in the usual way.

If the solutions are made up fresh as needed, all glass-ware kept perfectly clean, and if in every step of the process, except No. 3, care be taken to have all the fluids used neutral or slightly alkaline in reaction, uniformly good results may be expected by this method.

One very satisfactory modification of this method consists in the omission of the gold chloride and subsequent treatment, i. e., steps No. 6 and 7. The sections when mounted on the slide were allowed to dry, the paraffin removed and the sections cleared in xylol, and covered with neutral balsam

and cover-glass in the usual way. The result is greater contrast between the nerve-fibers and the other tissues than that seen after treatment with gold chloride. In my own preparations, especially in the case of very long series, it was the practice to finish the odd-numbered slides by this method and and the even-numbered slides with the gold chloride. In addition to being in some respects more satisfactory for study, the slides finished by the shorter method require a much briefer time and less labor for their preparation.

As a control method I have used the Ranson-Huber ('13) pyridine process, with decalcification in 7% nitric acid. The published accounts of this technique are so recent and so readily accessible that a description of it is unnecessary here. Its chief advantages are the beautiful contrast between the nerve-fibers and the other tissues, and the fact that decalcification is possible, so that whole heads of young rats may be studied in serial sections. The chief disadvantages encountered in its use are, first, the long time required, and, second, the tendency of the brain tissues to swell when washing in distilled water after the pyridine. It has not been possible so to modify the Bielschowski-Paton method as to permit of decalcification.

A Brief Statement of the Chief Results Obtained in This Investigation.

A few points stand out prominently as the result of the investigation that is described in detail in the succeeding sections of this paper.

1. The exceedingly early establishment of the general structural relationships between the nervous system and the other organs of the body. This comes at a time when the spatial relations are such

as to make easy the proper extension of the sensory and motor nerves to their respective peripheral areas of distribution.

2. Both the central and the peripheral portions of the nervous system are laid down, at least in ground-plan, for a longer or shorter time before their functional activity begins.

3. In the establishment of a sensory chain of neurones from the periphery to the center, the exteroceptive end-organ is the last link to be completed.

4. Immediately upon the completion of the structural development of the peripheral end-organ the definitive function of that particular sensory chain is established.

5. A functional activity once established may be further perfected through the gradual addition of other neurones to those at first constituting the receptive path and the association paths within the brain.

6. The gradual perfecting of the co-ordinating powers of the central nervous system which is a later development is to be explained in the same way.

7. The whole nervous mechanism up to the point, at least, where the definitive functions first appear, develops not from the effects of extrinsic stimuli, but along predetermined lines as the result of inherent forces probably to be thought of as the product of the hereditary constitution of the fertilized egg.

It is, of course, altogether probable that the normal course of events is influenced by many factors which gradually and in succession enter into the situation to complicate matters, such as the establishment of the circulatory and lymphatic systems, the excretory system, and probably some of

the ductless glands. But these are all factors inherent in the primary organization of the individual; they are therefore intrinsic factors in ontogeny. Extrinsic factors such as the stimuli of light, sound, or those of a chemical, electrical, or mechanical nature, etc., play little or no part in the establishment of the various functional activities of the nervous system, though they may later have an influence during the time when co-ordination is being gradually perfected.

The Nature and Function of the Neurofibrillae.

In the following description of structural conditions there will be noted the assumption that the presence of neurofibrillae is an indication that the nerve or tract concerned is capable of functioning. It becomes necessary therefore at this point to discuss the grounds for this assumption.

Neurofibrillae may be demonstrated by means of any one of several technical methods including those of Apàthy, Bethe, Cajal, Bielschowski, Donaggio, Paton, Ranson and Huber. They are constant structures in that by proper means they can always be found in the neurones of all parts of the adult nervous system of the vertebrates and in many at least of the invertebrates. Nevertheless Auerbach has denied their existence and Pighieri considers them to be mere artifacts, the inconstant products of the precipitation of various substances by the reagents used in fixation. On the other hand, and with good reason, Apàthy, Bethe, Cajal, and others, hold them to be normal constituents of the neurone. Hatai asserts that they constitute a reticulum lying in all parts of the neurone, the cross-meshes not ordinarily being seen, though he thinks himself able to demonstrate them by means of a special tech-

nique. In short it is the old controversy in special dress as to whether the structures visible in protoplasm that has been subjected to various fixing reagents are to be regarded as actually present as such in the living state or are the more or less altered and distorted products of such structures of the cell. Were our knowledge of the actual nature of living protoplasm more profound, possibly this particular form of the question would be answered. In the light of present-day results of cytological research it would appear that some structures seen under the microscope after the fixation of the tissue exhibit more of the effects of the fixatives than they do of the structure of the living protoplasm. It is highly probable that some of the granules and reticula so frequently seen and described are more or less the precipitation products of different constituents of the living protoplasm; on the other hand it can be demonstrated that mitochondria, spindle-fibers, and chromosomes, at least, are actually present as such in the living state. In some cases however what appear to be granules in fixed material exist in life as isolated portions of the living colloidal gel having a different degree of viscosity from the surrounding substance. Thus the neurofibrillae are either to be regarded as rows of such colloidal particles held more or less closely together in a linear arrangement by means of another constituent of the protoplasm differing from them in its degree of viscosity, or the fibrillae may consist entirely of such a viscid substance which has the form of strands differing chemically and physically from the other elements of the surrounding protoplasm.

If these considerations hold true, then the view of Koltzoff, upheld for the neurones by Goldschmidt, Szüts, and others, namely, that the form of any cell is determined by the shape of a solid

framework within it, must be materially modified. The so-called "Stützgerüst" of the cell is not an unyielding structure like the bony skeleton of a mammal or the steel-frame of a skyscraper, but rather a meshwork of a substance a little more viscid than some other portions of the protoplasm. The "skeletal theory" of cell structure proposed by Koltzoff seems to rely for its proof upon the analogy of the action of liquid masses when in contact with solid bodies. Thus Plateau has shown that *liquid* masses conform in their shape to that of the solid body with which they may be in contact.

The idea that in a neurone the neurofibrillae constitute this "Stützgerüst" has been advanced by Goldschmidt and others, but it has met with some serious objections. Thus Marinesco ('15) in a recent paper argues very soundly that (1) Koltzoff and Goldschmidt have not shown conclusively that the neuronal cytoplasm is a *fluid,* which it should be on the basis of the analogy just mentioned. (2) Brownian movements are not exhibited by the colloidal particles found in the cytoplasm of the neurone until the viscosity of the hyaloplasm has been reduced, as has been shown experimentally. (3) On the basis of his own observations, Marinesco maintains that the hyaloplasm and the neurofibrils are both more or less fluid gels which differ only in the degree of their viscosity, the neurofibrils being the more stable. (4) The tearing away of a spinal or cranial nerve usually results in the total destruction of the neurofibrillar structures; yet, on the other hand tumefaction followed by an atrophy of the neurone does not lead to such profound modifications of the cellular form as the theory of Koltzoff and Goldschmidt would seem to demand. (5) The destruction of the neurofibrils that follows shortly after the death of an animal does not result in the

collapse of the cell-body of the neurone. (6) The neurones of animals that have undergone hibernation or freezing exhibit marked changes in their neurofibrillae, so that the latter can hardly be considered to possess such a permanent character as the theory demands. In fact such observations have served to establish the fact that the neurofibrils undergo continual change. (7) After transsection of nerve trunk, the neurofibrils peripheral to the section undergo regressive modifications that end ultimately in their complete destruction, yet the axis cylinder as a whole does not crumble, collapse, or otherwise fall into such a dissolution as it should exhibit if the neurofibrils play only a mechanical role in the support of the hyaloplasm. (8) In various pathological states more or less extensive lesions occur in the neurofibrillar reticulum without and corresponding modifications of the cellular form.

It would appear therefore that the neurofibrils cannot be regarded as the "Stützgerüst" of the neurone. What then is their function?

This is a question much more easily raised than answered in the present state of our knowledge. Apàthy, Bethe, Paton, and others, hold the view that they function in the conduction of the nervous impulse. It is at least questionable whether the evidence which they advance is conclusive. Indeed, it seems probable that too much reliance has been placed upon the analogy so frequently made between the nervous system and a telegraph system in which the nerves and the nerve fibers of the former correspond to the cables of the latter, and the neurofibrillae to the individual wires. The experiments of Ducceschi and Bethe on the effect of the compression of nerve-fibers do not appear sufficiently conclusive.

A clue to the true conditions may be furnished by the fact that the relative proportions in the amount of the fibrillae and of the perifibrillar substance differ in medullated and in non-medullated nerve-fibers. It is well established that medullated fibers are better conductors than the non-medullated. This has generally been ascribed to an insulating power on the part of the myelin sheath though recent work would appear to render it probable that the latter may serve rather a trophic function. The fact that medullation does not begin anywhere within the central nervous system of the white rat until several days after birth leads to the suspicion that possibly the importance of medullation from the standpoint of insulation may have been overestimated in the past. On the other hand, the better conducting-power of the medullated fibers may be ascribed to the fact that they are made up of relatively a larger proportion of neurofibrils than of perifibrillar substance, the latter in fact being quite inconspicuous, while in the so-called non-medullated fibers the reverse is the case. In the latter type of fibers, the fibrillae form a small and inconspicuous core with a very thick sheath of perifibrillar substance surrounding them. It is evident that since the neurofibrillae and the perifibrillar substance are the only parts of the nerve-fiber that have a continuous distribution throughout the whole extent of the fiber, one or the other must be the conducting element. Where there is a variation in their relative amounts, therefore, the better power of conduction will lie with that fiber which has the greatest amount of the conducting element. Since then the medullated fiber is the better conductor and at the same time has a relatively greater quantity of neurofibrillae than of perifibrillar material,

as compared with the reverse condition in the non-medullated fiber, the conclusion is inevitable that the neurofibrillae, and not the perifibrillar substance, constitute the conducting element of the neurone. Since the perifibrillar substance certainly is just as much a continuous layer in the transverse direction as in the longitudinal one, and since furthermore the same is not true of the fibrillae, they being continuous only in the longitudinal direction, the fact, which has been demonstrated experimentally, namely, that an electric current is not transmitted *across* a nerve but only in a longitudinal direction, adds to the probability of the correctness of our conclusion. Furthermore it may be argued that in the so-called non-medullated fibers it is the perifibrillar substance that furnishes the needed insulation for the fibrillae, while in the so-called medullated fibers the lack of perifibrillar substance is compensated by the addition of the myelin sheath. To these considerations may be added the further argument which follows from the results of Paton's work on *Pristiurus* and others of the lower vertebrates, namely, that the functional activity of any part of the nervous system is never fully established until after the completion of fibrillation.

If therefore an absolutely conclusive answer cannot now be given to the question of the function of the neurofibrillae, it is most probable, in the light of our present knowledge in this field, that the power of conducting nerve-impulses lies rather in the neurofibrillae than elsewhere. At any rate, the presence of neurofibrillae may be taken as an indicator, a criterion of the functional state of the neurone, and as such it will be used in the description of structural conditions given below.

Experimental and Structural Data.

While the experiments described below show that there is a certain amount of overlapping of the periods when the various senses make their appearance, still in a general way it may be said that the order in which they attain functional activity is as follows:

1. Touch.
2. Equilibrium.
3. Smell.
4. Taste.
5. Hearing.
6. Sight.

It will be seen that certain minor inconsistencies appear in the record of the experiments on successive days. This is due to the fact that when hungry or after a period of rest the animals respond to certain stimuli more readily than they do after a full meal or when fatigued. In general, however, it is clear that after the first indication of functional activity on the part of any of the special senses, succeeding days reveal a gradual perfecting of the animal's powers. This is undoubtedly to be ascribed to a gradual increase in the perfection of the association centers, as well as to the addition of an increasing number of exteroceptive end-organs. For example, the sense of touch is at first manifested most clearly in the snout region at a time when there are present the anlagen of only a dozen or so vibrissae on either side. As development proceeds other vibrissae are added to those first present and the ordinary body hairs acquire a sensory innervation, as does also the integument generally.

EXPERIMENTS ON THE SENSE OF TOUCH.

The 7½ mm. embryos gave no evidence of having a sense of touch, although they were stimulated with a fine sable brush, and gently pricked with the point of a fine needle on various parts of the body, the limb-buds, and the head. Electrical stimulation with an induction-coil produced no apparent reaction except a variation in the rate of the heart-beat.

By the time the embryos had reached a length of 16 mm. (crown-rump measurement) slight but readily perceptible movements of the body were noted upon pricking with a fine-pointed needle. These were most marked when the stimulus was applied about the flanks and sides of the body and *the snout.* Stimulation with a fine sable brush failed to evoke any response. That the response to the needle-prick on the snout was due to nerve-innervation and not to direct stimulation of a motor mechanism is shown conclusively (1) by the fact that the movement called forth involved the turning of the head as a whole, and (2) by the additional fact that the sections show no sign as yet of the histogenesis of muscle in the snout region. Furthermore the reaction was too promptly made to permit of the stimulus being transmitted through the general protoplasm.

In embryos of 23 to 28 mm., crown-rump length, stimulation with the brush, as well as gentle pricking with the needle-point, about the shoulder, upper arm, hip, rump, and thigh, resulted in movements of the limbs or body-wall as the case might be. Stimulation of the vibrissal region of the snout

produced movements of the head decidedly more vigorous than before recorded.

Fetuses 3.5 cm. in length from tip of snout to base of tail were very active, squirming and kicking about while yet within the uterus. Upon removal they were found to be very sensitive to stimulation with the brush, needle-prick, and induction-current, fully as much so, apparently, as newly-born young. They responded to stimulation on the flanks, sides of body, front and hind-limbs, toes, tail, neck and head, by more or less violent wriggings and twistings of the body, movements of the limbs, spreading of the toes, etc. One hour after removal from the uterus, they responded with faint squeaks upon stimulation with the needle-prick, undoubtedly showing the presence of pain-sensation. Gentle stimulation of the flank with a sable brush caused the body to be bent laterad into the form of a C, that is, the head and posterior end of the body were turned toward the side stimulated. Upon a prolongation of the stimulus, the anterior and posterior extremities of the body were jerked back to or slightly beyond a straight line corresponding to the longitudinal axis of the body. When the stimulation was still further prolonged, writhing and jerking movements were made that persisted for a few seconds after cessation of the stimulation. Milder stimulation, as with a single hair, called forth little or no response except when applied to the snout, the region of the vibrissae being decidedly more sensitive than other regions of the head or body.

When young rats (4.3 cm. long) only a few hours old were gently stimulated by touching the sides of the body with a sable brush, they responded by contortions of the body, movements of the limbs, both fore and hind, and gave vent to audible squeaks. But here again it was found that the

region of the vibrissae was especially sensitive. SMALL ('99) notes for this stage (the earliest heretofore examined) in the rats which he had under observation that "they give little response to light pressure, as with a hair,—except upon the nose, which seems to be very sensitive. Mass pressure is not noticed unless comparatively strong."

Rats thirty to thirty-six hours old when stimulated with a small sable brush were found to be very sensitive about the vibrissae, flanks, and mid-dorsal line of the body. When stimulated on the flanks, some (the larger and more vigorous individuals) responded quickly with an attempt to push away the brush with the hind-foot of the same side, the toes being spread well apart; others (smaller in size but belonging to the same litter) made a less vigorous response, more apparent when the brush was applied to the ventral part of the flank. Apparently voluntary (?) scratching movements with the hind foot were noted at times in the larger individuals. There were distinct reactions to the needle-prick on the foot, shin, thigh, tail, hand, fore-arm, upper arm, shoulder, sides, flanks, top and sides of the head, cheeks, and region of the vibrissae. Electrical stimulation with an induction-coil applied to the back of the head, along the entire length of the spinal column, of the trunk and tail, the legs, sides of the body and belly, all resulted in decided reactions, the movements amounting to contortions in many cases. Stimulation of the feet in the same way produced a spreading of the toes to a slight but appreciable extent.

In the case of 55-hour-old rats, stimulation with a sable brush resulted in attempts to remove the irritating object by kicking and scratching movements of the hind legs and feet. They were most sensitive on the sides of the body and flanks, though

nearly as much so on the limbs. Stimulation of the top of the head and back produced the same responses but only after the lapse of several seconds, that is, after prolonged stimulation. Touching the region of the vibrissae resulted in twitching movements of the upper lips. Stimulation of the tail resulted in its being tucked in underneath the body and between the hind legs. Brushing the median side of the hind foot resulted *usually* in violent contortions of the hind quarters together with the drawing up of the hind feet along the sides of the body; frequently when the left hind foot was stimulated with the brush, the right one was used to scratch the right flank, or vice versa; a few seconds later the stimulated foot was also drawn up in the same way to scratch the flank on its side. The median side of the foot seemed to be more sensitive than the outer side.

Gentle pricking with the needle on the frontal, occipital and parietal regions of the head resulted in immediate response; the whole body was violently contorted and movements of the *hind feet* as though to brush off the irritation were noted. Pricking of the lower jaw or snout resulted in violent attempts to wipe off the irritating object with the fore paws, usually both paws being used simultaneously, and even overlapping each other, the one on the side stimulated being *underneath* the other. These movements were followed after repetition of the stimulus by an opening of the mouth, extension of the tongue, and movements as of swallowing. When the hind feet were in such a position that they could not be well used, the front feet were employed to wipe off the irritation on the back of the head. The tail, feet, legs, and forequarters were very sensitive to needle-pricks; the

hind-quarters less so. Reactions to electric stimuli were violent.

Small's results on this stage were in part markedly different from those recorded here. He says: "Irritating fluid (HCl) produced instantaneous responses from all. In addition to the motor reactions, there were vocal expressions and a striking acceleration of respiration. Reactions to the other stimuli were slow, varying from ten to fifty seconds."

In the case of three-day-old rats the skin seems not so sensitive as in earlier stages. Upon stimulation with sable brush on hind-quarters, hind-legs, flanks, sides of body, and back, no noticeable response was called forth. Brushing the shoulders and fore-limbs, sometimes, but not always, occasioned a movement of the hind-limbs as though to scratch or push off the irritating object. The same sort of stimulation applied to the top and sides of the head produced no apparent response. Stimulation, with the brush, of the snout and the region of the vibrissae, if prolonged, produced squeaks and movements of the head as though to avoid the irritating object, but *no* movements of the forelimbs and paws.

Gentle pricking with a needle of the rump, thighs, hind legs and tail produced no appreciable response. Pricking of the *hind feet* resulted in a violent attempt to tuck them under the body. Pricking along the vertebral column from the lumbar region cephalad, over the head, sides of the body (but *not* the flanks), fore-limbs and paws resulted in violent contortions of the whole body, rather than in any specific response of the parts directly stimulated. Response to electrical stimulation was not so violent as in earlier stages.

With five-day-old rats practically identical reactions were obtained. Small's results, again, are

not wholly in accord with those recorded here. He notes for the 5th to 8th days inclusively that the "Dermal sensitivity becomes more acute, though susceptibility to pressure is still greater on the nose than elsewhere on the body. Especially, greater when tickling is involved. A bristle drawn across the body elicits scarcely any response; but applied with the same pressure to the nose, it evokes squeaking and vigorous head-shaking" (on the 7th day). "When the toes are touched the rats squeak and jump so as to lift the body nearly off the floor. One, thus insulted, crawled away two inches."

Rats nine days old were very sensitive to touch all over the body, legs, and head, responding not only by muscular movements but also by squeaks.

When gently pinched on the cheeks and sides of the heads in front of the ears they sought to push away the offending object with their forepaws. When pinched gently on the top or back of the head the hind foot of the same side was brought forward to push away the forceps; the same reaction was evoked when the sides and flanks were gently pinched. Pinching of the toes sometimes produced an instant response—squeaking and retraction of the legs—but sometimes the response was very slow or even absent. The pinna of the ear was very sensitive to touch. Pinching the tail, rump, etc., resulted in squeaking and turning movements of the whole animal—sometimes it whirled end-for-end almost instantly.

At an age of twelve days there was not manifested such sensitiveness to light pressure, e. g., of a brush, as at previous times. A needle prick, except about the base of the vibrissae, must be accompanied by considerable pressure to evoke a marked response. Pricking about the region of the vibrissae

resulted in violent responses and vigorous rubbing of the region on both sides of the head with both fore-paws. Small notes that the "Dermal sensitivity [is] considerably heightened. One jumped violently when touched with the sharp corner of a piece of paper. Flanks, sides, back and feet are equally sensitive."

In rats sixteen days old the vibrissae were very long and in constant use. When pinched about the face with fine forceps, one grabbed them with its jaws and *bit them* forcibly enough to make a distinctly audible gritting sound. Otherwise this stage revealed practically the same conditions as are recorded for the preceding stage.

Structural Observations on the Tactile Apparatus.

In the 7½ mm. embryos a large number of association fibers are already present in the cord, and brain stem. The anlagen of the vibrissae are not yet apparent. The innervation in the snout region comprises two branches of the fifth nerve. Of these the ramus ophthalmicus profundus trigemini has the form of a small bundle of fibers, tapering off to a *single* fiber at the distal end, deep within the mesenchyme, connection with the more superficial tissue not yet having been established. The ramus maxillaris trigemini extends slightly anterior to the optic cup, but ends before reaching the surface ectoderm. Sensory fibers of the spinal nerves do not extend to the periphery.

In the 16 mm. embryos, about a dozen anlagen of vibrissae are present on each side of the snout. The vibrissae themselves do not extend to the surface. The ramus maxillaris trigemini in the form of a large trunk with many fibers runs to the snout region where it breaks up into a "brush" by the

spreading apart of its branches until finally some of the fibers end in a "basket" or reticulum in the follicles around the bases of the vibrissae. The ramus mandibularis trigemini has a similar distribution to the vibrissae on the lower jaw. Proximad the maxillaris enters the Gasserian ganglion through which none of its fibers can be individually traced, although it is possible to find many of them in connection with ganglion cells. In other words, the distal fibers of the trigeminus, so far as can be determined, are axones of neurones located in the Gasserian ganglion. The ganglion itself is connected with the anterolateral margin of the myelencephalon by a large trunk of fibers which run dorsad along the anterolateral face of the hindbrain for a considerable distance, then turn sharply caudad to enter the medulla in which they join or constitute a large ventro-lateral tract.

In the 23 mm. embryo the number of anlagen of vibrissae has increased to more than thirty on each side of the snout. Those present in the earlier stage described above are much farther advanced in their development than those whose appearance is more recent. In the former the vibrissa itself is distinct from the follicle and the usual structural characteristics of both are shown. The relatively simple "basket" of fibers noted in the follicles in the 16 mm. stage is represented now by a much more complex felted layer of fibers buried between two layers of the follicular cells and forming a fibrous lamina about equal in thickness to the follicular layer between it and the root of the vibrissa. Whereas in the 16 mm. stage only one or at most a very few fibers were distributed to each vibrissa, in the 23 mm. embryo each of the older vibrissae is innervated by a large number of fibers forming a well defined branch of the ramus maxillaris tri-

gemini. Moreover, the general ectoderm covering the snout has extending *toward* it a few branches of the same nerve. These fibers do not exist in sufficient numbers to constitute branches anywhere near the size of those innervating the vibrissae, and they follow in nearly every instance a course parallel to a small blood-vessel running toward the surface between the rows of vibrissae. So far as could be determined these cutaneous nerve fibers have not yet come into contact with the ectodermal layer covering the snout.

The motor branch of the trigeminus can be distinguished from the sensory branch at this time; it is completely fibrillated and can be traced proximad into the medulla in which it runs slightly posteriorly in a ventro-dorsal direction to its nucleus. The latter is well defined; apparently it has no correlation tracts connecting it with any other part of the brain. The proximal connections of the sensory bundles of the trigeminus are the same as noted in the 16 mm. embryo. They enter the medulla just posterior to the motor branch and turn sharply caudad in the ventro-lateral marginal velum of the hind-brain. No correlation tract between the trigeminus and the corpora quadrigemina can be detected. All portions of the trigeminus seem to be completely fibrillated. Correlated with the increased size of the trigeminal trunks there is a marked increase in the number of the neurones in the Gasserian ganglion from which fibrillated processes can be seen extending either proximad, or distad, or both. There is also noticeable a tendency for the fibers which extend through the ganglion for any considerable distance to be arranged in definite tracts which lie nearly parallel with each other and to the long axis of the ganglion itself.

The chief advance noted in 26 to 28 mm. embryos in connection with the trigeminal system, aside from a continuation of the lines of development just described for the 23 mm. stage, consists in the appearance of numerous fibers passing between the medulla and the corpora quadrigemina; that is, co-ordination between these two parts of the brain is certainly possible now, if not earlier. These correlational fibers are to a certain extent grouped into a great number of small bundles each with only ten to twenty, or possibly in some cases more, fibres. Consequently it is manifestly impossible to identify by name at this stage the tracts that will be present in this region in the adult.

In the 3.5 cm. fetuses the motor branch of the trigeminus is much larger than in the preceding stages, but runs in the same way to its nucleus of origin in the medulla. This nucleus likewise is larger in extent than before, though its cells are not apparently more numerous. They are, however, more widely separted from one another and in the spaces between them numerous correlation fibers from the lower levels of the medulla pass cephalad to the midbrain, or *vice versa*. The sensory fibers of the trigeminus are likewise more numerous than in the preceding stages. Many of them upon entering the medulla follow the same course as that already described for them in younger embryos; others enter more deeply into the substance of the medulla, some in fact almost reaching the floor of the fourth ventricle. Anteriorly a well defined portion of the sensory root fibers of the trigeminus pass in a dorsal direction through the antero-ventral portion of the medulla to the posterior corpora quadrigemina, and there are indications, though rather slight as yet, of a portion of this tract passing on into the anterior corpora quadrigemina.

The snout region of the newly born rat not only shows a greatly increased number of the vibrissae, but the anlagen of the ordinary body hairs are almost innumerable and the dermis contains a rich plexus of nerves which also extends through the stratum germinativum into the stratum intermedium of the epidermis. This is, of course, the usual type of ending for the organs of touch and general sensitivity, and those functions are therefore completely provided for at birth in the white rat. The fibrillar basket in the follicles of vibrissae can be seen to have the form of elongated cylinders at the base of which a bundle of nerve fibers leave the follicle at some distance, however, distad to the base of the latter structure, which extends deeply into the dermis. The distal ends of the various trigeminal branches are composed of a greater number of fibers than heretofore, and of course the same is true also of the main trunks of this nerve. Of its central connections nothing new can be said, and aside from an increase in the number of fibers in the tracts leading to the cerebellum and to the corpora quadrigemina, a condition well marked by the ninth day after birth, no further appreciable advances are made in the structure of the tactile system during the time under consideration in this paper.

In general, meaning by that to include other forms as well as the rat, the relations of the sensory roots of the trigeminus with the cortex are at best little understood. According to Edinger, "The cortical area and the central path of the sensory portion of the *nervus trigeminus* from the cortex to the capsula are yet unknown. Following pathological experiences, its fibers must lie in the posterior third of the capsule. The cortical tract of the trigeminal ends, in rabbits at least, in the ventral portion of

the thalamus. Leading up to it is a large bundle from the opposite nucleus of the bulb. And in this nucleus itself terminate the processes from the cells of the Gasserian ganglion. The ascending root contains the tactile nerves of the face as is shown by pathology."

Summary of Results on the Sense of Touch.

1. **7½ mm. embryos:**
   a. This stage, the youngest examined, gives no evidence of the possession of the sense of touch.
   b. A large number of correlation or coordination fibers are already present in the cord and brain stem. Both sensory and motor fibers of the spinal nerves are present though the former do not reach the periphery. The snout region is innervated by two branches of the trigeminus nerve, which, however, end within the mesenchyme i. e., do not reach the periphery. No anlagen of vibrissae are apparent.
2. **16 mm. embryos:**
   a. The tactile sense is present on the flanks and snout as evidenced by motor responses to needle pricks. There is no response to stimulation with a sable brush.
   b. About a dozen anlagen of vibrissae are found on each side of the snout; these are innervated by branches of the maxillary division of the trigeminus, which end in a basket-like reticulum in the vibrissal follicle.
3. **23 to 28 mm. embryos:**
   a. They respond to stimulation with a fine sable brush as well as with a needle-prick; the snout region is most sensitive, though stimulation about the shoulder, upper arm, hip, rump, and thigh, also evokes motor responses.
   b. There is a noticeable increase in the number of the vibrissae as well as greater complexity in the neurofibral basket in each vibrissal follicle. The

number of neuro-fibers of the trigeminus innervating the vibrissae is greatly increased. The general integument of the snout region has not yet received the terminations of other branches of the trigeminus, though many such are extending toward it, for the most part parallelling blood vessels in their course. In the 23-26 mm. embryos association paths exist between the medulla and the mid-brain.

4. **3.5 cm. fetus and new-born rats:**
   a. The tactile sense is still better developed over practically the whole of the body, tail and limbs. The snout is the most sensitive as shown by response to stimulation with a single hair. Pain or discomfort is now shown by squeaks.

   b. There is an increased number of vibrissae on the snout; the anlagen of ordinary body-hairs are very numerous, and the integument contains a rich plexus of nerve-fibers extending (in the snout) through the stratum germinativum into the stratum intermedium. There is an increased number of sensory fibers of the trigeminus ending in the snout region. The central connections are better marked and more extensive than in the preceding stages. The fibrillar baskets in the vibrissal follicles are now elongated, felted cylinders, from the base of which the neurofibers in a relatively large bundle emerge some distance distad to the base of the follicle itself.

5. **Older stages:**
   a. Throughout the older stages examined there is in general no particular advance in tactile sensibility over that just described. There is a continued superiority of the snout region over the rest of the surface in sensitiveness to tactile stimuli and the use of the vibrissae as "feelers" is more and more marked.

   b. The structural advance in the tactile apparatus during these later stages is confined to an increase in the perfection of the mechanism already described.

EXPERIMENTS ON THE SENSE OF EQUILIBRIUM.

The earliest indications of a sense of equilibrium were observed in the case of the 3.5 cm. fetuses. One hour after their removal from the mothers' uterus they were able to sit upright on the belly with the forepaws placed well apart and the head up. At intervals the head was raised and moved from side to side, then returned to a resting position with the "chin" on the bottom of the dish or on one fore-leg. They were able to regain this position after stimulation with a brush applied to the flank had caused them to bend the body laterad into the form of a C, and upon prolongation of the stimulus writhing and jerking movements of a somewhat violent character had followed. Turning them over on their backs did not result in attempts to right themselves, except very rarely, and then the efforts were very feeble.

Young rats nine to ten hours after birth crawled awkwardly about over one another, and nosed about in an evident attempt to find the mother's nipples. Without artificial stimulation they would roll over onto the belly, sides, or back at will; turned the head from side to side; kept their tails tucked beneath the body between the hind legs. When turned over on their backs by the experimenter they made awkward righting movements, which sometimes succeeded. They had much better use of their forequarters than of the hind; they could spread their front legs apart so as to support the head in an upright position. At eleven to twelve hours of age they were able to crawl over the edge of a Petri dish and to wriggle their way

through an inch of cotton wool. At thirty hours of age the tendency to lie on the belly rather than on the side was more strongly marked than heretofore. They were rather restless, crawling about from place to place. Apparently voluntary scratching movements with the hind foot were noted. The tail was held extended posteriorly, that is, was not tucked forward beneath the body as in the case of newly born rats. Frequent twitchings were noticed over various parts of the body, especially on the shoulders, hips, and flanks. In the case of 55-hour-old rats it was noted that when at rest they took various positions, but seemed to prefer to lie on the belly with the head held either in a straight line with the body-axis, or turned to one side, or even with the snout tucked down between the fore-legs. They were able to roll over voluntarily from one side to the other. Their movements were but little better co-ördinated than in the preceding stages. The 78-hour-old rats, when put into a Petri dish in the warm chamber lay flat on their bellies with the head extended in the line of the long axis of the body; the fore-limbs were spread more or less widely apart, and usually the paw and the fore-arm to the elbow rested upon the supporting surface. The hind-limbs were also spread well apart but not so widely as the fore-limbs. Occasionally all four (4) limbs were drawn under the body in such a way as to hold it slightly elevated above the surface of the dish. The tail generally extended straight backwards. They seemed rather "nervous," frequently changing their position, twitching various parts of the sides and legs, moving the latter forward and backward, turning the whole body so as to face now in one direction and now in another, and the tail was occasionally directed forward so as to lie alongside the body. When rolled over on the back

or side, they usually remained comparatively quiet for a few seconds, and then rolled back and regained the usual position with the belly down.

The young rats on the fifth day after birth had better co-ördination of their movements than in previous stages, though still far from complete. For instance, the left hind foot of one was much inflamed and swollen and the young rat spent much of his time at intervals in licking this foot. It was also observed deliberately washing its face by licking its perfectly normal front paw and then rubbing the face with it. These actions were performed not once but repeatedly.

When placed with the hind quarters hanging down over the edge of a small box-lid, they made only feeble and futile efforts to keep from falling off. They would occasionally raise a hind foot as though to catch hold of the upper edge of the box-lid, but finally would usually fall off without any further attempt, apparently, to save themselves. Occasional "stretching" movements were observed while the hind quarters overhung the edge of the box; they may have been attempts to regain a more comfortable position on top of the box-lid. There were also apparently voluntary attempts at scratching the flanks with the hind feet.

Nine-day-old rats crawled about with considerable agility; occasionally raised their heads to sniff. When at rest they lay on the belly with all four limbs spread well apart. When placed at the edge of the table top they moved along it with the feet and vibrissae of one side tracing the edge. When an attempt was made to push them head first over the table edge they braced themselves with their feet and pushed back with all their power. They righted themselves immediately when placed on their backs, although the movements were not

thoroughly co-ördinated, particularly those of the hind limbs and quarters.

At twelve days of age the rats *walked* in the manner of an adult, though the movements were still lacking somewhat in co-ördination; the latter was, however, noticeably better developed than heretofore. They hung back downwards from the experimenter's finger, holding on with fore-paws and head, or with all four feet and head, for a few seconds, and then finally managed to pull themselves over to the top side of the finger and thence to the back of the hand. When placed on a slide box they crawled around feeling the edge with their vibrissae and the ventral surface of the jaws. Sometimes they would stick their heads far over the edge of the box and then would turn around and crawl to near the center, where they would remain until stimulated to further movement. Small noticed twelve-day-old rats crawling to the edge of a table stopping, reaching over as far as possible without falling, "throwing up the head and *sniffing* in the very characteristic way of rats when orienting themselves," and then retreating.

At sixteen days of age their movements were all well co-ördinated. They crawled readily; their equilibrium was well established. They moved easily from end to end along the experimenter's finger without showing any sign of falling or of losing their balance.

Structural Observations on the Organs of Equilibrium.

In the 7½ mm. embryos there is no trace of semicircular canals. The auditory vesicle is large and spherical, its wall epithelial in character. There is a large endolymphatic duct running dorsad and ending blindly in the mesenchyme of the dorsal part

of the head. The eighth nerve is a short trunk only that cannot yet be separated into its vestibular and cochlear portions, and none of its fibers could be detected reaching the cells composing the auditory vesicle.

In the 16 mm. embryos the ear has reached a stage corresponding very nearly to that of the 20 mm. human embryo, as described by Streeter. The three semicircular canals are well formed, and the vestibular nerve sends a completely fibrillated branch to the ampulla of the superior canal as well as one to the ampulla of the lateral canal, these two branches arising from a common trunk a short distance from their terminations. Shortly before the division just mentioned, the vestibular nerve gives off the utricular branch. A longer fourth branch runs to the ampulla of the posterior semicircular canal. The sacculus is a bud-like projection from the posterior side of the utriculus and from it the cochlea arises by a slightly constricted neck, the ductus reuniens. The cochlea extends in a generally ventrad direction, making one complete turn at its distal end. The innervation of the sacculus seems to be by a branch of the cochlear and not the vestibular nerve as Streeter maintains for Homo; at least the vestibular branch to the posterior semicircular canal is not connected at this stage with the sacculus. The common trunk of the vestibular nerve emerges from the otic capsule and after reaching the brain cavity enters a ganglion (Accessory Ganglion?) from which it emerges *before* passing into the myelencephalon, to end in its nucleus close beneath the floor of the fourth ventricle. Distally the fibers of the vestibular nerve can be seen penetrating in among the cells that are beginning to elongate to become the sensory cells of the cristae acusticae.

In the 23 mm. embryo the cristae acusticae are prominent ridges about as high as broad at the base, and with the top of the ridge arched over in a very regular curve. The differentiation of the cells composing the epithelium covering this structure has not gone far enough to enable one to distinguish the sensory and supporting elements. However, it is clear that there is an outer layer of cells rather regularly arranged everlying a basilar layer in which the cells have no very definite arrangement. A small amount of endolymph is present in the ampullae. The core of the cristae is made up of a mass of mesenchymatous cells among which a few unmedullated fibers of the vestibular nerve make their way to end among the cells of the epithelial layers. The latter, moreover, do not yet have the cilia or sensory processes found later. The vestibular nerve has the same relations with the medulla as those described for the 16 mm. stage. A tract from the same general region of the medulla in which the vestibular nerve ends runs dorsad into the cerebellum, but any actual relationship between the two could not be determined in these preparations.

In the rat at birth and during the first day the semicircular canals are much larger than in the preceding stages. The cristae acusticae are not only larger but their cells are differentiated into a superficial layer composed of stoutly columnar cells; and a supporting layer of very slender columnar cells, in many instances much longer than the sensory cells. Each sensory cell is inclosed in a "stockade" of nerve fibers in such a way that a mechanical pressure exerted at any point must result in the stimulation of one or more nerve fibers. The peculiar terminal process projecting into the endolymph undoubtedly serves as a lever that magnifies the

sensitivity of the cell to movements of that fluid. Centrally the root of the vestibular nerve can be followed through the skull into the accessory nucleus thence on into the medulla, in the manner already described. Through the medulla its fibers course dorso-mesad, finally ending in a nucleus through which there also run correlational fibers caudad in the medulla and cephalad into the cerebellum. Medullation has not occurred in any of these tracts.

No further differentiations of any importance have been detected in connection with this apparatus in later stages.

The functions of the cerebellum, like so many other parts of the brain, are not thoroughly known; nevertheless it is generally agreed that the cerebellum contains the center "for the maintenance of the mechanical equilibrium of the body" (Sherrington, p. 348). If this be true, it is evident that the central connections for the main organ of equilibrium, the system of semicircular canals, are established at or shortly before birth. At this time also the maculae and cristae acusticae have their characteristic structural features developed to a functional extent. Were this the whole of the mechanism concerned in maintaining equilibrium it would appear that the rat at birth could maintain its proper orientation without difficulty, and this is indeed true to a large extent. But the fact that the ability to maintain equilibrium improves during the succeeding two weeks or more of postnatal life indicates that other factors are involved. One of these is undoubtedly muscle tonus, which probably comes as an effect of use. Moreover, it will be recalled that it was only at the time when the eyes become functional that the power of equilibration is perfected. This accords perfectly with the results of

investigations elsewhere on this sense. It is a well-established fact that the sense of sight has a very important relation to the maintenance of equilibrium.

The vibrissae are also used as organs of orientation in the rat and constitute another element in the mechanism of equilibration.

Summary of Results on Equilibrium.

1. **7½ mm. embryos:**
   a. There were no experimental results indicating a sense of equilibrum at this stage in development.
   b. There are no traces as yet of semicircular canals.
2. **16 mm. embryos:**
   a. There was no experimental evidence of a sense of equilibrium in this stage.
   b. The semicircular canals are well formed, and the ampullae are innervated by fibrillated branches of the vestibular nerve. The region of the cristae acusticae is indicated merely by an elongation of the endothelial cells.
3. **23 to 28 mm. embryos.**
   a. There was again no experimental evidence of a sense of equilibrium in these stages.
   b. The differentiation of the cells of the cristae acusticae is proceeding, but the sensory and supporting elements are not yet distinguishable. There are slight indications of a central connection with the cerebellum.
4. **3.5 fetus:**
   a. The earliest observed indication of a sense of equilibrium occured at this stage. One hour after removal from the uterus the young were able to maintain an upright position of head and body, and to regain this position when disturbed. When

turned over on the dorsum infrequent and feeble efforts were made to right themselves.

b. The structural features are practically identical with those of young rats during the first day after birth.

5. **First day after birth:**

a. During the first day after birth the young rats crawled awkwardly about; turned the head from side to side; made awkward righting movements when turned over on the dorsum, which sometimes succeeded.

b. The semicircular canals are larger than in the earlier stages described; the cristae acusticae have the sensory and supporting cells clearly differentiated; the former are inclosed each in a "stockade" of nerve fibers in such a way as to transmit easily any stimulus produced by a change in the position of the animal. The central connections of the vestibular nerve are well defined.

6. **Later stages:**

a. Throughout the later stages there was manifested a gradual perfection in the sense of equilibrium, accompanied by a gradually increasing power of coordination of movements.

b. The later stages witness the addition, through the establishment of various correlational tracts, of other factors concerned in the perfecting of the power of equilibration, notably (1) muscle tonus, (2) the use of the vibrissae, and (3) sight.

EXPERIMENTAL OBSERVATIONS ON THE SENSE OF SMELL.

The youngest stage tested for the sense of smell was that of the 3.5 cm. fetuses. When removed from the uterus and the fetal envelopes they were placed in a dry dish in the warm chamber, and respiration was soon set up; the mouth opened widely and closed, as though yawning, or possibly gasping for breath—one could hardly decide which, possibly both. They wriggled and nosed one another about as though in an effort to find the mother's nipples,— this occurred however only after the lapse of two hours or more from the time of their removal from the uterus. No perceptible reaction to various odors was detected, though when the brush dipped in an odoriferous substance accidentally touched the snout there was evident discomfort manifested—probably a *tactile* response however.

Young rats during the first day after birth seemed to perceive odors as evidenced by turning the head and movements of the snout as though sniffing. It was rather difficult to be sure of the results, however, since the responses occurred only after the lapse of a considerable time—15 to 30 seconds—and may have been "spontaneous" movements, i. e., due to other unknown stimuli. Small's observations on this point are in the main corroborative of the results recorded here. He notes: "Smell. 5 rats. All sensed violet, as indicated by expressive movements. Reaction, slow—about 15 seconds. One only objected. All showed dislike to cheese, if movement away could be so interpreted. Instantaneous convulsive reaction to HCl."

During the second day after birth no perceptible advance in the sense of smell was noted. The same turning movements of the head and twitching of the snout were evident, though the reaction time was still long—15 seconds or more—so that it was impossible to be sure of the relation of cause to effect. Small notes that in his rats there "seems to be slight advance in sense of smell, for they made no objection to the odor of cheese. Other odors elicited same responses as first day."

On the third day after birth the olfactory sense seemed a little better developed. The reaction time was shorter, ten seconds or less in some cases. Distinct sniffing movements of the nostrils followed the presentation of a piece of cheese. Small records for his animals at the corresponding stage that "only one of the five showed aversion to violet, and two to clove and asafoetida. Spirits of camphor and pennyroyal brought expressions of disapproval from all. Irritating fluid (HCl) produced instantaneous responses from all. In addition to the motor reactions, there were vocal expressions and a striking acceleration of respiration. Reactions to the other stimuli were slow, varying from ten to fifteen seconds."

On the fourth day after birth the olfactory responses to various foreign odors (violet-water, cow's milk warmed until it steamed, xylol, tobacco smoke) were more clearly defined than on the preceding days, except that the reaction time was if anything, longer, ranging from ten to twenty seconds, or even more. Small's record for this stage is a follows:

"Smell. Reactions to violet, camphor, pennyroyal, and clove, show less aversion; those to asafoetida are quicker and show more dislike. In four cases out of five there seemed to be a pleasurable response to cheese-odor—in one case accompanied

by what sounded like a pleasant squeak. The fifth one paid no attention. In case of camphor and pennyroyal, it was easy to distinguish between the act of sensing the odor and the affective response. They sensed pennyroyal quickly—about 5 secs.—sniffed with deep respiration—then slowly averted the head."

Rats on the fifth day after birth when first removed from the nest were disappointing in their responses to odors. At times they seemed to discriminate between those which might be considered pleasant and unpleasant, and then again, showed utter indifference to them. On the whole the results were so contradictory that it was impossible to feel sure on this point. The reaction time in all cases was so long that one could not determine whether the movements may not have been due to other stimuli than those of odors. However, after they had been kept away from the nest several hours, and the mother had again been handled for a few minutes, they exhibited a noticeable increase in the degree of their activity upon being taken up in the hand for replacement into the nest. They "nosed" around and nibbled at various places on the palm and fingers as though seeking the mother's nipples. This may have been due to hunger and a feeling of warmth in the hand. SMALL'S record for the corresponding period in his observations is terse—"nothing new in regard to the special senses." However, on the 7th day he notes that "the tests for smell seem to show a growing indifference to all but the positively painful stimuli —irritating fluids, e. g., HCl." For the 8th day his statements appear rather contradictory; he says: "Reactions to odors become more individual. On the whole they tend to become indifferent.

Glacial acetic acid and carbolic acid gave negative reactions."

On the ninth day after birth the young rats, would raise their heads to sniff when tobacco smoke was blown over them. An extra strong puff from a pipe was followed by reflex movements and a weak regurgitation. They reached after a brush dipped in xylol and held one-fourth inch in front of the nose (they eyes were not yet open), until the head had been extended nearly half an inch directly forward; then they stopped and paid no further attention to the odor, withdrawing the head to the resting position. The snout at this time is well developed, having very much the form of that in the adult. SMALL records that during the 9th to 11th days, "the special senses show no new features."

In twelve-day-old rats there was again a very marked olfactory response, when a brush dipped in xylol was held a short distance in front of the nose. The head was raised, turned from side to side, and the nostrils alternately dilated and contracted as though sniffing the odor. Upon gradually removing the brush to a distance of six to eight inches, the rats moved forward a few inches (two to three) sniffing with the snout elevated as they moved. A similar response was made to the odor of alcohol. SMALL noticed twelve-day-old rats "throwing up the head and *sniffing* in the very characteristic way of rats when orienting themselves." On the fourteenth and fifteenth days, SMALL noted their ability to "sense odors at a much greater distance than previously."

By the sixteenth day young rats appear to have the sense of smell as well developed as have the adults. They move directly toward cheese and miscellaneous food stuffs put into the cage for the

mother to eat. SMALL notes that his rats at this age "recoiled quickly from camphor. Moved quickly toward brown-bread, dog-biscuit, and honey held at a distance of one inch. Appeared not to dislike iodoform or wintergreen."

In short, the sense of smell may be present, in a rudimentary form, at most, at birth or within a few hours thereafter. It is gradually perfected during the course of the first two and a half weeks of postnatal life as the rat's relations to its environment become more complex. Probably the earliest odor sensed under normal conditions is the body odor of the mother. Since the nest is saturated with that odor, and other surroundings have it to a less degree, the very young rats may be more strongly influenced to remain quietly in the nest during the mother's absence than would otherwise be the case. At any rate such a hypothesis would account for the very early appearance of this particular sense, though of course temperature and contact sensations probably also enter into the situation.

Structural Observations on the Organ of Smell.

In the 7½ mm. embryos the olfactory pits are well developed and open widely to the exterior. The future olfactory area is indicated by three pockets in the dorsal portion of the pit. There is no rhinencephalon nor an olfactory nerve.

In the 16 mm. embryos the olfactory vesicle is large and the number of pockets in its dorsal area has increased to eight. The olfactory epithelium is much thickened in the olfactory area but otherwise no indication of the distinctive histogenesis of the olfactory cells is apparent. The olfactory nerve is present and has the form of a short brush of nerve-trunks converging to a small area of union

with the olfactory lobe. The latter is a short evagination from the anterior end of the prosencephalon and contains a large ventricular cavity, which opens widely at its posterior end into the lateral ventricle of the cerebral hemisphere. In the region of the olfactory vesicle the olfactory nerve branches are distributed to various parts of the olfactory epithelium and to Jacobson's organ. From their earliest appearance the olfactory nerves differ greatly from all other nerves. The fibrillation is not so distinct and there is a large intermingling of mesenchymal (?) cells which in later stages constitute the sheath cells of the nerve branches; in fact, from the 28 mm. stage onward the fibrils are entirely inclosed by the sheath cells, giving the olfactory nerve a characteristic appearance by which it can be distinguished at a glance from all other nerves in the preparation.

In the 23 mm. embryo the fibrillation of the olfactory nerve is most clearly seen; in the 26 mm. embryo, the fibers are entirely inclosed by sheath cells except at the distal end of the most anterior branch. The sheath cells are elongated parallel to the long axis of the nerve and have distinctly elongated nuclei. The olfactory epithelium is still several cell layers thick but many of the cells whose distal ends constitute the surface of the olfactory pockets are becoming distinctly columnar, some at least extending fully half-way or more through the entire thickness of the epithelium. Their nuclei are elongated while those of the shorter more deeply situated cells are rounded or oval. In the 23 mm. embryo the cells of the rhinencephalon resemble mesenchymatous tissue, having large oval nuclei and numerous branching protoplasmic processes. The definite formation of axones can be detected. In the 26 mm. embryo, on

the other hand, the tractus lobi olfactorius is plainly indicated as a distinct bundle of non-medullated fibers, which runs from the anterior commissure, of which it forms a part, on either side in a ventro-latero-anterior direction *toward* the olfactory lobe, which, however, it does not reach. Other olfactory tracts in the brain are not distinguishable at this time.

In the 3.5 cm. fetus the tractus lobi olfactorii is a rather large bundle of fibers that begins in the lobus olfactorius posterior, and runs in a dorso-posterior direction for some distance and then turns obliquely mesad, dividing into two smaller bundles, which reunite after running almost parallel for a short distance. The reunited bundle runs in a postero-dorso-mesal direction until it merges with the anterior commissure, of which it forms the anterobasal portion. It then passes across to the opposite side of the brain, where it leaves the commissure and passes in an antero-latero-ventral direction to the dorsal portion of the olfactory lobe of that side. Its distal end in both cases is enlarged and spread out into the form of a brush. Other olfactory tracts are not distinguishable. The olfactory nerve branches are distinctly associated with if not covered by the sheath cells already described.

In the rat during the first day after birth the olfactory epithelium comprises sustentacular cells many of which appear to be ciliated; a few typical olfactory cells are shown by the silver method. They are long and slender with relatively large nuclei and have a process from the basal end which enters the adjacent olfactory nerve branch. The tractus lobi olfactorii is somewhat larger and perhaps better defined than in earlier stages. It extends well forward into the olfactory lobe but not as yet into the bulbus.

By the third day after birth it has reached not only the bulbus but apparently to the region of the glomeruli. Its fibrils are more distinct, especially at its distal end than they were previously, and the whole tract is much larger.

Succeeding days simply bring about the further development of these various parts along the lines already described.

Summary of Results on Smell.

1. **7½ to 28 mm. embryos.**
   a. No practicable means for testing the sense of smell in these earlier stages was devised.
   b. During these stages the olfactory apparatus is being gradually laid down, both as regards its central and its peripheral portions. The histological differentiation of the olfactory epithelium has not advanced sufficiently far to enable the sensory cells proper to be identified.
2. **3.5. fetus:**
   a. No absolutely certain response to olfactory stimuli was obtained in this stage.
   b. Both the central and distal portions of the olfactory apparatus show appreciable development over the preceding stages, but sensory cells in the olfactory epithelium are not apparently fully differentiated.
3. **First day after birth:**
   a. Apparent responses to olfactory stimuli were obtained in rats of this age, though the reaction time was long.
   b. The olfactory epithelium contains a few cells which are apparently fully differentiated as sensory cells. The central connections are better developed than before.

4. **Later stages:**

   a. There is, on the whole, a gradual perfecting of the olfactory sense from day to day.
   b. **Pari passu,** there is a gradual perfecting of the olfactory apparatus.

EXPERIMENTAL OBSERVATIONS ON THE SENSE OF TASTE.

The 3.5 cm. fetuses were able to make very feeble swallowing movements, but otherwise no results were obtained with liquids placed in their mouths.

In the case of young rats during the first day after birth, various experiments were tried to test their sense of taste. With a saturated solution of cane sugar in tap water, presented on a camel's hair brush, the first response was an attempt to push the brush away with the forepaws, probably on account of a tickling sensation when the brush touched the lips and snout. There was no audible squeaking noted. After the brush had been inserted into the mouth, they sucked away at it for several seconds, and upon the attempt being made to remove the brush, they held on with the jaws so firmly that the head and fore-quarters could be lifted from the dish in which they lay without them loosening their hold.

With a saturated solution of sodium chloride in tapwater, there were evident signs of discomfort displayed, and distinct attempts were made with the fore-paws to push the brush away. These movements were accompanied by quite audible squeaking. After the brush had been forcibly inserted into the mouth, sucking and swallowing movements followed, with no further evidence of discomfort.

With a solution of 1% acetic acid in tapwater, the evidence of distaste or at least of annoyance was even more marked. No sucking movements could be perceived following the insertion of the

brush into the mouth; more persistent efforts were made to keep the mouth closed and thus to keep out the annoying object. The squeaking was louder and longer than in the other tests, and the movements of the fore-paws to push the brush away from the mouth were made with greater persistence and force. These experiments were all tried on several different individuals with like results in all cases.

SMALL'S observations on rats of this age were as follows:

"Taste. Tested with sugar-solution, warm milk, and strong salt solution. These were applied to the lips with fine brush. In each case, the rats squeaked and wiped at the offending stuff with fore-paws. Movements rather incoordinated. The movements are: brushing and pushing away with the fore-paws; averting the head; movement of the whole body. In case of the salt solution, the reactions were more vigorous, accompanied by voiding of urine.

"Clear water called out the same characteristic reactions.

"From this similarity of response, I infer that there is no differentiation of tastes, as pleasant and unpleasant. They are all unpleasant."

Rats of the second day showed no perceptible advance in taste over the previous day.

On the third day taste seemed a little better developed; warm milk and sugar solution were received without protest and swallowing reactions followed. When the brush was wet in Ringer's solution and applied to the lips the front legs were used in efforts to brush away the irritation, and no attempt to nurse could be detected. On the fourth day the gustatory responses could not be more clearly determined than on the preceding day.

On the fifth day, several liquid substances,—milk, sugar solution, salt solution, dilute vinegar, and even tap water—when presented to their lips on a brush caused expressions of discomfort, such as averting the head, wiping away the brush with the fore-paws, squeakings, and, if the stimulation was prolonged, wriggling away on the part of the whole animal. SMALL notes for the corresponding period: "Nothing new in regard to the special senses."

The nine-day old rats displayed nothing new in regard to the sense of taste; the same was true at twelve days of age. The seventeen day old rats pretended at least to eat various kinds of food that had been placed in the cage for the mother. Did not exhibit any particular choice as to what they tried; the whole performance may have been merely an imitation of their mother's actions, for their eyes were now open and functional—a condition not occurring in the previous stages. SMALL records for this stage that "one ate honey when a drop was put into his mouth. Tried to gnaw brown-bread when a crumb was put into his mouth. After that when the brown-bread came within smelling range he would go toward it. Chewed a tiny piece, holding it in his paws in a well-bred rat's way. I gave a little piece to another one. He took it in both paws and chewed it. The others scented it and tried to help, but he quickly drew away with his treasure. There seems to be immediate association between smell and taste. Though not conclusive, the evidence points that way. Another one declined to eat sealing-wax after smelling it, and spat it out when a piece was put into his mouth."

Observations on the Organs of Taste.

In the 7½ mm. embryos no trace of any part of the glossopharyngeus nerve could be detected running to the mandibular arch. The mandibular branch of the trigeminus is a large bundle of fibres, which ends as a well-defined brush in the mesenchyme of the mandibular arch. A branch of the facial nerve runs into the base of the hyoid arch, and is likewise fibrillated.

In the 16 mm. embryos the lingual branch of the glossopharyngeus nerve runs to the posterior part of the tongue and its fibers are distributed among the muscles of the superficial layer. The mandibular branch of the trigeminus innervates, so far as can be determined, the rest of the tongue. No indications of taste-buds are present. Over the surface of the anterior two-thirds of the tongue, however, there are at least ten longitudinal rows of dome-shaped papillae, each consisting of a single layer of cubical cells forming the dome, and in the nearly spherical central cavity of the papilla there is a small number of nearly spherical cells. In a few instances nerve fibers can be detected entering the open base of the papilla and ending in a glomerulus or plexus around the central cells. A single median circumvallate papilla is fairly well-defined on the posterior portion of the tongue, and in this there is a relatively large plexus of nerve-fibers belonging to the glossopharyngeus. No taste-buds can be detected in the epithelial covering of this papilla.

In the 23 mm. embryo conditions are practically the same as those just described, allowing, of course, for an increase in size in all the parts mentioned. In the circumvallate papilla, some of the nerve fibers now extend toward, if indeed they do

not end among the epithelial cells of its surface. No taste-buds could be demonstrated. Over the anterior two-thirds of the upper surface of the tongue the dome-shaped papillae are present and show little if any advancement over the preceding stage described, except an increase in size.

In the one-day-old rat these dome-shaped papillae are much larger in size than before; their outermost layer of cells is somewhat flattened and covered with a thin cuticle; the inner cells are taking on a form and arrangement suggestive of a taste-bud, but only one such structure is present in each papilla, and that is situated in the center of the distal surface of the papilla. Nerve fibers run in among the central cells.

In the five-day old rat the dome-shaped papillae are larger and the number of nerve fibers running to each is much greater than before. Otherwise they appear very much the same.

In the nine-day old rat, however, quite a marked advance can be seen. The papillae on the whole are larger; their surface epithelium is much thinner and arched into a dome and in its center has appeared a small orifice surrounded by special cells. Beneath this outer layer, the cells of the stratum germinativum are elongated and arranged in somewhat the same manner as the elements of a taste-bud. The innervation is by fibrils of the trigeminus. At this time also the circumvallate papilla has numerous taste-buds of the usual type lying within its epithelial layer. Taste-buds also occur in the walls of the outer margin of the groove surrounding the circumvallate papilla.

Summary of Results on Taste.

1. **Before Birth:**

   a. The 3.5 cm. fetus were able to swallow, but neither in them nor in any preceding stages were there obtained any evidence of a sense of taste.

   b. At no time previous to birth could taste-buds or other fully differentiated organs of taste be demonstrated.

2. **First day after birth:**

   a. The results of tests for a sense of taste at this stage were very uncertain; apparently anything applied to the mouth produces a sense of discomfort. Sugar-solution, however was received with much less objection than salt or acid solutions, and may possibly have been perceived as having an agreeable taste.

   b. True taste-buds are not demonstrable in the preparations in hand; the dome-shaped papillae (fungiform) over the anterior part of the tongue are developing an organ of sense faintly suggestive in its general form and arrangement of a taste-bud, though decidedly not a typical one.

3. **Older stages:**

   a. Though it was exceedingly difficult to distinguish between annoyance or discomfort and a sense of taste, it was apparent, especially in the later stages, that this sense was present and gradually being perfected.

   b. There is likewise a gradual increase in the histological differentiation of the organs of taste until by the ninth day, at least, taste-buds are distinctly formed on the sides of the circumvallate papilla, and a decidedly different organ in the dome-shaped (fungiform) papillae.

EXPERIMENTAL DATA ON THE SENSE OF HEARING.

Absolutely no response to sound was noted before the twelfth day after birth. At that time a sharp clapping of the hands occasionally seemed to produce a response, i. e., the raising of the pinnae and turning of the head so as to face the direction of the sound. At other trials there was no apparent response. The same results were obtained by the ringing of a small hand bell. The shrill sound made by drawing in the breath sharply between the nearly closed lips several times was followed by a "nervous start," quite as characteristic but not quite so pronounced as that made by much older rats.

On the sixteenth day hearing is well established. Previous to this time the external auditory meatus is more or less closed by a cellular plug which would effectually obstruct the passage of all sound waves except in the case of very loud or very shrill noises. Attempts to remove this obstruction always resulted in so much hemorrhage and pain, or in so much damage to the ear, that no success was attained in attempts to secure an unobstructed passage for sound waves previous to the time when the meatus opens by natural means, i. e., the degeneration of the cells composing the plug.

SMALL'S observations and those of WATSON also are in complete agreement with those recorded here.

SMALL's record is as follows:

"Hearing. The bursting of a bag three feet away caused them to jump quite out of the nest. Later, clapping hands sharply at a distance of 10 feet caused the quick recoil peculiar to rats. Did

not run. A sharp "sh" at 3 ft. brought their heads up. Word "rats" in a low tone at 1 ft. caused a slight jump. Rustling of paper produced the same result. Whistling brought up the head as if listening. Even at the very dawn of ear-consciousness there seem to be differences of emotional reaction to different elements in the 'big buzzing confusion' around them. Every concussion elicits a startled movement; the gentle, prolonged note, e. g., whistle, on the contrary, produces a reaction indicative of unscared attention."

Observations on the Organ of Hearing.

In the 7½ mm. embryos the auditory vesicle is large and spherical with an epithelial wall and a well-defined endolymphatic duct running dorsad and ending blindly in the mesenchyme of the dorsal part of the head. The acustico-facialis ganglion is a large and definitely delimited mass of cells, with numerous fibres connecting it with the myelencephalon but no fibres have as yet reached the cells composing the wall of the auditory vesicle.

In the 16 mm. embryo the ear has developed to the stage very nearly corresponding to Streeter's 20 mm. human embryo. The endolymphatic duct is long, slender, and ends distally in an enlarged saccus endolymphaticus. The utriculus and sacculus are distinctly formed, the latter being a bud-like projection from the posterior side of the former. From the sacculus, the cochlea arises by a slightly constricted neck, the ductus reuniens, and extends generally ventrad, making one complete coil at its distal end. The spiral ganglion extends along the median one-half or two-thirds of the cochlea, or at least it cannot be detected for some considerable distance from either the proximal or distal ends of the

cochlea. It is made up of ovate bipolar cells. Those in the distal portion of the ganglion have as yet no fibrillated processes; those more proximal in position have fibrillated processes at both poles, but the distal ends do not enter the epithelium of the cochlear canal, though in places they come into contact with the cochlear epithelium. No trace of an organ of Corti can be seen.

In the 23 mm. embryo, the organ of Corti is indicated merely by two low ridges in the endothelial lining of the cochlear canal. One of these is broader than the other and represents the beginning of the membrana tectoria and adjacent parts; the other more narrow will become the sensory portion of the organ of Corti. Except that the cells of this region are columnar and longer than those elsewhere lining the canal, no histological differentiation can be perceived. These ridges are present only in the proximal portion of the cochlear coil, not yet having appeared toward the distal end, except as indicated by a general thickening of the endothelium on one side of the cochlear canal.

In the one-day old rat the external auditory meatus is indicated in the sections as a long flattened and folded tube whose lumen is entirely obliterated by a plug of cells similar in all respects to those which compose the raphe palpebrarum or area of separation between the eyelids before the latter are open. The organ of Corti shows an advance in size over the preceding stage described; the membrana tectoria is rather well developed. The ridge that will give rise to the sensory portions of the organ of Corti is well marked but differentiation into hair-cells and rods has not yet occurred. The organ is not equally well developed throughout its whole extent, the

median portion showing greater differentation than either end. The limbus spiralis has made its appearance. The fibers of the cochlear nerve have not yet established any visible relation with the sensory portion of the organ of Corti.

In the five-day-old rat the external auditory meatus is not only larger but its walls are still more complicated by the development of folds or ridges, so that a cross-section of it may be V-shaped, Y-shaped, ∞-shaped, or ⅄-shaped. Along its central extent a lumen is beginning to appear through the disintegration of the cells composing the raphe; at either end it is still plugged with a solid mass of ectodermal cells. Internally the scala vestibuli, scala tympani, and cochlear duct are all present; the organ of Corti is larger and differentiation of the hair-cells and rod-cells is beginning though they are not distinct as yet.

In the nine-day old rat the limbus spiralis is well defined; the scala vestibuli and scala tympani are much larger than in the preceding stages. There is no vas prominens; the ligamentum spirale is well developed; the lamina spiralis membranacea is complete; the lamina spiralis ossea is not yet even chondrified. Hensen's cells are very large, shortly columnar, and 4 or 5 in number in each section; a row of cubical cells (the cells of Claudius) are distinguishable from the adjacent endothelium. The sulcus spiralis has not yet formed. The cells of the organ of Corti proper have not attained their definitive differentiation; however, neurofibrils from the ganglion spirale reach their bases. The lumen of the external auditory meatus is still obliterated both proximally and distally by the plugs of ectodermal cells.

In the thirteen-day old rat the ear shows a general advance in all its parts. The vas prominens has developed; the lamina spiralis ossea is

chondrified. The organ of Corti has differentiated fully for at least the greater part of its extent. The tunnel of Corti is large and bounded by the inner and outer supporting rods. The inner and outer hair cells can be seen with the fibrils from the ganglion spirale ending about them. The lumen of the external auditory meatus is more or less open throughout its whole length, though the detritus of the old cellular plug still remains. The latter is however no longer cellular, but rather seems to have undergone liquefaction, and at no point apparently completely fills the meatus. The structural conditions at this stage would indicate the possibility of the perception of some sounds at least.

In the sixteen-day old rat, aside from growth in size, the conditions are practically those described for the thirteen-day old rat. The detritus in the meatus has mostly disappeared. The organ of Corti has differentiated for most or all of its extent. So far as the structural conditions are concerned, the apparatus would appear to be able to respond to any sound stimulus.

Summary of Results on Hearing.

1. Absolutely no response to sound was noted before the twelfth day after birth. From that date until the sixteenth or seventeenth day there is a gradual increase in the ability to perceive sound.
2. Previous to the twelfth day the portions of the ear concerned with the perception of sound have been undergoing a gradual development but had not yet reached that degree of differentiation of the organ of Corti necessary for the perception of sound. By the twelfth or thirteenth day, the organ of Corti is apparently differentiated for at least part of its extent, though the lumen of the external auditory meatus is not fully opened. The next few days witness the completion of the differentiation of the apparatus of hearing.

EXPERIMENTAL DATA ON THE SENSE OF SIGHT.

Absolutely no response to light was obtained before the opening of the eyes on the sixteenth or seventeenth day. At practically all the preceding stages the eye had been tested with an electric flash-light without appreciable result.

On the sixteenth day one only out of a litter of six had its eyes open and functional; it responded quickly to movements made before its face and turned its head from side to side to follow moving objects with its eyes. The others did not get their eyes open until the seventeenth day, at which time sight was fully established in them also.

SMALL says of his experiments on this stage:

"Sight. When brought into a strong light they did not wink or show uneasiness, though they soon closed their eyes, and seemed to become drowsy. A stroke of the hand one inch in front of the face caused winking and a slight recoil of the head."

Observations on the Organ of Sight.

In the 7½ mm. embryo the eye is in the stage of the optic cup; the lens is a hollow vesicle lying deeply within the mouth of the cup. There is no apparent differentiation in the retinal layer. The area between the lens and the ectoderm is filled with loose, spongy mesenchyme. The choroid fissure is not closed. No fibrillation can be detected in the optic stalk, i. e., there is no optic nerve as yet developed.

In the 16 mm. embryo the lens is a solid oval body with the diameter in the future pupillary

axis somewhat the longest. Its anterior surface consists of a relatively thin layer of columnar cells. The margin of the optic cup shows a decided but rather gradual thinning out of the retinal layers, but no other indication of the ciliary body is apparent. The surface of the retina toward the cavity of the cup is supplied by a rich plexus of small blood-vessels and the fibrillar layer of the retina has begun to differentiate. The remainder of the retina shows no further differentiation into distinct layers. Its nuclei are relatively large and oval in outline; they are apparently more numerous than in the preceding stage.

The surface of the lens is covered with a very rich plexus of small blood-vessels. The chamber of the vitreous humor is relatively small and shallow, and contains a small amount of substance that in the preparations has the appearance of a sparse network of fibers, somewhat like a very loose mesenchyme minus the nuclei. There is no anterior chamber. The area between the lens and the ectoderm is filled with a rather densely packed mesenchyme, in which on the side next to the lens numerous blood-vessels can be seen. The development of the eyelids and socket is indicated by the presence of a groove on the surface of the head surrounding the optic area and dipping in to a distance of one-third or more around the optic cup. The arteria centralis retinae is a relatively large and distinct vessel forming a central core in the optic stalk where the latter joins the optic cup. Less than 180 μ outside the cup the artery emerges from the stalk through the remnant of the choroid fissure and thence posteriorly the two are independent of each other. The cavity of the optic stalk is still present and while throughout about one-half of its length its walls are in contact with

each other, still it can be easily traced into the ventricle of the brain. The optic nerve is developing in the form of numerous fibers in the ventral portion of the optic stalk. Cross sections show it to be large toward its retinal end, indicating that processes from the retinal cells are growing toward the brain.

In the 23 mm. embryo, the lens is more nearly spherical, if anything the diameter in the pupillary axis is the shorter. The anterior surface consists of a layer of columnar cells. The posterior surface of the lens is covered by a rich plexus of small blood-vessels. The retinal wall is thicker than in the preceding stages. The fibrillar layer is better developed. Many of the cells of the retina proper are columnar and some extend nearly or entirely through that structure. The third of the retina nearest to the vitreous humor is made up of cells oval in form and not densely packed together; the other two-thirds is composed of cells more columnar in form and more closely packed together. The cavity of the vitreous humor is a little larger than in preceding stages and has, in the preparations, the same sort of a reticular content through which passes a cone-shaped plexus of small blood-vessels from the optic nerve to the lens. The ciliary body is indicated by a very decided thinning out of the wall of the optic cup, and consists of columnar cells arranged in one plane, i. e., none of the folds so characteristic of the ciliary body have yet begun to form. The region of the future cornea and anterior chamber is occupied by a rather densely packed body of fibrous mesenchyme. Between this and the eyelids, which now cover the eye completely, there is a distinct cavity. The eyelids have fused into a continuous layer but the line of their future separation is indicated by a raphe bounded

on either side by a row of columnar ectodermal cells, the stratum germinativum of the margins of the lids. The optic stalk is wholly replaced by the optic nerve, that is fibers from the retina extend entirely to the brain. The arteria centralis retinae is relatively smaller than in preceding stages and enters the optic nerve almost at the exact point where the latter enters the eyeball.

In the rat during the first day after birth the shape of the lens is about the same as in the preceding stage described. The epithelial layer over its anterior surface now extends about two-thirds of the way around it and consists, at least in its most anterior area, of cells which are cubical or even slightly flattened instead of columnar. The surface of the lens is still richly supplied with a plexus of small blood vessels. The vitreous humor is greater in amount and in the preparations appears more granular or homogeneous rather than reticular, and through it there runs the conical plexus of bloodvessels from the retina to the lens, already mentioned. The ciliary body has two distinct folds with slight traces of others. The retina exhibits indications of six or seven different layers though its histological differentiation is otherwise hardly more than begun. There is no anterior chamber; the region of the cornea is thick and composed of a densely packed fibrous mesenchyme. The eyelids are much better developed than heretofore though still united by a raphe of ectodermal cells. Anlagen of eyelashes are present in considerable numbers. Glands are making their appearance along the inner margins of the lids in the form of tubular ingrowths of epidermis, while in the mesenchyme, sphincter and other muscles are in process of differentiation. Within the brain the optic tracts are a distinct bundle of fibers that

pass up through the optic thalami into the anterior corpora quadrigemina. Many other tracts are present also, but in the absence of medullation it is extremely difficult to trace them with certainty; however, it seems probable, to say the least, that by birth or shortly thereafter all the tracts within the brain connected with the primary optic centers, i. e., those in the corpus geniculatum laterale, the superficial portion of the anterior corpora quadrigemina, and the pulvinar, are laid down. The relations of these centers to cortex of the occipital lobes could not be made out.

In the five-day-old rat the lens has practically the same structure as at birth. The plexus of bloodvessels on its posterior surface is still well marked. The cavity of the vitreous humor is somewhat larger and its contents somewhat greater and denser than in earlier stages. Differentiation of the retina is proceeding but rods and cones are not yet distinguishable. The ciliary body exhibits an increased number of folds. The anterior chamber is present and the iris is beginning to be formed. The development of the lids shows a decided advance in every respect, but the raphe is still a thick layer of cells.

In the nine-day old rat the optic nerve and the lens are practically in their definitive condition, though the latter still is supplied with its plexus of blood vessels over its entire posterior surface. The ciliary body has at least seven folds; the anterior chamber and the iris are better developed than before. The cavity of the vitreous humor is much more extensive. All layers of the retina are distinguishable, the rods and cones apparently being in process of formation.

In the twelve-day-old rat the most noticeable advances are to be found in the ciliary body and

the retina. The former is distinctly marked off from the latter, in which the rods and cones are fairly well defined. The lens still possesses its plexus of blood vessels as heretofore described. The cornea and the secondary structures in that region are all in process of advanced development. The lids are however still closed and no light can reach the eye.

In the sixteen-day old rat (frequently not until the seventeenth day), the cells of the raphe palpebrarum have degenerated and the lids are separate. The rods and cones are much better differentiated than heretofore, and are undoubtedly functional; all the other retinal elements are also apparently fully formed. The plexus of bloodvessels to the lens is still present, though much reduced.

Summary of Results on Sight.

1. Absolutely no response to light was obtained before the opening of the eyes on the sixteenth or seventeenth day.
2. Before the twelfth day after birth the eye is undergoing the usual course of development. At this time (twelfth day) the rods and cones are fairly well defined, but the accessory structures are less fully developed and the closed lids prevent the entrance of any but possibly the very brightest light. By the sixteenth or seventeenth day, the lids open and the function of sight is fully established.

THE CAUSES OF DEVELOPMENT AND OF DIFFERENTIATION IN THE NERVOUS SYSTEM.

One of the most striking facts in connection with this investigation is one which must have been forced upon the attention of all who have studied the interrelations of organs in the development of the embryo of any vertebrate species, namely, the early appearance of the peripheral portion of the nervous system. At a time when it is inconceivable that distinctly nervous functions can be possible or at least of any importance to the embryo, the chief nerve trunks are all laid down, together with most or all of their important branches. For example, the vestibular and cochlear nerves are well developed in the 23 mm. rat fetus, not to speak of still earlier stages, while it is absolutely impossible that the function of hearing can have been established. Indeed, if our experiments can be relied upon, the very first indication of an ability to detect sound comes not earlier than the twelfth day after birth. Yet here in the fetus which has passed through only about two-thirds of its prenatal life, the nerve of hearing is apparently fully formed, at least fibrillation is complete, and this as we have seen is most certainly to be regarded as an indication of the establishment of the power of functional activity.

The anlagen of the vibrissae in the 16 mm. embryo have not more than reached the surface of the epidermis of the snout and it can hardly be supposed that the fetus has need of a delicate sense of touch to maintain itself within the amniotic sac.

And yet, the maxillaris and mandibularis branches of the trĭgeminus are completely fibrillated and end in very large and complex basket-like networks in the follicles of the vibrissae. It is inconceivable that in these and other cases that might be cited the nerves and end-organs develop in response to functional activities or even functional needs on the part of the fetus at this or any preceding stage in its existence. The condition as stated exists, however, and demands an explanation.

The earliest stages in the development of the peripheral nerves have been studied experimentally by HARRISON ('10) and others, and the results obtained, especially from the cultivation of tissues *in vitro,* shed a flood of light upon the question raised above. HARRISON finds that all tissues exhibit a specificity in their tendency to undergo each its own peculiar type of histogenesis, as the result of which certain cells *in vitro* become muscle cells, others epithelial, others connective tissues, others nervous, etc. This tendency is inherent in the cells concerned and reveals itself irrespective of the nature of the external conditions, so long as the latter are not detrimental to the well-being of the cells themselves. In short, a neuroblast is potentially a nerve-cell long before it is definitively such, owing to an internal organization that has been handed down to it through all the cell-generations that have intervened between the neuroblast stage and the oösperm. Indeed, it is not altogether a mere inference, as the work of Whitman, Wilson, Conklin, Lillie, and others, has shown that its possibilities were predetermined or prelocalized in the egg at or before fertilization. In short the development of the nervous system in general, and the differentiation of its constituent parts in particular, as is likewise true of all other organ systems as

well, are the products of a predetermination in the oösperm; a process of *endogenesis,* as Conklin has termed it, and not of epigenesis.

Furthermore the fate of each neuroblast and its products is likewise predetermined and there follows the histogenetic differentiation of the neurones of the central nuclei, motor or sensory as the case may be, and of the peripheral ganglia, as the result of an "immanent force" that needs no direct outside stimulus for its production. Thus HARRISON shows in the case of the formation of the axone that the outgrowth takes place:

> "without the application of any external physical force and . . . . occurs even when the normal surroundings are radically modified. That the original direction taken by the outgrowing fiber is already determined for each cell before the outgrowth actually begins, so that when it does begin it is dependent upon forces acting from within, follows first from the fact that the nerve fibers within the embryo tend to grow out in a given direction even when quite different surroundings are substituted for the normal, and secondly, from the fact that the nerve fibers which grow into the clotted lymph, are there surrounded on all sides by an isotropic medium, which cannot conceivably be held to produce movement in a definite direction."

In other words these structures are represented by something in the oösperm, whose nature can only be conjectured, and they appear not as direct responses to the needs of the embryo, but in anticipation of those needs, because of the inherited tendencies and forces immanent in the oösperm and localized as development proceeds in the parts con-

cerned. They are "racial or inherent adaptations which are not first called forth by the contingent stimulus to which they are the appropriate and useful response" (Conklin ('15)).

This early establishment of peripheral connections on the part of the nervous system receives its proximate explanation in certain mechanical conditions that exist at an early stage in embryonic development but *not later.* Assuming the truth of the neurone hypothesis, the question of how any certain nerve reaches unerringly its proper termination,—a question that has provoked much discussion,—receives an easy answer.

HARRISON'S experiments show that each neurone sends out its axone in a predetermined manner and direction; that this axone is in the form of a protoplasmic process or pseudopodium which extends outward from the neuroblast toward its peripheral termination; that this process grows from a terminal bulb—Cajal's cône d'accroisement—which with its changing pseudopods reaches out constantly in various directions, but ultimately extending through a distance of a millimetre or more until it reaches the muscle-plate or epithelium with which it is destined to connect. *That this activity must take place early in embryonic life is naturally what one would expect, since it is only in these early stages that the neuroblasts of the neural tube lie within the specified distance—about a millimetre or less—from the parts they are destined to innervate.* On the basis of adaptation and natural selection it is plain that only those embryos that thus early establish these connections can develop properly and so survive.

As HARRISON points out very clearly from his own results, and as has been shown by the observations recorded above on the white rat, the neuroblasts that thus early come into direct relation with

their peripheral end-organs are relatively few in number, but having once made the connection they elongate whenever and wherever needed as the growth and shifting of parts goes on so that when the ultimate relationships have become established the nerve paths have also been marked out, and later nerve processes growing out from neighboring neuroblasts, in relation to the greater functional needs of the embryo or as opportunity is afforded them, find their course already determined for them and have no trouble in reaching their own particular end-organs. This early growth period of the neuronal processes is clearly a *stereotropic* response, as HARRISON'S work shows; the later connections of the fibers with the individual cells of the end-organs is probably due, as HARRISON says, to *chemotaxis*. It is hardly possible on any other grounds to explain how it comes about that where both sensory and motor fibers pass out in the same nerve trunk the latter turn aside to terminate in muscle cells, while the former pass on their way to end in epithelial sense cells.

CORTICAL CONNECTIONS IN THE RAT.

The cortical connections with the lower centers of the brain in mammals are chiefly made through the *corona radiata.* In this, fibers from all parts of the cortex are gathered together and pass caudad into the thalamus, the cerebellum, the medulla, and the cord; without doubt other fibers arising in the lower centers pass cephalad via the same route to reach the cortex. In the higher mammals there are other bundles confined to the hemispheres which connect more or less distant parts of the pallium with each other. In the rat, however, in common with many others of the lower mammals, these cortical association tracts are very poorly developed. The corona radiata on the other hand is a prominent structure even at birth and it may be assumed from the known relations in higher mammals and man that its presence may be regarded as conclusive evidence that connections between the lower centers and the cortex have already been established. While there are probably no *medullated* fiber paths present in the brain of the rat at birth, nor indeed for several days after that event, nevertheless the medulla, the cerebellum, the mid-brain, and the diencephalon contain many non-medullated fibers, and the optic tracts, the olfactory tracts and lobes, the anterior, posterior, and habenular commissures, the corpus callosum, the external capsule and the deeper layers at least of the cortex exhibit the same condition. Hence, in view of the sparseness of association tracts in the cortex of the adult rat, and of the facts just stated, it seems not improbable that most of the associations possible later in life are already established at birth or very soon

thereafter. Certainly by the tenth day after birth the cortical connections are pretty definitely established, though owing to their primitive and probably rather diffuse character it has not been possible with my preparations to map them out. This is probably due to the lack of *medullation* of these fibers, and might be considered as vitiating our contention. However, WATSON ('03) has shown conclusively that such an objection has no force in this connection. Briefly put WATSON found that though

> "at birth (and during the first twenty-four hours after birth) the rat is not only capable of making many co-ördinated movements, but is also capable of receiving sense impressions . . . . no medullated fibers are present in either the peripheral or the central nervous systems."

Furthermore, during the first day after birth,

> "there must be, too, some pathway between sensory and motor nerves, because the rat moves when his tail is pinched, sucks when the stimulus of the mother's teats touches his mouth, scratches his nose with his forepaw when he smells something unpleasant. . . Granting now (and the evidence seems conclusive) that we have motor responses to sensory stimuli at birth, we must admit a pathway from skin to muscle. Such a pathway involves peripheral sensory neurones, central neurones, and finally motor neurones. During the first few days, at least, impulses must travel over the unmedullated axis cylinders of all these neurones. Co-ördination in the movements mentioned above grows rapidly better. At eight days . . . the rats are able to crawl vigorously and, when crawling to show some selection of path

by sniffing and going in different directions. . . . Sensitivity for smell, taste, and dermal stimuli has increased rapidly since the first day. . . . Whether or not at eight days the cortex is necessary for the responses which the rats make to the various stimuli may be a question. (If the rats were really smelling out a path, it would of course be necessary.) But, assuming that the cortex is not involved in these movements, we still have to account for the neural pathway in the lower centers over which these impulses can travel. Granting that the fibers carrying the impulses from a given sensory area are all medullated, and granting that the motor fibers which go to the corresponding muscles in any particular case are also medullated, if nevertheless medullation is lacking in some or all of the pathways within the central nervous system, then, so far as the physiological reaction taken as a whole is concerned, we have function without medullation."

A further quotation perhaps may be permissible because of its bearing on other aspects of the problem dealt with in this paper. WATSON finds that during the period from the tenth to the thirteenth day after birth in the rat there is present the capacity for

"forming and retaining definite associations. The solving of the problems given to the rats at the above ages would require the use of the olfactory tract (probably at thirteen days the auditory tract was also involved), some secondary tract to the cortex, the cortex itself, the pyramidal tract, and of course the peripheral nerves. If we examine the medullation process

> at this age, we find that the olfactory tract is entirely unmedullated, that a secondary medullated tract to the cortex does not exist, that the cortex is entirely unmedullated, and that the pyramidal tract contains but few medullated fibers."

He concludes therefore that "medullated fibers in the cortex of the rat are not a *conditio sine qua non* of the rat's forming and retaining definite associations."

If then, as WATSON has shown so conclusively, medullated fibers are not necessary for the establishment of associations in the cortex, and if, as my preparations show, a multitude of such non-medullated fibers are present at birth and many more within a few days thereafter in both the brain stem and the hemispheres, then it must be granted that the central links in the chain of neurones constituting the connections between the exteroceptive organs and the motor mechanism are present, and functional at this time, if the presence of neurofibrillae be a safe criterion. Why then is not the rat at birth able to *see* or *hear*, as well as to *feel* and to *maintain his equilibrium?* The optic and auditory nerves are completely fibrillated *long before birth;* the central connections are probably already established at birth or within a few days thereafter. The motor mechanisms that would be involved in the response to stimuli of light or sound waves are in good working order even before birth. Even the eye muscles are differentiating and their innervation established as early as the 16 mm. stage in the rat.

In short, the chain of neurones from the exteroceptive organ to the motor mechanism is complete for sight and hearing, possibly at birth, certainly within a few days after, and several days

before the function is established. *The block in the circuit is the extero-receptive sense-organ.* The rat cannot hear before the twelfth or thirteenth day, nor see before the sixteenth or seventeenth day after birth because it is not until those dates respectively that the ear and eye have reached a functional condition. Looking back over the experiments and structural observations recorded above on the senses of touch, equilibrium, smell and taste, it will be found that there too, *in each case the function is established when and only so soon as the proper peripheral sense organ has reached its functional state.*

The course followed in the development of the special senses and their correlated mechanisms is not just what one would expect on *a priori* grounds. After the earlier differentiation of the neural tube, the central connections between sensory and motor nerves are established in the cord, at least, and probably in the medulla also before or simultaneously with the appearance of such nerves, which very soon establish their distal connections. This is followed almost immediately by the completion of the motor mechanism; then comes the establishment of the central connections with the higher portions of the brain, and last of all the peripheral end-organs attain functional capacity. Then, and not until then, are stimuli from the outside world able to start a reaction that travels from sense-organ to central connections and thence out to the motor mechanism. That the apparatus as first established is not perfected has been shown above, but its later development follows in the paths already laid down, and consists probably in the successive addition of neurones to the class of those already functional.

This order of development is not what is demanded by the Lamarckian hypothesis. If structure were to follow from the effects of extrinsic stimuli, the logical order would be: peripheral sense organ, sensory nerve, central connections, motor nerve, and finally, motor end-organ. But such is clearly not the case. It follows therefore that the forces which bring about the development of the mechanism of the special senses and their motor connections, are *intrinsic;* they are forces brought into the organism by heredity, that is, they are inherent in the germplasm. The whole process is due to germinal organization though doubtless with enough plasticity to allow for a considerable degree of adaptation to minor environmental changes, and in a secondary sense controlled in a measure by the correlated development of the circulatory, lymphatic, excretory, and other systems of the body. Such adaptive modifications however do not affect the fundamental course of development; they concern only its minor retails.

GENERAL SUMMARY.

1. Fifteen stages in the development of the white rat, ranging from 7½ mm. embryos to young seventeen days after birth, have been examined from the standpoints both of structure and of function in an attempt at a correlation between the two as regards the development of the special senses.

2. The nature of the neurofibrillae is discussed and the theses are supported: (1) that they are actual structures of the living neurone; (2) that (a) either they are composed of rows of colloidal particles held more or less closely together in a linear arrangement by means of another constituent of the protoplasm differing from them in its degree of viscosity, or (b) they consist entirely of a viscid substance having the form of strands differing chemically and physically from the other elements of the surrounding protoplasm; and (3) that they are not to be regarded as the so-called "Stützgerüst" of the neurone.

3. The function of the neurofibrillae is discussed and the conclusion is reached that they constitute the conducting elements of the neurone.

4. Experimental and structural data are presented on the sense and apparatus of touch which are interpreted as showing:

(a) That both the sensory and motor nerves, as well as the central correlation paths between them, are laid down very early in embryonic life—were in fact present in the earliest stage studied, the 7½ mm. embryo.

(b) That the sense of touch is established somewhat later in embryonic life, at or before the

16 mm. stage, *upon the development of a tactile end-organ;* in the first instance this organ has the form of a neurofibrillar basket or reticulum in the vibrissal follicle.

(c) That the sense of touch is increased and perfected through (1) the addition of new vibrissal organs, and (2) through the innervation of the integument itself.

5. Experimental and structural data are presented on the sense and apparatus of equilibrium, which show:

(a) That a sense of equilibrium is first apparent upon the completion of the end-organ concerned, viz., the sensory cells of the cristae acusticae in the ampullae of the semicircular canals.

(b) That the power of equilibration is gradually perfected through increased powers of coordination with the tactile apparatus (vibrissae), and the organs of sight (eyes) as well as the establishment of the general muscle tonus.

6. Experimental and structural data are given for the sense and apparatus of smell. It is shown:

(a) That no certain response to odors was made until the olfactory epithelium contains fully differentiated olfactory sense-cells.

(b) That the olfactory tracts in the brain develop previous to and independent of the peripheral organ of smell.

7. Experimental and observational data on the sense and apparatus of taste are set forth, which show:

(a) That the trigeminal and glossopharyngeal nerves are both concerned with taste.

(b) That both these nerves and their central connections are completed long before birth and long before a sense of taste is present.

(c) That taste comes some time after birth upon the development (1) of peculiar gustatory organs on the anterior part of the tongue, and (2) of taste-buds on and around the circumvallate papilla.

8. Experimental and observational data on the sense and apparatus of hearing are presented, that indicate:

(a) The early establishment of the auditory (cochlear) nerve and its central connections.

(b) The late development of the organ of Corti.

(c) The dependence of the sense of hearing upon the establishment of the definitive structural conditions in the end-organ of hearing (organ of Corti).

9. Experimental and observational data on the sense and apparatus of sight are given which indicate:

(a) The early establishment of the optic nerve and its central connections.

(b) The very late differentiation of the retinal elements and the accessory structures of the eye in general.

(c) The fact that sight is not possible until the whole apparatus is in working order, of which the last element to be perfected is the sensory end-organ.

10. The causes of development and of differentation in the nervous system are discussed and the conclusions reached:

(a) That the development of the nervous system in general, and the differentiation of its constituent parts, are the products of *endogenesis,* or predetermination in the oösperm, and not of epigenesis.

(b) That these structures appear not as direct responses to the needs of the embryo, but in anticipation of those needs; not under the influence of their specific, definitive environmental stimuli, but because of the inherited organization and forces in the oösperm.

(c) That the early establishment of the peripheral connections on the part of the nervous system receives its explanation in the mechanical conditions existing at an early stage in embryonic development but *not later,* viz., that it is only in these early stages that the distance between the neural tube and the surface of the embryo is within the limit of independent growth of the neuronal processes.

11. The fact is shown that in the case of each sense the chain of neurones from the exteroceptive organ to the motor mechanism is completed and the sensory function established only when the proper peripheral sense-organ has reached its functional state.

12. It is pointed out that this unexpected order of development is contrary to any hypothesis of extrinsic causes, and that the forces concerned in the development of the mechanism of the special senses and their mōtor associations are those inherent in the organization of the germ-plasm, and may be only secondarily modified or controlled by other factors.

EPILOGUE.

The author is fully aware that this paper is only of a preliminary nature, outlining the field and establishing a few land-marks or base-lines for further investigation. As fast as the material can be obtained the relatively wide gaps in the above-given account of the rat will be filled in, and in addition comparative studies on other mammals are already planned and partially under way. Thanks are due to the National Academy of Sciences for a grant of $500.00 with which has already been purchased the equipment necessary to continue this work. Circumstances render it desirable, however, and the results so far obtained seem sufficiently important to warrant their early publication rather than to await the more detailed account that can come only after the expenditure of a much greater amount of time and labor than has been so far available for this study.

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