EARLY FETAL ACTIVITY IN MAMMALS*

DAVENPORT HOOKER

The study of embryonic and fetal activity is not new. Its roots stretch far back into biological history, but no review of the earlier work can be given here, nor is it necessary. Leonard Carmichael[6] of Brown University has presented such a review in the second chapter of the revised second edition of *A Handbook of Child Psychology*. Though, in the treatment of certain controversial points and in the interpretation and evaluation of certain of the publications there reviewed, I may be inclined to differ with Carmichael's presentation, it is an excellent summary to which those who might be interested in following an historical review in detail may refer.

Not only does the study of fetal activity have an honorable past; it also has an exciting present. Investigations into the early fetal activities of mammals are now being carried on in at least six institutions: by Angulo at The Wistar Institute of Anatomy and Biology in Philadelphia; by Windle at Northwestern University; by Carmichael at Brown University; by Sir Joseph Barcroft at Cambridge University, England; by Tilney at Columbia University (in each of these cases, with their co-workers); and by the Department of Anatomy at the University of Pittsburgh. This widespread interest is indicative of the problem's appeal to what are ordinarily considered to be widely divergent interests, as, among those engaged in the study of this problem in the institutions named, are included: embryologists, neuro-anatomists, endocrinologists, physiologists, psychologists, clinical cardiologists, clinical neurologists, and psychiatrists. Furthermore, each is securing results of importance to his field, even though, as we may see later, the various interpretations of these results do not always harmonize.

It is my purpose to review the principal findings of a number of these workers, though not of all; to discuss their points of difference; and to present, as clearly as may be, the issues and thus lead

---

* The third Harry Burr Ferris Lecture in Anatomy, delivered at Yale University, February 18, 1936.

From the Department of Anatomy, University of Pittsburgh School of Medicine; Physiological and morphological studies on human prenatal development, publ. no. 6.

up to a discussion of what is known regarding early human fetal activity. With one exception, only work on mammalian forms will be discussed. That exception is the work of Coghill, which, because it was pioneer work and presented a new concept of the origin of reflexes, is vital to the discussion.

Nearly thirty years ago, Coghill[8, 9, 10, 13] began a carefully planned series of "correlated anatomical and physiological studies of the growth of the nervous system in Amphibia." The majority of his studies have been made upon the embryos and larvae of the salamander, Amblystoma. The eggs, embedded in jelly, are laid in ponds, and from these eggs develop the embryos so extensively used by experimental embryologists. The earlier stages are soft and inert, except as they are moved by the cilia that cover the body, but when they reach Harrison stage 33, they begin to respond to light tactile stimulation, for which Coghill used a human hair. He has described and statistically validated a series of physiological response stages in the developing embryos which, with their characteristics, are as follows:

1. *Non-motile stage.* Naturally, all organisms that cannot move are non-motile, but Coghill has restricted the term to that brief stage in which the muscular tissue is sufficiently developed to respond to electrical stimulation but still lacks the nervous connections necessary for reflex response to a light tactile stimulus.

2. *The early flexure stage*, which follows rather abruptly on the foregoing. When the ectoderm is stimulated tactually, the muscles of the neck region (usually of the side opposite to that stimulated) contract, bending the head to a sharp angle with the trunk. This is the only activity of which the organism is capable at this stage in response to tactile stimulation over the sensitive area of the ectoderm. It should be noted that some embryos may, at first, show a contraction to the ipsilateral side, but soon all give contralateral responses. Also, in the beginning of this stage, the embryos may show alternating periods of response and failure to respond.

3. *The coil reaction stage* is a continuation of the early flexure as the neuromuscular mechanism of additional, caudally situated myotomes becomes established. Its final phase is a tight coil in which the head and tail meet or overlap.

4. *The S-reaction stage* "is characterized by the reversal of a flexure before it is completely executed as a coil." As the original contralateral response sweeps toward the tail, the head end starts an

ipsilateral contraction. At first, only one or two waves constitute the entire response; gradually, however, more and more waves pass along the body and give rise to

5. *The swimming reaction* when their frequency and vigor lift the organism from the substratum.

These, then, are the five stages of primitive activity in Amblystoma. In none of them are nervous elements above the lower portion of the medulla called into action. In all, the sensory mechanism decussates, carrying the impulse to motor cells on the opposite side of the spinal cord. In the last two stages, the contraction of the upper muscle segments gives rise to a proprioceptive stimulus which recrosses the cord to begin the second flexure that produces the sinuous S-shaped curves of the body.

In passing, it might be noted here that certain of these stages were observed and figured by Preyer as long ago as 1885[16]. However, Preyer failed to determine their sequence and to grasp their essential character. Coghill has definitely established that the expansion of the activity pattern is dependent upon the expansion of the neuromuscular mechanism. In each of these stages, the entire embryo capable of response reacts to the stimulus. In consequence, in each of these stages, the embryo gives a total response. Coghill speaks of this as a "total pattern." His further study of the development of appendicular locomotion clearly shows that limb movement is, at first, a part of the total response. Only later does the shoulder, then the elbow, and finally the wrist and fingers, develop the capacity for individual action apart from the whole. The same is true of the feeding and other reactions.

In a way, I think it possibly unfortunate that Coghill has used the term "pattern." The existence of patterns is denied by many and is rather generally associated with the principles of Gestalt psychology. It is true that the emergence of individual reflexes from a total response, as described by Coghill for Amblystoma, has been gathered to the Gestalt bosom. However, I wish to emphasize that the total response, from which individual reflexes emerge, was forced upon Coghill by his functional-morphological findings, and was not evolved to give aid and comfort to the Gestalt point of view. I mention this, because failure to recognize this fundamental fact has befogged the issue for some investigators.

Coghill's work on Amblystoma has clearly shown that, in this form, the sensory-motor mechanism at first is expanded by the integration of additional structural components as they develop. This primary expansion of the sensory-motor mechanism is accompanied by an expansion of the total response. The exteroceptive responses are found to be fully integrated from the start. Later, completely differentiated neural mechanisms are added to the functioning structure, with the result that specific reflexes are emancipated or, to use Coghill's term, "individuated," from the total response.

Coghill's concept of the development of specific reflexes by individuation from a total response was new and revolutionary. It was, and is, opposed to the generally accepted concept, according to which complex reflex patterns are developed by the successive addition, one to another, of originally isolated, specific reflexes, which are secondarily integrated to produce the complicated reflex patterns of the adult. Coghill's concept has had a profound effect in many fields. It is basic to an evaluation of all subsequent work.

Angulo's work on the development of activity in the rat was a direct outgrowth of Coghill's interest in the correlation of behavioral and morphological development. The study of the development of activity in the rat fetus was originally undertaken by Swenson, while a graduate student under Coghill at Kansas, but his doctoral thesis on this subject was, unfortunately, never published. He withdrew from the work before the completion of the investigation and Angulo, to whom the morphological part of the study had been assigned originally, included a complete resurvey of the functional phase in his work.

Angulo's paper on "The prenatal development of behavior in the albino rat" was published in 1932[1]. Using as a stimulator "a coarse hair," he analyzed the capacity of the rat fetus to respond to such stimulation. He has recorded a series of 30 response types successively exhibited by the fetal rat from 336 hours of insemination age to birth. The first sign of motility, in response to the type of stimulation used (presumably tactile in nature), was found by Angulo at 378 hours, or the latter part of the 15th day, after insemination and "consisted of a slight bending of the head" toward the side opposite to that stimulated, "involving only the neck region," and occurring after stimulation of the snout. This initial, contralateral response was of small amplitude.

A little later (384 to 407 hours), the contralateral response has spread caudally and become a true lateral flexion of the trunk, including the fore, and later the hind limbs, which are passively moved by the girdle muscles of the trunk. Then, in order, come head extension, later involving opening of the mouth and protrusion of the tongue, lateral flexion of the rump with passive movement of the hind limbs, ventroflexion of the trunk, independent movement of the forelimbs, and so forth.

An examination of the sequence and nature of the reactions recorded for the rat fetus by Angulo reveals a development of responses to tactile stimulation in this form which closely parallels those described by Coghill for Amblystoma, though they are not identical with them. The contralateral trunk response is of the same general character in each. The limbs move at first with the trunk muscles, only later independently. The progression of responses is caudalward and distalward. Hence, Angulo concluded, the development of tactile reflexes in the rat is by individuation of specific responses from the total pattern originally appearing.

Angulo's morphological work has given evidence that the nervous pathways are perfected in advance of being used. This is a confirmation of Coghill's conclusion in Amblystoma and is, in turn, confirmed by the studies of the Pittsburgh group. It is important that this be borne in mind, as it throws light on at least one of the points now in controversy. It seems probable that the delay between the appearance of definite tracts and their capacity to function is due to the long period of time required by the differentiation and, if I may use the term, the "maturation" of synaptic connections. This point has been stressed by Bartelmez*, of Chicago, who has emphasized the absence of any exact histological criterion for determining the readiness to function of synapses.

The mammalian work of Windle and his students has been chiefly with cat embryos, but more recently has included those of the rat. In the earlier of the contributions on the cat, Windle and Griffin[21] state: "the movements of embryos and young fetuses are, to a large degree, massive and general. With few exceptions, there seems to be a gradual evolution or individuation of the more discrete unit reflexes from the total pattern. In some cases, however, reflex movements seem to make their appearance with little or no relation to the primitive behavioral background" (p. 186). Further investigation has swung Windle's emphasis from the concept of

* Personal communication.

individuation of specific reflexes from a total pattern (a concept agreeing with the views of Coghill and Angulo), to those "few exceptions," reflex movements which appeared without evident relation to any total pattern.

In more recent papers, Windle[19, 22] has further studied the cat fetus and finds that, during the early part of the 24th day, while the fetuses are between 13 and 14 mm. in length, early reflex responses can often be secured, while spontaneous movements first appear at the end of the 24th day. These reflexes "occur in the forelimb some time before they can be observed in the neck. They may be evoked by tapping on the amnion, pressing slightly on the limb, or flipping the limb with a fiber needle . . .; they do not follow light tactile stimulation of the limb" (19, p. 488). Furthermore, they can be elicited only during the first few minutes after delivery of the embryo from the uterus and can be secured but once. The slightest anesthesia or disturbance of the placental exchange mechanism causes these reflexes to disappear. They are always homolateral.

Windle's belief that these are true reflexes rests upon seven criteria: 1) the contraction is quick, 2) is not necessarily maximal, and 3) usually follows application of the stimulus after a just perceptible latent period, 4) the relaxation of the muscles involved is quick, 5) contractions cannot be successively obtained in small embryos as there is a long refractory period, 6) the locus of stimulation does not mold the response, and 7) the mother and the fetus must be in normal condition. Direct stimulation by faradic current or by pinching produces contractions that are strongly contrasted with those of the reflex, as the contraction is slow, always maximal, without latent period, slow in relaxation, easily obtained successively, determined by the plane of the electrodes, and obtainable in fetuses even after the cessation of the heart beat.

The work of Windle and Baxter[18, 20] with rat fetuses expresses the same conclusions as in the cat. In the rat, they find that primary motor cells form at 272 hours (early on the 12th day) after insemination. Primary sensory elements appear before 300 hours. Collaterals appear between 350 and 368 hours. At 376 to 378 hours some embryos give the reflex-like twitches of the forelimbs after flipping of the limbs, but no head movements. Forelimb and head reactions occur independently and are not integrated at 384 hours.

It will be noted that there exists in the work of Angulo and

Windle a direct contradiction. At 376 to 378 hours after insemination, Windle finds only the homolateral twitch of the forelimb when it is flipped, but no head movements following stimulation of the snout. At 378 hours, Angulo reports the first contralateral flexion of the neck when the snout is stimulated. All of which points to two things: 1) the importance of adequate staging of fetuses, as Harrison has done for Amblystoma and as Nicholas has recently done for the rat and 2) the importance of using large numbers of animals. I prefer, however, to delay consideration of these matters until the discussion introductory to the work on human fetuses.

From Carmichael's laboratory have come several studies on fetal behavior, chiefly on the cat and the guinea-pig. Coronios[11] reports on the development of behavior in the fetal cat. His charts, showing the succession of activity in the fetus as a total organism and by body regions, indicate that motility begins at the 23rd day of insemination age with the lateral movement of the head, and proceeds according to a plan closely paralleling Angulo's work on the rat. The sequence would indicate an individuation of specific reflexes from a total pattern, progressing in a cephalocaudal direction. In his discussion, Coronios states: "The development of behavior progresses from a diffuse, massive, variable, relatively unorganized state to a condition where many of the reactions are more regular in their appearance, less variable, better organized, and relatively individualized" (p. 377). However, he has a suspicion that there may have been another response to be found in the 23-day stage, a barely perceptible movement of the forelimbs. This suspicion of the presence of local responses before the total pattern in the cat, becomes a definite finding in the study of the guinea-pig fetus by Carmichael[7], who states: "The first true behavior of the fetal guinea-pig involves neck and forelimb reactions which are released by unknown, i.e., 'spontaneous,' stimulation at 28 days. The first exteroceptively aroused reaction was a patterned response, following pressure stimulation of the ear, which involved neck and forelimb muscle responses at 31 days" (p. 479). Carmichael is of the opinion that "what seem to be premature and all-inclusive generalizations in regard to integration or individuation, maturation or conditioning," should be abandoned and "detailed factual scales" substituted.

Since the publication of this work, Bridgman and Carmichael[5] have been continuing the investigation on early fetuses of the guinea-pig and have amassed evidence of specific movements in the neck and forelimb prior to body responses. The issue is joined. Let me briefly restate it.

Angulo presents evidence that the first response of a reflex type is exteroceptive in nature and believes that the Windle-Carmichael early specific response is the result of direct stimulation.

Windle adduces evidence, partly physiological, partly morphological, to show that his early responses are true reflexes, the specific nature of which is not stated. Unfortunately, Windle's morphological evidence is open to question, because of the virtual absence of criteria for determining the time at which synaptic connections become functional. Hence the appearance, even the capacity to take silver impregnation, of nerve fibers is by no means simultaneous with their ability to function.

Carmichael believes the early responses observed by Coronios and by Bridgman and himself to be proprioceptive in nature.

It thus becomes evident that in the kind of stimulation used and in the nature of fetal reflexes lies the decision. Let us examine the evidence on these points.

The type of stimulation used in fetal work is of great significance. It may be remembered that Coghill used a human hair on Amblystoma embryos. Angulo used a coarse hair. Windle used metal and fiber needles, cactus spines, and other, blunter instruments. Carmichael used many types of stimulators, but chiefly a metal or fiber needle, a coarse hair, or a brush.

The choice by Coghill of a human hair as a stimulator to produce tactile stimulation in Amblystoma was not mere chance. A needle, even a stiff hair, would readily penetrate the ectodermal covering of the amphibian embryo. In the early mammal fetus, the integument is slightly thicker, but none the less delicate. Though a horse-hair of relatively fine caliber may be used, it is possible to penetrate the skin with stiffer hairs. I have recently been using a series of graded stimulators, human and horse hairs, which are just stiff enough to maintain, as they bend, a delicate chainomatic balance against weights of 10, 25, 50, or 100 mgm. In younger fetuses in good condition, it is rarely necessary to go above 50 mgm. hairs to secure reaction to tactile stimulation. A cactus thorn has also been used, but this definitely may produce direct mechanical stimulation of the muscle. Among others, Minkowski (as will be noted specifically, later), in working with early human fetuses, has warned that rigid stimulators clearly cause direct muscle stimulation.

In my opinion, "weighted" esthesiometers, of the type mentioned, are the only proper method of applying stimulation to secure reflexes. I say this with full knowledge of the fact that an expert may use needles or thorns with sufficient lightness of touch to give only tactile stimulation. After 30 years of embryological experimental work, it seems to me advisable to use stimulators which offer the least possibility of producing an unintentionally strong stimulus.

It should be stated that the weakest point in this whole investigation is our ignorance of the nature of the sensory end-organs of the fetal peripheral nervous system. Lacking information on this subject, we cannot be too exact regarding the action of a given stimulator.

When we consider the kinds of reflexes that may be elicited from embryos we find a contrast between Amphibia and mammals. The Amphibia, like the fishes, have a temporary sensory mechanism in the cells of Rohon-Beard which receive excitation from both the integument and the myotomic tissue. The same nerve cells receive both proprioceptive and exteroceptive impulses. Because of this, no difference between responses caused by these two types of stimulation can be perceived. The type of stimulator used by Coghill was carefully calculated to produce only tactile stimulation. No one has ever questioned Coghill's results on Amblystoma. Indeed, they are accepted by Windle and his adherents. The type of response studied by Coghill in Amblystoma was clearly exteroceptive in nature, and the Coghillian sequence refers specifically to that type of reflex.

In the mammals, as in birds, no Rohon-Beard cells are present and true reflex activity is delayed until the spinal ganglion cells have developed. Furthermore, the connections between sensory and motor mechanisms are by no means so direct and relatively simple in the mammals as in the Amphibia. There appears to be some evidence that proprioceptive reflexes may antedate the exteroceptive in maturation, though it is by no means certain that this is true. Carmichael has told me that he considers his early guinea-pig responses of the Windle type to be proprioceptive. He very courteously demonstrated such a response to me last summer. It is certain that the movement, whatever its nature may have been, followed the return to posture of the fetal body after it had been passively bent by pressure on one side of the amnion. If these movements are reflexes, they can only be proprioceptive.

Angulo[2] contends that Windle's limb-tapping response is not a reflex of any type and his evidence is of two kinds. He has found a response to limb-tapping or flipping in rat fetuses of 362 hours insemination age, which continued after complete curarization of the embryo. Such embryos failed to give responses to exteroceptive stimulation, either before or after curarization. There may be some question whether this is a cogent refutation of Windle's contention, as Windle claims his response can only be secured immediately following removal of the fetus in amnio from the uterus, and then only once. However, it may well be that Angulo may have mastered a technic rendering repetition of the response possible.

Angulo's other contention that Windle's limb-flip response is not a reflex has reference to its latent period.* He argues that latency can be used as a criterion of reflex action only in studies on adult material. He states that Krasnogorski has shown a latent period of 31.6 milliseconds (sigma) for direct stimulation of striated muscle in a premature child. With his own equipment, Angulo states: "I find that at 16 days after insemination (in the rat) the latent period is from ½ to 1 second or 500 to 1,000 sigma."

Where does this leave us? I confess I am not physiologist enough to know. But I believe that, even should these responses prove to be reflexes, they are proprioceptive in nature and, therefore, do not affect the validity of the Coghillian sequence in tactile (exteroceptive) reflexes.

Now let us turn to the work on man. First and last, a great many observations have been made on human fetuses during the early months of pregnancy. Many observations have been recorded in a more or less desultory fashion, but the literature contains only two organized studies, one by Minkowski[15], the other by Bolaffio and Artom[4], and it is from organized studies only that valuable results are secured. To the discussion of these two published studies, I shall add some notes from a third, still in progress.

Minkowski's material was obtained from hysterotomies performed as a therapeutic measure in the interest of the continued life and health of the mother. The material used by Bolaffio and Artom was similar in nature. Such material is rarely over six lunar months of gestation age and, by reason of the incomplete development of the pulmonary alveolae and atria, is incapable of survival, usually living for a period of minutes only.

* Personal communication.

Before entering upon a discussion of the results of the studies mentioned, I wish to consider briefly certain points wherein the difficulties of work on early human fetuses surpass those on infrahuman species. The first concerns the quantity of material. In experimental infrahuman material, fetuses may be secured in almost any desired quantity and at any age. Embryologists are familiar with the fact that only by using a large number of developing organisms can proper sequence of stages be secured. Reference has already been made to the fact that Angulo reports tactile reflexes of the head at 378 hours after insemination in the rat, while, at the same age, Windle failed to secure such responses. Such a conflict points to the need for an empirical staging of such fetuses, and of the study of a large number of cases. We think of human monovular twins as having identically the same inheritance and as being so similar in height, weight, build, appearance, and mentality as to confuse relatives and friends. They are sometimes called "identical twins." Yet, I have clear-cut evidence that one pair of human early monovular twins were not only of different lengths, but differed from one another in the number of ganglion cells in corresponding spinal ganglia to a greater extent than did other unrelated early fetuses of a slightly greater age. Early fetuses are highly labile organisms, readily affected by environmental factors. How, then, can we expect the fetuses in the cornua of a rat's uterus to be all of the same stage (which they definitely are not) or a 378-hour rat fetus in Philadelphia to be in the same stage of development as a 378-hour rat fetus in Chicago? Only by using a large number of cases and by emphasis on functional staging can parallelism be secured.

In work with human fetuses, Minkowski and the other investigators mentioned have been forced to accept those stages of development which chance has provided. It is difficult to unify the work of different investigators, especially in different countries, because of the small number of cases and a lack of agreement on length-age relations.

Much work has been done in attempting to secure a fairly accurate standard for length, either crown-rump (sitting height) or crown-heel (standing height), and menstrual age. No such curve can be considered as infallible, any more than can height-weight charts for children or adults, but they are invaluable as checks. In the experience of the anatomical group at Pittsburgh, the Streeter data[17] for crown-rump length have seemed to fit best the known menstrual ages of our series of human fetuses. Recently, Doctor Edith Boyd of Minnesota has constructed a new formula* for crown-rump length and menstrual age from the data given by Streeter, Mall, the Minnesota group, and the Pittsburgh data.

Minkowski has used the Haase formula in reporting his results. In comparison with the crown-rump data, which we find more accurate, his age assignments are too young by about two and a half weeks at first, diminishing in discrepancy to the end of the third month. This fact should be clearly borne in mind in interpreting his results. In discussing his work, I shall adjust his age assignments to agree with present practice in this country, on the basis of his measurements.

Material of the type used by Minkowski is not abundant. During a period of 5 or 6 years he was able to test physiologically a total of 75 fetuses, about one-third of which were in the second half of gestation. In this country, the amount of material is smaller. It, therefore, comes close to being a duty to test and record each such fetus that becomes available. To have adequate material for a proper study will require many years of effort in a large number of centers.

The study of early human fetal activity is hampered, not only by the paucity, but also by the condition of the material. In animal experimentation, the placental connections of the fetus are preserved intact. Under such conditions the process of asphyxia is reduced to a minimum, though my experience with early stages of the rat indicates that the minimum has a distinct magnitude which decreases with the age of the fetus. Early human material is a by-product of an operation to ameliorate disease. As such, its removal must be as expeditious as possible. As a result, such material is undergoing asphyxia from the beginning. As previously stated, such material, if in the first half of gestation, is structurally incapable of continued existence beyond a very brief period. If old enough to react, it may

---

*
$$L = 682.6e^{-\frac{210.98}{A}},$$
$$\log L = 2.820106 - \frac{83.259015}{A},$$
$$A = \frac{83.259015}{2.820106 - \log L},$$
where L is crown-rump length in millimeters and A is menstrual age in days. (Personal communication.)

exhibit spontaneous and reflex behavior for a matter of minutes only. All attempts to increase the reactive period by supplying oxygen in various ways have proved futile. As a result, all conclusions drawn from human fetal activity must be carefully weighed with the effects of asphyxia in mind.

One other caution regarding the validity of observations on human fetal activity must be mentioned—the effects of maternal anesthesia upon the fetus. Different anesthetics affect the fetus to different extents. It would appear that novocaine, as a local or spinal anesthetic, has little, if any discernible effect on the fetus. Fetuses from such cases will be spoken of as unanesthetized. If morphine is used as a preliminary medication, the long reflexes of the fetus (those occurring in parts of the body distant from the region stimulated) may be subdued or abolished. Ether anesthesia, with or without preparatory morphine administration, also may subdue these long reflexes. In both of these cases, only local responses can be secured. Avertin abolishes practically all fetal reflexes for a period of about an hour and a half after administration to the mother.

Minkowski's 50 early cases were derived from hysterotomies done under local anesthesia produced by novocaine, in some cases with preparatory morphine. Immediately on extraction, the fetus and its membranes were placed in physiological saline warmed to 40° C. The membranes were opened at once and stimulation begun. Notes were dictated to a stenographer. Cinematographic recording was not used.

Minkowski's work is remarkable in the care with which each item is recorded, but is, in my opinion, open to criticism in the analysis and interpretation of some of the results on the younger fetuses. Movements are too rapid in execution to be properly analyzed on sight. Cinematographic recording is essential for this purpose. In spite of this objection, which I think I can demonstrate to be valid, Minkowski's work is classic.

Though his work was chiefly directed to a study of the plantar reflex, Minkowski gives important information on other activities and responses. He observed spontaneous movements in small fetuses, beginning at two and one-half months of age. He states that the movements of such fetuses involved the head, the rump, and the extremities, and "were, in the majority of cases, slow, irregular, of a peculiar vermicular character and of little locomotor value." "A definite rhythm or a coordination of the individual movements could not be determined. In many ways, these movements are reminiscent of pathological, athetoid movements in adults."

In beginning the discussion of early human fetal reflexes, Minkowski lays particular stress on the need for great care in stimulation. "Because of the small size of fetal relations, especially in young individuals, it is clearly possible that superficial stimuli may press deeper and directly stimulate the muscles lying under the skin. Consequently, on the one hand, idiomuscular reactions may result (because of the great sensitivity of fetal muscle to direct stimulation), which mask the true reflex at times; or on the other hand, . . . it is possible that (responses) may be influenced not only through muscular stimulation, in other words, not simple skin reflexes, but actual skin-muscle reflexes may occur." I have made this quotation because it expresses the basic reason for the doubts held by Angulo and shared by some others, myself included, concerning the actual reflex nature (Windle and Carmichael) of early movements in rat and guinea-pig. Minkowski does not give much credence to the Coghillian sequence, so far as human fetal activity is concerned, though he states: "with increasing age, reactions following upon external stimuli become somewhat more specific and localized."

To test the reflex character of responses, Minkowski severed the spinal nerves as they emerged from the spinal canal. By this means he was able to prove that reactions following deep stimulation or percussion were not reflex in nature, as they could still be elicited. Hence, these responses were necessarily due to direct mechanical stimulation of the muscle. He also demonstrated, by ablation of the cerebral hemispheres, that the cortex exercises no appreciable influence upon the nature of fetal reflexes until the latter part of gestation.

I shall defer consideration of the specific reflexes observed by Minkowski as I wish to consider them in conjunction with observations from another study.

Some mention must be made of the work of Bolaffio and Artom[4], though its value is far less than is that of Minkowski. Their material consisted of 12 fetuses of from 55 mm. to 370 mm. in length and of an indefinite number older than that.

Some of the methods of stimulation were crude (dropping onto a surface, percussion, use of a blunt lancet, etc.), though electrical stimulation was also employed. The youngest fetuses were admittedly anesthetized and apparently most of the others of the first group of 12 were not examined soon enough after delivery to secure evidence of cutaneously excited reflex activity, so far as can be determined from the protocols.

Bolaffio and Artom conclude that, in the human fetus, at least from the 3rd month, muscular reflexes are present "in the form of slow contractions which have a tendency to be diffuse and generalized. As the fetus develops the contractions become more rapid and the tendency to diffusion is diminished, until it disappears toward the beginning of the 6th month."

In general, these investigators place the beginning of most of the specific reflexes at the 6th or 7th month. This is at variance with the results secured by Minkowski and others. So far as early fetal activity is concerned, the work of Bolaffio and Artom is of little assistance.

Since the fall of 1932, it has been my privilege, from time to time, to examine and test physiologically a number (23) of fetuses secured from hysterotomies performed for clearly established clinical reasons. In some cases, it has been possible to secure fairly good cinematographic records of activity. I am very grateful to a number of clinicians for their courtesy in permitting me to use this material which, in the normal course of events, would have been turned over to the pathologists for routine examination. The functional investigation on activity is already being supplemented by others on electrocardiography and the structure of the heart, on the finer anatomy of the nervous system, and on the structural development of the endocrine organs. Other studies are contemplated. As these various studies on development, made on the same tested material, are correlated, we find ourselves evolving a new embryology, based on functional considerations.

Three fetuses, of 16, 19.5, and 20 mm. C-R length, estimated at 7, 7½, and 7½ weeks, respectively, of developmental age, were non-motile. In all of these, maternal anesthesia, with avertin in the youngest case and morphine in the other two, casts possible doubt on the actual non-motility. This doubt might be greater were it not that the next case of 22 mm. C-R length, 26 mm. C-H length, of an estimated developmental menstrual age of 8 weeks, was also non-motile. Morphine was administered 13 minutes before delivery, but it is doubtful if this would suppress all activity. The structure of the nervous system leads us to believe that this fetus may have been in a stage just prior to the beginning of activity. It is possible that it might have reacted had it been in a sensitive, rather than a latent phase, as Coghill found in Amblystoma on the verge of responsive behavior.

The next stage is one of 25 mm. C-R length, 30.4 mm. C-H length, and estimated at a developmental age of a little over 8 weeks. Though morphine had been administered twice (1 hr. 45 min.; 45 min.) before delivery, it responded to tactile stimulation in the neck region by a contralateral flexion of the body musculature involving the limb-girdle muscles.

Three cases of about 9½ weeks' developmental age have been observed. One of these was abnormal in that it was edematous along the dorsal region. The other two were derived from hysterotomies done under spinal anesthesia without preparatory morphine and, hence, were apparently unanesthetized. Both responded identically. The reflexogenous area was over the nose and upper lip. Tactile stimulation in this area evoked a complicated response which may be described as follows: a contralateral flexion of the body musculature with rotation of the rump, accompanied by a downward movement of both upper extremities and a slight rotation of the head. It is a fairly stereotyped, coordinated movement departing from and returning to the typical posture of all such fetuses. I am quite convinced that the earliest spontaneous movement observed by Minkowski and stated by him to be "of a peculiar vermicular character" and uncoordinated, was this activity. Spontaneous movement observed in these two cases was identical with the reaction described, except that it occurred in bilateral rhythms.

If we examine the stages of this reaction, it is noticeable that the fetus changes from what may be termed its habitual posture to a response posture, followed by a quick relaxation to the habitual posture. In different responses of this type, the duration of the reaction varied from less than 1 to a little over 2 seconds, the difference being due to the period during which it "held" the response posture.

It should be noted that, at a little over 8 weeks, the reflexogenous area was in the neck. At this stage (9½ weeks) it was in the nose-mouth region, as it is in older specimens. Sections show that, in the former case, the spinal fibers of the trigeminal nerve had not established central connection with the cervical nerves, while in this case they had. From this age on, the facial area dominates the neck region in reception of stimuli.

This stage also shows local movements which arise only after prolonged stimulation. A very similar response may be aroused by percussion of the arm musculature, without the necessity for summation.

Three fetuses at about 11½ weeks of developmental age have been observed, one of which was unanesthetized, though all showed spontaneous activity and responded to stimulation. In the latter respect, the morphinized fetuses failed to exhibit long reflexes. The type of reaction of the unanesthetized case is more complicated than the last described. The reflexogenous area is again over nose and lip.

On unilateral stimulation, the response consists of the following elements: the head is rotated and slightly laterally flexed toward the contralateral side; the body is slightly laterally flexed to the contralateral side; both arms are slightly rotated outward, then sharply inward, so that the half flexed forearms are first separated, then approximated, as if to clap the hands; the rump rotates slightly; both thighs extend and rotate slightly.

If stimulation is given across the midline, an interesting modification of this response results. As both sides have been simultaneously stimulated, the head is sharply extended backward, as is the body, so that a state of opisthotonus results. The upper extremities move much as in unilateral stimulation, the lower are sharply extended.

The bilateral response is fairly stereotyped, but the response to unilateral stimulation varies greatly. The head, in returning to posture, may be rotated to the ipsilateral side. If stimulation has been extended laterally over the face, the head may rotate first to the ipsilateral, before rotating to the contralateral side. Local responses are frequent, occurring in the head (rotation), wrist and fingers (partial flexion), and in the lower extremity, on stimulation of the plantar surface. The results of palmar and plantar stimulation will be considered later.

By 14 weeks of developmental menstrual age, as shown by an unanesthetized fetus, of 88.5 mm. C-R length, 121.5 mm. C-H length, almost all responses are localized or individuated. A group of fetuses of 12½, 13, and 14 weeks of developmental age, though morphinized or etherized, indicate that the process of individuation proceeds rapidly during this period. Mimetic responses, in the form of contractions of the orbicularis muscle, of what used to be called the Musculus levator labii superioris alaeque nasi, and lip, mouth, and tongue movements, have become firmly established. The trunk is capable of various kinds of responses. The extremities no longer exhibit movements of a marionette-like stiffness. Except for respiration, almost all specific reflexes of the new-born are represented.

Permit me to review at this point the nature of the general responses of human fetuses as shown by Minkowski and the study just outlined. It must be borne in mind that the validity of these conclusions is limited by the amount and condition of the material upon which they are based.

At approximately 8 weeks of developmental menstrual age, response to tactile stimulation appears. As far as may be determined from the inadequate data available, the first response is a lateral flexion, to the contralateral side, of the neck and trunk on stimulation of the neck region. In this response, the extremities are passively moved by the girdle musculature which is called into play along with the trunk muscles.

The only earlier response ever recorded for a human fetus is that of Yanase in 1907[23], who states that on stimulation of a 20 mm. C-R fetus the arm moved. Unfortunately, the information given by Yanase is slight, both as to the nature of the stimulus and the time after placental separation at which the response was secured. With but one exception, the period during which all fetuses examined by me would respond to tactile stimulation did not extend beyond ten minutes after the beginning of placental separation, usually it was less.

Beginning a relatively short time after the cessation of tactile responses, individual muscles or muscle groups may contract either on stimulation of almost any type or entirely without stimulation of any kind. Yanase, who was studying peristalsis in human fetuses, reports that his specimen failed to show spontaneous peristaltic movements, nor could they be secured after mechanical stimulation. The movements of the arm of this fetus appear to me to be due to rigor. From my experience with mammalian fetuses of various kinds, I am unwilling to accept Yanase's report as one of normal activity.

From simple lateral flexion of the body, the nature of the response expands to include the shoulder joint and rump. This occurs at about 9½ weeks and was observed by Minkowski. At about this same stage, Minkowski reports the first plantar response, nearly two weeks before it has been observed by any others. On prolonged stimulation of the palm, an upper extremity response has been secured. Nevertheless, the response at this stage is still largely a total pattern, in Coghill's sense.

At 11½ weeks, the principal response is again total, involving the elbow joint and the lower extremity. According to the study reported, the palmar response slightly antedates the plantar. This is at variance with Minkowski's findings. At the stage under consideration, the separation of specific responses from the total pattern has clearly begun. During the next 2 to 2½ weeks, the process of individuation continues rapidly, until at 14 weeks, respiration is about the only specific activity not represented in, at least, an imperfect stage.

Minkowski describes the responses through this developmental level as uncoordinated, of little locomotor value, and athetoid. It must be realized that Minkowski approached his fetal work from the standpoint of a psychiatrist and neurologist with a clinical background of adult abnormalities. My approach is entirely different, as it has a background of experience in embryonic, larval, and fetal activity in fish, Amphibia, reptiles, and mammals. From that viewpoint, these responses, far from being uncoordinated, represent a very high degree of coordination.

The interpretation which I would give to the results of the studies of human fetal responses is, of course, quite clear. Every bit of evidence, from the work of Minkowski and from the other unfinished study of which I have been speaking, indicates that the responses of human fetuses to tactile stimulation follow a Coghillian sequence: first, the expanding total pattern; then, the rather rapid process of individuation of specific reflexes from that total pattern. I have said "a Coghillian sequence," for it is not the sequence of Amblystoma, of the rat, cat, or guinea-pig. No two groups of animals show identically the same sequence in fetal activities. If a sufficiently continuous series is examined, I now believe that a sequence will be found, but there may be telescopings of the sequence in some places or expansions in others. In some respects, the human sequence appears to be telescoped near the beginning, so that activities follow one another rapidly in appearance. Minkowski is personally unsympathetic to the idea of a Coghillian sequence, but his facts seem to substantiate such an idea.

I would now like to turn attention for a moment to a consideration of several specific reflexes. Minkowski states that the oral reflex, a movement of both upper and lower lips, is the "earliest, most constant, and most definite fetal reflex." He refers the beginning of the oral reflex to the 2nd or 3rd month. Even when adjusted to fit our tables, this is a little earlier than it has been observed by others. There is a suspicion of it at 9½ weeks, but it first becomes clear-cut and constant at about 13 weeks, at which time the orbicular, alar, and upper lip responses suddenly appear.

It may well be that additional unanesthetized cases earlier than this may bring the time of appearance of these reflexes nearer to that reported by Minkowski.

When it has once appeared, the orbicularis response is found, whenever sought, up to the 5th month. It consists in a contraction of the orbicularis muscle of one eye when the skin over its lateral portion is stimulated. Unlike most other recently appeared reflexes, it does not disappear with asphyxia, but persists as the last reflex to be obtained. By light pressure stimulation its appearance can be continued almost indefinitely after cessation of response to tactile stimulation. As the fetus passes 18 weeks of developmental age, this response becomes increasingly difficult to elicit. If (and when) it ceases is unknown.

The alar-upper lip reflex has a similar but shorter-lived history. It appears definitely at the same time as the orbicularis response and causes elevation of the angle of the upper lip and ala of the nose to produce a sneer-like distortion of the face. When present, it occurs with the orbicularis response, but appears to cease shortly after 18 weeks of age. It is persistent in the presence of asphyxia, though not as persistent as the orbicularis response.

The palmar response is described by Minkowski as localized, "often the flexion of the fingers; flexion and abduction, often opposition of the thumb, so that a grasping motion occurs, in which the hand is more or less closed into a fist." Such a grasping reflex he noted in a 65 mm. C-H fetus (about 10½ weeks), and proved it to be a true reflex by destruction of the cervical cord. He also noted opposition of the thumb on stroking of the thenar eminence.

Evidence is available which shows clearly the antecedents of the first response, though it has not been observed as early as seen by Minkowski. At 11½ weeks, light stimulation of the palm caused, after some summation, a barely perceptible flexion movement of the fingers, accompanying a slight flexion of the wrist. This double response was also present in another slightly morphinized fetus of this age. Fetuses a week older failed to show any response of this type, partly because of narcosis, partly because it was not sought early enough in the observations. At 13 weeks, the fingers flexed somewhat more. At 14 weeks, a fairly respectable "fist" was made, but it was not of a closed type, nor did the thumb play much of a rôle in the flexion. This is true of all cases observed in this study, two of which were about 5 months of age. The grasp does not hold an object placed within it until 22 weeks, and then but feebly.

As previously mentioned, Minkowski's purpose in his fetal studies was the investigation of the plantar response. On the basis of his findings, he has divided the manifestation of the plantar response in the fetus into four stages on the basis of its nature. In the first, or embryonal phase, he found, in fetuses of about the 9th to the 10th week of mean menstrual age, the first plantar reactions. This he calls the neuromuscular transition phase, as he believes it to represent a transition from the earlier idiomuscular, aneural reaction to one in which a true reflex arc in the cord determines the response. At this time, the toes may be dorsiflexed or plantarflexed, the response being very variable. The direction of the flexion is apparently determined by the greater excitability of the dorsiflexors or plantarflexors at the moment of stimulation. This phase has been observed, in the study reported here, at a much older age (11½ weeks) than that in which it was observed by Minkowski, but only at this age has plantarflexion of the toes been seen.

Minkowski's second, or early fetal spinal, phase he found in fetuses from about the 10th week to the 15th. At this time, dorsiflexion of the toes, especially of the great toe, with some fanning of the toes, overweighs plantarflexion. Moreover, in this phase, there is no doubt that this is a spinal reflex. In my experience, true dorsiflexion of any but the great toe is relatively slight, but marked dorsiflexion of the great toe and fanning of all toes appears to be a constant component of this phenomenon from 12 to 18 weeks. Also, response to plantar stimulation always involves the ankle, knee, and hip joints.

The period from 4 to 6 months Minkowski considers to represent a third or tegmento-spinal phase, in which the tegmentum controls the nature of the response, as shown by sectioning of the central nervous system. At this time both dorsiflexion and plantarflexion of all toes may be secured by either plantar or dorsal stimulation, though dorsiflexion is the more characteristic.

The fourth, or pallido-mesencephalo-cerebello-tegmento-spinal phase, extends to birth. Here the dorsiflexion type is met almost exclusively.

Time does not permit either more detailed or more extended examination of the development of specific reflexes; indeed, I can but touch upon the remaining phases of our investigation.

In his study of Amblystoma, Coghill was interested not only in the activity of the embryo, but also in the correlation of that activity with the structural development of the nervous system. Similarly, Angulo, Windle, Minkowski, and we of the Pittsburgh group have attempted to secure adequate correlation of activity in the mammal fetus with the nervous system morphology. Angulo, Windle, and we have used the same material subjected to physiological tests for the morphological study. Unfortunately for this purpose, Minkowski had severed nerve roots and sectioned the nervous system at different levels, so that his material was unfit for morphological study. He, therefore, adopted the much less satisfactory method of examining morphologically other specimens of about the same level of development.

The morphological study of the nervous system of mammalian fetuses is tremendously time-consuming and, beyond the earliest stages, very difficult to evaluate. Its complex nature almost defies correlational analysis. As a result, none of the studies, except Minkowski's, is considered as complete and Minkowski did not attempt a detailed analysis.

However, it may be of interest to get some idea of the grosser phases of spinal development in the upper cervical cord from studies made by Doctor Ira D. Hogg. A non-motile fetus, 22 mm. C-R length, 8 weeks of menstrual age, shows a very undeveloped state of the dorsal funiculus containing the afferent fibers, a few ventral commissural fibers from a nucleus situated in the midregion of the gray matter, the fascicles of the spinal accessory nerve and the motor cells of the cervical and spinal accessory nerves.

With increase in age, the following points become evident: 1) enlargement of the dorsal funiculus; 2) increase in the number of collaterals passing to the gray matter from the dorsal funiculus; 3) increase in the number of commissural fibers; 4) a gradual appearance of long tracts among the fibers of the fasciculi proprii; and 5) a rapid increase in fiber development within the cord.

At a higher magnification, synaptic connections may be observed. Also, the increasing amount and complexity of the general stroma of the cord are clearly demonstrated.

Spinal ganglion cell counts on this material, made by McKinniss[14], fail to show any right- or left-sided preponderance in the early fetuses examined as has been claimed for the adult by Arnell[8] and others. The increase with age in the number of ganglion cells has been clearly brought out by this survey, as yet incomplete. One point of interest is the relatively small number of mitotic figures found, but a little computation will show that the total number of cells present at birth can be more than met by the percentage of dividing cells observed.

On the endocrine side, Doctor J. C. Donaldson has been following the development of the various ductless glands. This constitutes a unique opportunity for the correlation of the structure of these organs with the physiological-neurological phases of the investigation. Time does not permit further discussion, though some interesting points are already emerging from this study.

The last phase of our work already in progress is the electrocardiographic study being carried out by Doctor George G. Burkley and Doctor C. Russell Schaefer[12]. Successful electrocardiograms have been secured from nine physiologically tested fetuses as well as from a number of other untested fetuses which were spontaneously aborted. Fetal electrocardiographic procedures are not seriously affected by maternal anesthesia, nor does asphyxia play an important part until its terminal stages. Records have been secured from all four leads. In the three limb leads, and in standard chest leads, the major deflections present in adult electrocardiograms are present in the fetal, though some variations from the normal adult pattern were found. One, which may be of interest, occurred in the 4th, or chest, lead. In all fetuses of our series, the T wave was positive, though normally negative in the adult pattern. The oldest fetus of our series was 22 weeks of menstrual age and had exhibited Ahlfeld's sign, irregular and spasmodic chest movements of a respiratory nature. One of the spontaneously aborted fetuses, not in the functional series, of 25 weeks' menstrual age, showed T-4 negative, as it was in all the viable prematures and as it is in the adult. There is evidence from other sources that young children sometimes show positive T-4, though rarely, and that it may be due to the placing of the leads on the chest. It is perhaps interesting to note this indication that at the 6th month of fetal life the adult type of T-4 appears, unless it be due to the position of the lead contacts.

The preceding, very superficial survey is merely intended to indicate to what extent the morphological and functional components of such a study may be correlated.

In closing, may I briefly review the present status of work on the activities of mammalian fetuses?

1. Doubt has been cast on the applicability of the Coghillian sequence in mammalian fetal reflex development, but there appears to be evidence that the supposed exceptions are not of the exteroceptive type, to which the Coghillian sequence alone applies.

2. The nature of the sequence of activities in mammalian fetuses is specific for each form, though a general fundamental pattern is usually recognizable. In consequence, the data secured from infraprimate, possibly from infrahuman, forms cannot be applied in detail to man.

3. There is need for a thorough investigation of fetal activity in some primate, and great need for the extension of observations on early human fetuses using modern methods of recording, especially cinematographic recording. Only by this means can personal bias be eliminated.

4. There is need for careful physiological studies of fetal muscle-nerve excitability.

5. In general, these investigations have raised more questions than they have answered.

References

1 Angulo y Gonzalez, A. W.: J. Comp. Neurol., 1932, *55*, 395.
2 Angulo y Gonzalez, A. W.: Proc. Soc. Exper. Biol. & Med., 1935, *32*, 621.
3 Arnell, Nils: Upsala läkaref. förh., 1933, N. F. *39*, 97.
4 Bolaffio, M., and Artom, G.: Arch. di sci. biol., 1924, *5*, 457.
5 Bridgman, C. S., and Carmichael, L.: J. Gen. Psychol., 1935, *47*, 247.
6 Carmichael, Leonard: Origin and prenatal growth of behavior. Chap. 2, [in] A Handbook of Child Psychology, 2nd Ed., 1933, 31.
7 Carmichael, Leonard: Gen. Psychol. Monogr., 1934, *16*, 337.
8 Coghill, G. E.: J. Comp. Neurol., 1914, *24*, 161.
9 Coghill, G. E.: J. Comp. Neurol., 1916, *26*, 247.
10 Coghill, G. E.: Anatomy and the Problem of Behavior. Cambridge University Press, 1929.
11 Coronios, J. D.: Gen. Psychol. Monogr., 1933, *14*, 283.
12 Heard, J. D., Burkley, G. G., and Schaefer, C. R.: Am. Heart J., 1936, *11*, 41.
13 Herrick, C. J., and Coghill, G. E.: J. Comp. Neurol., 1915, *25*, 65.
14 McKinniss, Mary E.: Anat. Rec., 1936, *65*.
15 Minkowski, M.: Abderhalden's Handbuch d. biol. Arbeitsmethoden, 1928, *Lief. 253*, 38.
16 Preyer, Wilhelm: Specielle Physiologie des Embryo, Leipzig, 1885.
17 Streeter, G. L.: Contrib. to Embryol. (Carn. Inst. Wash. Publ. no. 274), 1920, *11*, 143.
18 Windle, W. F.: Anat. Rec., 1934, *58*, 42.
19 Windle, W. F.: J. Comp. Neurol., 1934, *59*, 487.
20 Windle, W. F., and Baxter, R. E.: J. Comp. Neurol., 1936, *63*, 189.
21 Windle, W. F., and Griffin, A. M.: J. Comp. Neurol., 1931, *52*, 149.
22 Windle, W. F., O'Donnell, J. E., and Glasshagle, E. E.: Physiol. Zool., 1933, *6*, 521.
23 Yanase, J.: Arch. f. d. ges. Physiol., 1907, *119*, 451.