tion such problems are the sphere of a surgical team, and although I remain a firm advocate of segregation of fracture patients I believe that in the "danger zones" the segregation should only be one department of a general hospital containing personnel capable of dealing efficiently with any emergency.

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THE INTRA-UTERINE DEVELOPMENT OF RESPIRATORY EFFORT*

BY

SIR JOSEPH BARCROFT, F.R.S.

Late Professor of Physiology, University of Cambridge

The attempt to explore a subject so well worn as the regulation of respiration by approaching it from a new angle is admittedly a daring one; but a fresh approach seems to be the only excuse sufficient to justify the effort. In the present introduction, therefore, I shall put before you some glimmerings on the matter, as a crude attempt made to build it up from the developmental standpoint: developmental not in the philogenic but in the ontogenetic sense—that is, by studying the phenomenon as it gradually unfolds in the life of the mammalian foetus to see what sort of picture we obtain. Study of the regulation of breathing demands an understanding of the phenomenon of respiration, and as that appears to be bound up with the essence of movement itself you must bear with me if I start at the very beginning.

Stage I: The Initiation of Movement

The first neuro-muscular movements observable in the sheep foetus appear on the thirty-fourth day of foetal life—not quite a quarter of the way through pregnancy, which in the sheep is normally about 147 days. The foetus is perhaps the size of the thumb-nail, but it is large enough to admit of the appropriate stimulation of the sensory fields which correspond to the endings of individual nerves. The very first movement to take place is obtained from stimulation of the area just over the lip and under the eye: this corresponds to the position to which the maxillary branch of the trigeminal nerve has grown. The movement obtained is a slight lateral one of the head, and appears to be asymmetrical because the stimulus is asymmetrical: in the next few days the nerve grows down to the snout, at which time stimulation of that organ (involving the nerves from both sides) produces asymmetrical throwing back of the head.

It is interesting at the very outset that a nerve so intimately connected with respiration as the maxillary branch of the trigeminal should be the first to evoke movement.

Stage II: The Earliest Rhythmic Movement

Within the next week, or even the next three or four days, the capacity of the foetus for movement has advanced in quite a number of ways, of which four may be singled out: (1) the sensory area, stimulation of which can evoke movement, becomes much enlarged; (2) the adequate stimulus alters in nature; (3) the extent of the response becomes greater; (4) the response becomes rhythmic. To consider these in a little more detail:

1. Not to go further than the trigeminal nerve, the maxillary branch has now come to innervate a much greater area by, say, the fortieth day than was the case on the thirty-fourth. Moreover, the supra-orbital branch of the ophthalmic division has come into play. Thus, from considerable areas around the snout and eyes stimulation by a glass rod or a faradic current will evoke a response.

2. The repercussion of the enlargement of the sensory field means that a much less intense stimulus if applied to the enlarged area will evoke a response. Thus a drop of saline falling in the eye from no more than a centimetre will initiate movement; or, *in utero*, a current set up by the injection of warm saline into the sac, if it impinges on the face, will have a like effect.

3. As the days pass, more and more muscles become involved in the response. Starting with a simple movement of the neck muscles, it comes to involve the longitudinal muscles of the back; later those of the limbs and tail, as well as those of the throat and trunk: by the forty-second day the diaphragm is formed, and it too is involved.

4. The response has become rhythmic. No movement is sustained for any length of time, but the whole response lasts perhaps a half to three-quarters of a minute, in that it consists of a rhythmic series of individual spasms. Each spasm involves, as indicated above, a great part of the whole musculature of the living foetus. The conditions which determine its periodicity have not been defined.

This perhaps is the place for a word about the phenomenon spoken of as "spontaneous movement." Most users of this phrase, ourselves included, have safeguarded themselves by saying that it means no more from their pen than an admission of inability to ascribe any definite form of stimulus to the movements. The phenomenon is evident enough, and is that in first opening the uterus the foetus as seen in the sac is undergoing rhythmic movements similar to those described above. In view of what has just been said about the ability of currents in the amniotic fluid and slight changes of pressure to produce foetal rhythms, we are sceptical as to the spontaneous nature of these rhythms, using the word "spontaneous" in the sense of something which starts in the central nervous system without the interference of stimuli from an afferent field.

Stage III: The Individuation of the Generalized Rhythm into Somatic Movement and Respiratory Movement

If the rhythm be set up by stimulation of the snout with a glass rod at about forty days the following may be seen. The first, or the first and second, of the individual mass movements which constitute the rhythm differ from the succeeding movements as follows. The extensor element is more pronounced. The head is thrown back—a composite movement which consists of an extensor and a flexor component; in the subsequent movements the extensor component drops out and the head nods forward. During the seventh week of foetal life the two sorts of movements diverge in type, till at the forty-ninth day the initial somatic movement is a long-drawn-out spasm, while the tendency of the subsequent rhythm is for all the muscular movements to be shed except those of the diaphragm, the thorax, and the throat. Here, then, is the essence of the neuro-muscular mechanism of respiration. It consists of three components: the sensory stimulus, the immediate somatic response, and the subsequent respiratory response. I am fortunate to have Professor Adrian as my chairman: neither in his presence nor in his absence would I make any attempt to say by what chain of events in the central nervous system a foetus can start with a hit on the nose or rump and end with an effort to get up, followed by the movement of a breathless attack; I know he would not allow

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me to say that the stimulus is turned into the response, but I am in hope that his own contribution will help to bridge the gap.

We have, then, the germ not only of the respiratory mechanism but also that of its regulation, for the three factors enumerated (the sensory stimulus, the immediate somatic response, and the subsequent respiratory response) are related to one another quantitatively: the stronger the stimulus the greater the somatic response and the greater the respiratory effort which follows it. At seven weeks the system has become very delicate. It is almost impossible to hold the foetus so quiet as to avoid the liminal stimuli required to initiate respiratory movement. Whether these stimuli are proprioceptive or whether they are due to alterations of pressure on the surface I cannot say; but the result is evident: quite a small movement initiates a respiratory rhythm in an otherwise quiescent foetus, whilst in one which already exhibits a rhythm muscular movement is associated with an alteration of the rhythm in three respects—(1) the frequency increases; (2) the movements become deeper; (3) the area of movement spreads. In short, the foetus exhibits the cardinal characteristics of forced respiration. It seems difficult to escape the conclusion that even at the seven-week stage nervous regulation of respiration—the phenomenon demonstrated by the classical experiment of Krogh and Lindhard—has been laid down. The nervous regulation of respiration, as opposed to the chemical, is, then, the first in time to be evolved, and appears to be part of the very essence of movement. Up to this date asphyxia has no effect upon bodily movement—respiratory or otherwise—except to obliterate it.

Time and space forbid a discussion of the anatomical basis of the individuation into somatic movement and respiratory movement. This much may be said: the individuation is coincident with the functional appearance of the midbrain, and demonstrates the first phase in the progressive forward development of the brain; for if the foetal brain be transected between the medulla and the red nucleus the pattern of movement reverts to a modification of the six-week stage—that is, a simple rhythm of a respiratory type.

Stage IV : Inhibition in Relation to the Asphyxia Factor of Respiration

From the end of the seventh week the foetus undergoes a remarkable change: from being on a hair-trigger it becomes increasingly inert. Stimulation elicits little movement, either somatic or respiratory. The foetus appears almost dead. That it is not may be demonstrated by three different procedures, application of any one of which will produce a reversion to the lively seven-week stage. These are: (1) transection of the central nervous system at the middle of the forebrain; (2) exposure; (3) and in the present connexion most important of all, asphyxia—that is, occlusion of the umbilical cord.

The first of the above procedures demonstrates the general nature of what is taking place. The section is made at any time after the fiftieth day, and the foetus allowed to grow on in the uterus so that there may be no question of traumatic stimulation. It then becomes clear that the alteration from the quiescent to the active stage is a matter of *release*. The lower centres are released from one in the upper part of the forebrain but below the cortex; in fact, the whole foetus after the seventh or eighth week is maintained in a condition of profound inhibition. Respiratory movement is no excep-

tion to this general condition; its existence at any time, or if it exists its degree, depends upon the issue of a battle between sensation and inhibition. The chemical factor in the regulation of respiration is in part the abolition of inhibition. Inhibition represents another phase in the forward functional development of the brain. Any circumstance which promotes sensation in the foetus will make for increased respiratory movement, the natural factor being somatic movement. Any factor which tends to reduce inhibition will have the same effect. If the two take place simultaneously their joint effects might be expected to be greater than that of either separately.

Stage V : The Onset of Birth

Such would appear to be the case at birth, for which the foetus is now fully prepared.

Increased Sensation.—The organism is at this stage introduced into a new environment, and one calculated enormously to increase the number of stimuli from sensory areas: stimuli of cold and touch from the skin; proprioceptive stimuli from the limbs, which are now able to move freely; and, not least, stimuli from the embryological origin of sensation, the maxillary division of the trigeminal nerve.

Depressed Inhibition.—At the same time the inhibition is depressed by asphyxia. This fact has two repercussions: (a) direct, (b) indirect.

(a) We are now in a position to give some quantitative estimate of the degree of asphyxia necessary to release the foetal respiratory mechanism. It amounts to a reduction of the percentage saturation of the blood from the brain—that is, gleaned from the sinuses—to about 20 to 10 per cent. oxygen saturation. At the level of asphyxia respirations will start.

(b) But release also takes place in other directions; reflexes generally become heightened, and the proprioceptive afferent stimuli resulting from the movements liberated may be an appreciable addition to the increase of sensation.

After the first breath—that is, after the chest has actually expanded and respiration has become established on a tentative basis—a whole new set of sensory stimuli come in from the respiratory area itself—the nose, the throat, the lungs, the diaphragm, and the chest wall. It will be for future research to sort these out and to determine whether or not to the end the regulation of respiration is a battle between sensation and inhibition. In the foetus, inhibition had the upper hand so completely that respiratory movements did not normally take place once it had been established; post-natally, on the other hand, sensation has the upper hand, inhibition merely damping the respiratory movements.

Some Pathological Forms of Forced Respiration

In the light of what has been said I find it interesting to review the possible cause of certain forms of hyperventilation that are associated with obvious dysfunction of the higher parts of the brain. Two which I may instance are found in coma and cerebral haemorrhages. It has always appeared difficult to me to associate these with stimulation of the respiratory centre, and therefore it seems not out of place to inquire whether they are not due to some form of release of medullary centres from an inhibition centre placed in the upper part of the forebrain. At all events, granting the existence of such a centre it would seem wholly reasonable to suppose that influences which deprived the cortex of its consciousness might extend their devastating influence to the upper part of the thalamus.