FORCES DRIVING THE RESPIRATORY ACT[1]

A FUNDAMENTAL CONCEPT OF THE INTEGRATION OF MOTOR ACTIVITY

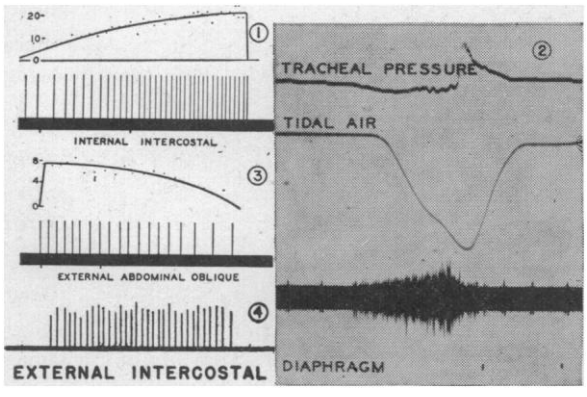
By Dr. ROBERT GESELL

PROFESSOR OF PHYSIOLOGY, UNIVERSITY OF MICHIGAN

THE report I am about to give is based on the work of many, but I have drawn heavily on the investigations of the physiology staff at Michigan in my interpretations. It will be apparent that the views presented differ from the present-day conceptions of motor integration and respiratory control, and, therefore, it is important to keep in mind a distinction between fact and theory as I proceed.

Life's most basic and most pressing need is a continuing supply of oxygen proportionate to changing energy requirements. Elimination of CO_2 comes next in order, for the CO_2, which is formed in the combustion, increases the hyrogen-ion concentration of the living cell and hampers oxidation in direct proportion to its accumulation. Thus oxygen lack and carbon dioxide excess, by virtue of their effects upon living structures, provide chemical forces which drive the machinery of breathing. These forces act directly on the center and reflexly through the outlying chemoceptors. Though providing steady drives they provoke periodic respiratory activity. Our subject in to-day's symposium is the consideration of the central integration of this rhythmical phenomenon of breathing.

Since the act of breathing is the end resultant of trains of signals coming from the brain and cord, our most direct approach to the problem is a systematic study of these signals. In analyzing the action potentials of respiratory muscles, we learn how the mechanical power is adjusted in each respiratory act. This is illustrated for inspiration in Fig. 1, obtained by the application of closely approximated bipolar electrodes to the surface of the internal intercostal muscle. The frequency of twitch rises slowly during the period of inspiration and then suddenly falls to zero in the early stages of expiration.



FIGS. 1–4

If the electrodes are widely separated, as was the case in Fig. 2, obtained from the diaphragm they combine the potentials of the included fibers in fusillade form, giving again a characteristic triangular pattern. The steadily rising shadow indicates a rising strength of contraction resulting from an increasing frequency of muscle fiber twitch and from a progressive recruitment of new active elements. The rapidly falling shadow depends upon a rapidly decreasing frequency of twitch and upon a rapid decruitment. It indicates a sudden waning of muscular contraction. The slowly rising electrical gradient corresponds with a slow filling of the lungs, as witnessed by the gentle decline of the tidal air and tracheal pressure records. The rapidly falling gradient conforms with the sudden emptying of the lungs.

The purposiveness of such contractions is clear. As the chest expands and the resistance of distortion mounts, the mechanical power of inspiration increases. Once the potential energy for expiration is stored, nothing is lost by a rapid release of tension in the inspiratory muscles. It, therefore, seems of utmost significance that the slowly augmenting pattern of potentials found in the inspiratory muscles is characteristic for the inspiratory phase of breathing at all stations of the respiratory reflex arcs.

The activity of the expiratory muscles during eupneic breathing is definitely less than that of the inspiratory muscles. Nevertheless, we found sufficient number of expiratory discharges to follow them through the expiratory arcs, as was done for the inspiratory signals. In contrast to the inspiratory potentials, which show only one pattern of discharge, the expiratory potentials show two characteristic patterns. One is the rapidly augmenting type, in which the strength of contraction or frequency of discharge falls off slowly, as illustrated by the external abdominal oblique in Fig. 3. It is the mirror image of the slowly augmenting inspiratory pattern. The other is the steady state type, more or less rectangular in shape, as shown in Fig. 4. The rapidly augmenting and the steady state types of discharge like the inspiratory discharges are also found at various stations in the expiratory arcs.

[1] A paper delivered at the symposium on "Respiration" before the American Society for Pharmacology and Experimental Therapeutics, Toronto, 1939.

It may, therefore, be concluded that there are three patterns of discharge common to the respiratory act—the slowly augmenting, the rapidly augmenting and the steady state. These types are subject to minor modifications which, however, need not concern us in this discussion.

We are inclined to adopt the theory of automaticity of central discharge, but how shall we explain the characteristics of the patterns? Are they a product of the architectural arrangement of the centers or of the periodic sensory bombardments accompanying each respiratory act? Respiratory potentials obtained during curari paralysis, which eliminates periodic afferent signals, show only the slowly augmenting and the steady state patterns indicating their dependence upon architectural structure. The rapidly augmenting pattern is regarded as a reflex modification of the steady state pattern.

These conclusions bring us to the fundamental aspects of nerve cell discharge, upon which we must now build. As early as 1926, we proposed an electrochemical theory of automatic firing of nerve cells. It was based on the far-reaching findings of Child on electrical gradients and on the astounding effects of such gradients upon the iron nerve model of Lillie. According to our theory, a constant current, self-engendered in the cell, flows through the cell body, out of it and back in again through the immediate environment (see Fig. 5). At the point of emergence,

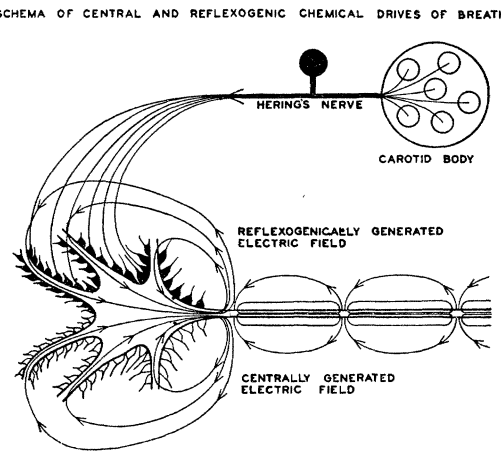


FIG. 5

the neuromembrane alternately breaks down and rebuilds, producing periodic activation and recovery, thus mimicking the phenomena so easily seen in the iron nerve model. This view is now modified and expanded to explain the phenomenon of motor integration, for our hypothesis looks upon the electrotonic current as the master tool of integration. Not only is it thought to generate signals in purely motor centers, but it is believed to be the source of rhythmical firing wherever it occurs, including all sensory receptors. It is the means of transport of electrical disturbances wherever they arise. This hypothesis rests upon substantial biological support, as exemplified in the work of Romanes, Pfluger, Garten, Child, Lillie, Osterhout and Hill, Adrian, Gasser, Hoagland and others.

Granting self-excitation by a self-engendered electrotonic current we may in turn expect a direct proportionality between frequency of discharge and the magnitude of the electronic current as a physiological mechanism of control such as established by Lillie for the iron nerve. What, then, is a possible automatic mechanism of adjustment of neuro-cellular potential drop? Accepting the views of Craigie, Holmes, Dunning and Wolf, and Gerard, of a high cellular metabolism, as compared with that of the neuraxon, we may assume a strong electrotonic current emerging at the axon hillock. Holmes places the metabolic ratio at 10 to 1. If these metabolic rates are now doubled by a rise of temperature, the metabolic gradient increases form 9 to 18 and theoretically doubles the rate of firing of the axon hillock, thus offering a hypothetical explanation of the hyperpnea of hyperthermia. It is suggested that excess of CO_2 and lack of O_2 adjust the potential drop by the process of selective membrane depolarization at the dendrites and cell body.

Chemical reflexogenic control of nerve cell firing originates in the chemoceptors of the carotid body. The ultimate similarity of the basic mechanism of reflex and central chemical drive of breathing is indicated in our combined schema of centrally and reflexogenically generated electric fields. Central drive is shown in the lower half of the schema and reflex drive in the upper. We propose that each afferent signal impinging at the neuron membrane produces a condition of local negativity which increases the prevailing potential drop in proportion to the number of impinging afferent signals. Numerical variation of afferent drive would accordingly function as a reflexogenic chemical control of breathing.

Believing that neurocellular excitation may be caused by an increased neurocellular potential drop, we propose that inhibition may resolve itself into a decreased potential drop, for example, inhibitory signals impinging on the neuron membrane, in a region below the electrical equator, say, in the proximity of the axon hillock, would reduce the potential drop. The emerging electrotonic current would be opposed, and the frequency of firing would diminish. On this basis, excitation and inhibition are fundamentally the same. We have accordingly connected all supposedly excitatory fibers with the excitatory poles of the reticular cells. Supposedly inhibitory fibers have been connected with the inhibitory poles (see Fig. 6).

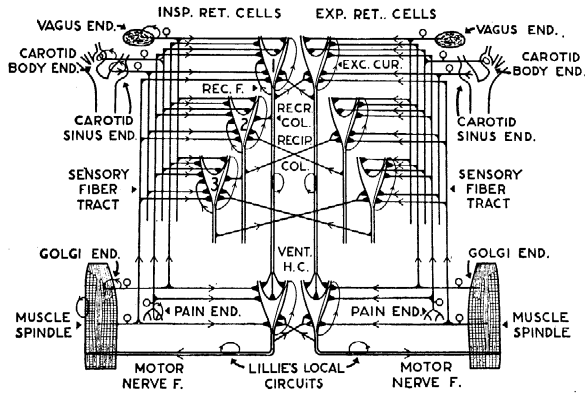


FIG. 6

So much for the basic chemical drives. They are continuous and steady and, therefore, by themselves should produce a steady and continuous firing of the reticular cells, yet the respiratory mechanism responds with periodic discharges. Here we have turned to the concepts of Gasser in building our hypothesis of motor integration, for he has shown a mechanism by which the phrenic nerve is made to respond in a rhythmical way to a uniform train of shocks. We may now consider the production of a periodic response to the steady chemical drives. The phenomena of acceleration and recruitment seem to be important.

We propose that recurrent collaterals offer a simple mechanism of acceleration. The nerve cell need only tap its own neuraxon stream of signals and lead them back to the excitatory pole which gave them birth, to increase the electrical negativity of the excitatory pole and, therefore, the potential drop. This speeds the discharges at the axon hillock, which now return with augmented force to increase the electrotonic drive still more. This progressively and repetitively increasing effect can not continue indefinitely, for progressively increasing activity lowers the ability of the cell body to meet repairs. Growing fatigue gives rise to a disproportionate increase of the threshold of excitation. The re-excitation component which has been built to high values, therefore, suddenly weakens and the fatigued cell stops firing. During inactivity, normal excitability returns and the cell responds once more to its electronic current and passes through the acceleration cycle just described.

Accelerated firing is but the smaller part of each periodic increase of muscle power in the slowly augmenting type of contraction. Recruitment of additional elements, in our experience, is the more important. Though individual phenomena, acceleration and recruitment are inseparable, for acceleration of one reticular cell may be the deciding factor for the recruitment of another. What, then, is a simple mechanism of recruitment? We suggest that the purely motor connections of one reticular cell with the other (Retzius and Lenossek) supply the structural requirements. It is accordingly assumed that highly sensitive reticular cells at the head of the reticular column act as pacesetters for the group. A periodic stream of signals once started, let us say in the pace setter cell No. 1, travels in its reticulospinal neuraxon to its anterior horn cells. On its way, this stream is tapped by collaterals which carry signals to cell No. 2, which is still quiescent, but near the threshold of excitation. Cell No. 2 then fires and sets off cell No. 3. Recruitment continues down the reticular column until cell No. 1 ceases to fire. Absence of signals from cell No. 1 brings cell No. 2 to rest. Cell No. 3 follows suit. Decruitment is more rapid than recruitment, as might be expected from the sudden falling off of cell No. 1. These are our theoretical explanation of the rhythmical recurrence of inspiratory activity.

We must now explain the steady state discharges on the expiratory side. This pattern of activity needs neither the recurrent accelerating collaterals nor recruiting collaterals. Without these mechanisms of periodic augmentation and interruption, the reticular cells theoretically should fire uniformly and indefinitely under a steady drive as they do.

Since both inspiratory and expiratory reticular cells are subject to continuing central and reflex chemical drives, how do they contrive to alternate in activity? Our hypothesis of reciprocal interaction is this. Pacesetting cell No. 1 on the inspiratory side leads off. Collateral signals go to the inhibitory pole of its expiratory mate, which at that moment is still active. These signals inhibit the expiratory cell and slow its discharge. As inspiration waxes the inhibitory action on the opposing cell increases and stops its firing completely, but the expiratory cells are also supposedly connected by collaterals to the inhibitory poles of their inspiratory mates. As the expiratory cell is inhibited and slowed, it withdraws its restraint on inspiratory cell No. 1. This is tantamount to excitation, for the effects of a potential drop in the inspiratory cell are the same, whether the inhibitory pole turns less negative or the excitatory pole more negative. Inspiratory cells thus draw their own excitation from their opposing cells.

We may now return more specifically to the role of sensory impulses in motor integration. We believe that both the inspiratory and expiratory reticular cells possess continuous inherent electrochemical drives and that both are driven by continuous reflexogenic chemical drives as well. When cyanide is injected into the carotid artery to reach the carotid body during the inspiratory phase, it augments the inspiratory act which is in progress. On the other hand, if cyanide is injected during the expiratory phase of breathing, it increases the expiratory contraction which is still

under way. Even though the inspiratory and expiratory reticular cells are under continual bombardment from the outlying chemoceptors, only one group is capable of responding at a time. This single, alternating, selective activation is considered a result of the efficient dual reciprocating mechanism which we have just described. Dual drive (inspiratory and expiratory from a single set of receptors) may be a most important neurophysiological principle, holding not only for the continuing chemical and pain drives but for the periodic drives initiated in the proprioceptive endings of muscle, tendon and lung with each respiratory cycle.

The periodic modification of each respiratory act by transient proprioceptive discharges must now be considered. The vagal nerves which function in a periodic way are generally regarded as inhibitory. According to Hering and Breuer, Gad, Head and Adrian each filling of the lungs stimulates the inhibitory vagal endings and, thereby, inhibits the inspiratory act. After central inhibition wears off a new discharge of the automatically active center occurs. Inspiration is, therefore, prolonged when the vagi are blocked. Virtually all workers disregarded or overlooked the significance of expiration. This point of view is illustrated by a quotation of Adrian's. He states: "An explanation along these lines (*i.e.*, inspiratory inhibition) was in fact given in the classical paper of Henry Head from Hering's laboratory, though it appeared then that the expiratory endings might play some part in the effect." Had physiologists been more reluctant to abandon the expiratory reflexes which Hering and Breuer so clearly demonstrated by inflation of the lungs and had physiologists given more attention to the accelerating action of the vagi on the velocity of the inspiratory act itself rather than the frequency of breathing, the inhibitory theory of vagal function might not have gained the prominence it has to-day.

We shall now consider the vagal stretch reflex as an excitatory drive and determine whether this view meets the facts of vagal physiology. Compare, for example, the velocity of three inspirations in the same dog under three intensities of vagal reflex drive. First, under zero vagal drive with the vagi blocked, second, during normal eupneic breathing, and third, with the lungs superinflated. The velocity is lowest during vagal block, greatest during superinflation and intermediate during eupnea. Comparable though not as uniform effects have been noted in the expiratory gradients, tentatively indicating the possibility of a normal expiratory drive as well.

If the central end of the vagus nerve is subjected to intermittent blocks of faradic stimulation, breathing is stopped as it is by continuous stimulation. Such results have been accepted in the past as proof of the inspiratory inhibitory action of the vagi, but if a second continuous drive is added to this intermittent stimulation, such as central stimulation of the saphenous nerve or chemical stimulation of the carotid body, the effects of vagal stimulation are reversed. Each faradic block may produce an inspiration instead. These results are difficult to reconcile with inhibition.

Final evidence of the driving action of the vagal stretch reflex is found in an augmentation of inspiratory potentials above normal when the lungs are artificially inflated during the inspiratory phase, and frequent augmentation of expiratory potentials when pressure is applied during the expiratory pause. This leads to the more logical interpretation that the vagus is an excitatory nerve and that it may possibly exert a dual drive, one to the inspiratory muscles and the other to the expiratory muscles, in a manner similar to the chemoceptors and nociceptors. The action differs, however, in one important respect, for the signals impinge upon the centers in periodic showers, increasing with each inspiratory inflation and fading away with each expiratory deflation. This waxing of each inspiratory vagal discharge exerts a most effective reinforcement of the slowly augmenting inherent discharge of the center, for as the resistance to inspiration increases the center is automatically driven to fire more intensely. Thus vagal action bolsters inspiration in direct proportion to the degree of pulmonary inflation. When breathing suddenly shifts to the expiratory phase, the vagal drive is suddenly transferred to the expiratory muscles. Vagal expiratory drive is, therefore, at its maximum at the onset of expiration and at its minimum at the close of expiration when the lungs are emptied. We see in this relation a possible reflexogenic mechanism of changing the basic steady state contraction into the rapidly augmenting type, for as vagal drive subsides expiratory contraction diminishes.

Finally, we wish to propose why prolonged artificial inflation of the lungs produces slowing or stoppage of breathing. There are reasons for believing that it may provoke a prolonged reflex tonic discharge of the expiratory reticular cells. These cells in turn are thought to exert an equivalent inhibition of the inspiratory reticular cells via the reciprocating collaterals. This inhibition continues until it is overcome by the accumulating chemical drives of the resulting asphyxia which act more powerfully on the inspiratory side. Only when that moment arrives does inspiration start once more. Such explanation of inspiratory inhibition would call for a fundamental re-analysis of so-called reflex inhibition in all motor integrations.

Little is known of the function of the Golgi endings.

Fulton and Pi Suner regard them as tension receptors. Since the tension of the inspiratory muscles increases as they meet with increasing resistance during inspiration, the signals which the Golgi endings send out must increase, as do those of the vagal endings. We, therefore, propose that Golgi signals bolster the inspiratory act as do the vagal signals. This effect is readily demonstrated in the augmentation of action potentials of an inspiratory muscle by occlusion of the trachea during inspiration.

Still less is known about the muscle spindles. Fulton and Pi Suner and Matthews point to the significant fact that these sensory end organs are arranged in parallel with the contractile fibers. They, therefore, suggest that the spindles are released of their strain when shortening of the muscle occurs. In this mechanical arrangement we see the possibility of another automatic mechanism of reflex bolstering of contraction, for if the muscle spindles are inhibitory the inhibition which they produce would diminish as contraction progresses.

In conclusion, we may say that though we have attempted to analyze only the forces which drive the respiratory act, the principles outlined may be basic to a fundamental concept of the integration of motor activity in general.

SCIENTIFIC EVENTS

THE BEIT MEMORIAL FELLOWSHIPS

A MEETING of the trustees of the Beit Memorial Fellowships for Medical Research, at which Sir Alfred Beit, Lord Onslow, Lord Harlech, Lord Rayleigh, Lord Macmillan, Professor T. R. Elliott and Dr. H. L. Eason were present, was held in London on July 19. According to the London *Times* resignations from the advisory board of Sir F. Gowland Hopkins and Sir Patrick Laidlaw were received and the vacancies were filled by the appointment of Dr. R. A. Peters, Whitley professor of biochemistry, University of Oxford, and of Dr. Paul Fildes, bacteriologist on the scientific staff of the Medical Research Council.

The following elections to fellowships were made:

Fourth Year Fellowships (value £500 a year).—Isaac Berenblum, M.D., M.Sc. (London). To continue his work on the production of cancer by skin irritants, and to study the metabolism of living cells in tissue culture. At the School of Pathology, University of Oxford.

Thomas Arthur Howard Munro, M.B., Ch.B., F.R.C.P. (Edinburgh). To continue his studies of the rôle of inheritance in mental disorders. At the Royal Eastern Counties Institution, Colchester.

Albert Neuberger, M.D. (Wurzburg), Ph.D. (London). To extend his work on the chemistry of amino sugars in elucidation of the structure of natural compounds. At the department of pathological chemistry, University College Hospital Medical School, University of London.

Richard Julius Pumphrey, M.A., Ph.D. (Cambridge). To continue his studies on the nervous system of Cephalopods and on the auditory processes in insects. At the zoological laboratory, University of Cambridge, and the laboratory of the Marine Biological Association, Plymouth.

Junior Fellowships (value £400 a year).—Vernon Hollis Booth, B.A., Ph.D. (Cambridge). George Henry Lewes Student, 1935–38. Ramsay Memorial fellow for chemical research, 1938–39. Proposed research—(1) the internal constituents of bacteria by means of a wet-crushing mill; (2) carbonic anhydrase. At the physiological laboratory, University of Cambridge.

Eric George Lapthorne Bywaters, M.B., B.S., Hons. (London), M.R.C.P. Assistant clinical pathologist, Middlesex Hospital, 1935–36; Rockefeller research fellow in medicine, 1937–38. Proposed research—rheumatoid arthritis. At the British Post-Graduate Medical School, University of London.

Wilfred Ingram Card, M.D. (London), M.R.C.P. Since 1935 medical registrar and tutor to the medical unit, St. Thomas's Hospital; Louis Jenner research fellow, St. Thomas's Hospital, 1938 and 1939. Proposed research—the inhibition of gastric motility and secretion by experimental studies on man. At the medical unit laboratories and Sherrington School of Physiology, St. Thomas's Hospital Medical School, University of London.

Hans Heller, Ph.D. (Prague), M.B., B.Ch. (Cambridge). Assistant to professor of pharmacology, University of Vienna, 1929–34. Proposed research—the antidiuretic principle of post-pituitary extract. At the medical unit laboratories, University College Hospital Medical School, University of London.

Maxwell Shaw Jones, M.D. (Edinburgh), D.P.M. (London). Walter Smith Kay research fellow in psychiatry, University of Edinburgh, 1934–36; Commonwealth Fund fellow, 1936–38. Proposed research—insulin treatment of schizophrenic mental states. At the Maudsley Hospital, Denmark Hill, University of London.

Barnett Levin, B.Sc. Hons., Ph.D. (London). Pedler research scholar, Institute of Chemistry, 1931–32. Since 1932 lecturer in chemistry at Guy's Hospital Medical School, University of London. Proposed research—the effect of spatial configuration of antigens on immunological reactions. At the clinical chemical laboratories of the London Hospital, University of London.

Ian Mackenzie, M.B., Ch.B., F.R.C.S. (Edinburgh). Vans Dunlop scholar in bacteriology, University of Edinburgh, 1933. Rockefeller research fellow, 1938. Proposed research—immunological investigations on constituents of tumors. At the department of surgical research, University of Edinburgh.

Alexander Francis Rawdon-Smith, M.A., Ph.D. (Cambridge). Senior student of the 1851 exhibition, 1936–37 and 1938–39. Rockefeller Foundation fellow, 1938. Proposed research—congenital deafness. At the physiological laboratory, University of Cambridge.