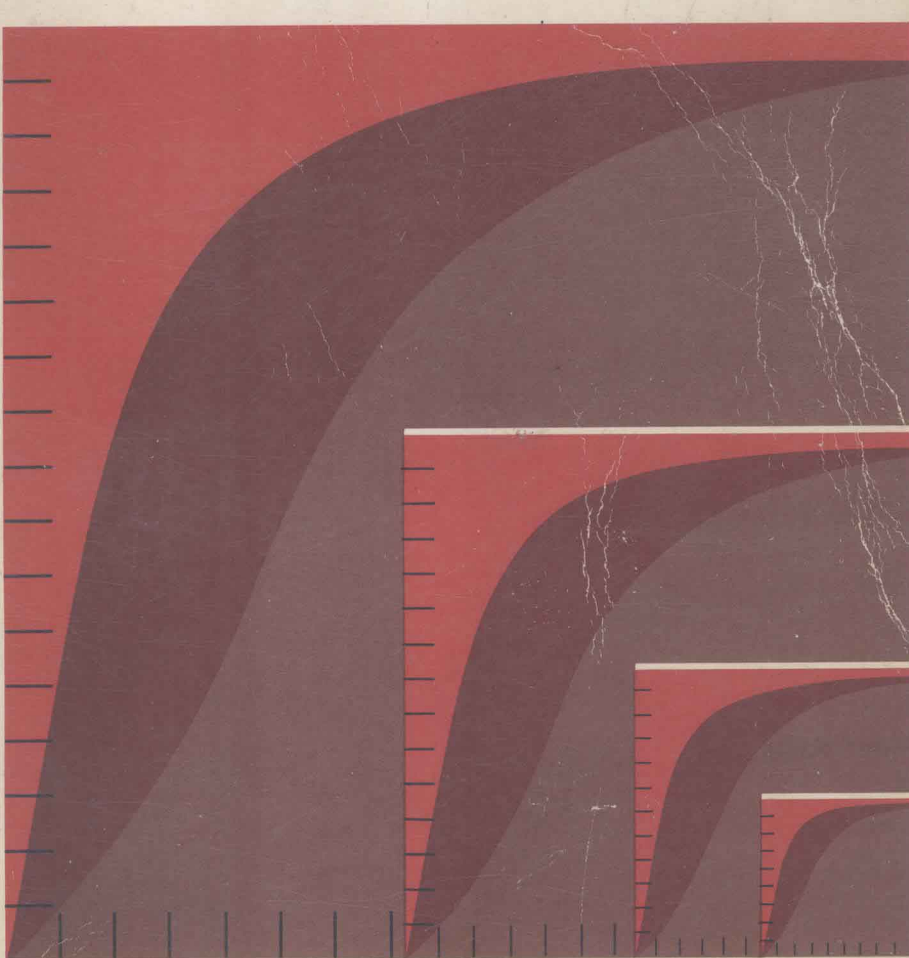
The Chemical Basis of Physiological Regulation

E. J. W. Barrington



SCOTT, FORESMAN SERIES IN UNDERGRADUATE BIOLOGY

The Chemical Basis of Physiological Regulation

E. J. W. Barrington F.R.S.

University of Nottingham

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FOREWORD

In recent years interest in Biology has focused with increasing sharpness on two contrasting areas—the molecular basis of activities of cells and organisms and behavior and population studies. New concepts along with new and more precise methods of laboratory research have resulted in an explosive growth of information. This rapid increase of knowledge, which is doubling every two years, is the concern of all biologists. How may the changing emphasis in biology and the accompanying mass of new information be presented to the beginning student? How can he be adequately informed about areas necessary for further exploration, such as taxonomy, structure, and function, and at the same time be made aware of the new, conceptual dimensions of these areas? Such questions have caused considerable discussion, and suggestions for modification of the introductory course have ranged from abolishing it completely to making it entirely a problems course, with all the logistic and administrative difficulties such an approach would encounter.

One point seems clear. Early in his scientific studies the student must appreciate that science is a continually changing body of knowledge, not a fixed mass of information, and he must gain some concept of how growth in scientific understanding occurs. No clear method exists for achieving these objectives. Actual laboratory experience with someone actively engaged in research would be the most effective means, but opportunities of this kind can be provided for only a few students. Another approach, and one more readily available, would be to have each student read about such experiments, preferably in the words of the investigators themselves. In this way the student might look over the shoulders of those who are performing the experiments and gain some insight into how growth in understanding of the science is brought about.

There are two principal difficulties with the second suggested approach. First, adequate access to scientific journals would be difficult to provide. The cost of subscribing to and storing anything close to complete coverage of biological journals is prohibitive for most colleges, and the single copies of those journals available are woefully inadequate reading sources for large classes. Second, the language of scientific papers might confuse the beginning student. Careful selection and considerable annotation of material would clearly be necessary, and this alone would probably be inadequate. In order to appreciate the significance of newer studies in a particular area, the student would need a firm understanding of that area. Any treatment that would provide the background for such understanding for all the major segments into which biology has traditionally been divided (embryology, physiology, genetics, etc.) and which also would include a discussion of the newer concepts in these fields would need to be of formidable size. But could this be done for a few topics which are of fundamental significance to understanding present-day biology? And could these topics be presented in a form readily available to the student?

To test the possibility of this approach, a brief outline of the idea was sent to a number of biologists to invite their opinions. As a result of the interest shown, several agreed to undertake discussions of topics within their own areas of interest. This group met and discussed the objectives and nature of the series of volumes that would be prepared. The present series is the result of these efforts.

The topics chosen for discussion were selected in the belief that they exemplify the changing emphasis of modern biology. For each of these topics an attempt is made to establish fundamental principles and to indicate how the area is advancing by experimental work. There is a certain logic in the order of the volumes, proceeding as they do from ultrastructure, macromolecules, and the principles of biochemistry to physiological regulation and the biology of populations and evolution. Each volume, however, is complete in itself and may be used alone or in combination with some or all of the others, as the nature of the particular course and the objectives of a particular instructor dictate. In any case to provide either the terminal student with a sound grasp of the field or the biology major with an adequate background for further exploration, the topical approach utilized in this series would need to be supplemented by lectures on those areas of biology not covered in the volumes.

The Scott, Foresman Series in Undergraduate Biology is designed for use as basic texts for introductory biology courses, as useful supplementary material for lectures and laboratory work in other biology courses, and as review or supplementary sources for specialized, intermediate courses. It is hoped that these volumes may afford the student some idea of the recent and significant change in focus of biology and some concept of the excitement and challenge of this rapidly moving science.

Samuel A. Matthews, *Williams College*

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CONTENTS

CHAPTER 1 The Uptake of Oxygen

■ LIFE AS AN OPEN SYSTEM

When a man shows great vigor and drive, he is sometimes said to have fire in his belly. It is a compliment that is not taken literally, although there was a time when it might have been. In classical Rome, for example, Cicero held it to be "a law of Nature that all things capable of nurture and growth contain within them a supply of heat without which their nurture and growth would not be possible." From this he inferred "that this element of heat possesses in itself a vital force that pervades the whole world."

Cicero was describing, in a way that now seems strange, a feature that characterizes living organisms and differentiates them from the non-living material which surrounds them. The material of the universe always tends toward a state of increasing inertness. If it is hot, it cools. If it is moving, it will ultimately stop. If it is capable of chemical change, it undergoes reactions that result in a reduction in the amount of what is called its free energy, which is that part of its energy available for chemical work. This property of matter is closely connected with the concept of entropy, which relates the free energy of materials to their degree of organization. According to this concept, a decrease in the free energy of a material system means an increase in its disorganization, and, because of this, a reduction in the possibility of further change within that system. This increase in disorganization is called an increase in entropy, for entropy is essentially a measure of the amount of disorder within a system.

The trend toward the increasing inertness of matter is embodied in the second law of thermodynamics, which states that changes in the material of the universe are unidirectional and irreversible, and result in a progressive increase of entropy. The universe, in short, is slowly "running down." It is apparent, however, that if these considerations applied without modification to living material, maintenance of life upon this earth would be impossible. In the long run all men are dead. But before man reaches this end, he has maintained a high level of activity in a body that preserves for many years a recognizably uniform appearance. Moreover, living organisms perpetuate themselves either by the transmission of germ cells or by a variety of nonsexual methods. Within living matter there is a potential immortality, however difficult the environmental hazards. However, this does not mean that living matter is an exception to the second law of thermodynamics.

Maintenance of life depends upon chemical reactions which replenish the energy lost by the activities of living systems. This process is possible, because two types of chemical reactions occur, namely exergonic and endergonic. While the first results in a reduction of free energy, the second effects an increase in free energy and sustains living systems by enabling them to take energy from an outside source, the sun. Photosynthetic organisms as well as important groups of photosynthetic bacteria and unicellular organisms initially capture the sun's energy and build it up by endergonic reactions to form energy-rich compounds of complex molecular constitution. Such compounds constitute the food that is the energy supply of animals.

Thus life maintains itself by functioning as an open system replenished by an external source of energy. Materials flow through this system to undergo chemical reactions called metabolism. The flow, moreover, is not passive and automatic. It is an active process that can be controlled and regulated by the organisms that it nourishes, so that these organisms maintain what is called a steady state in a constantly fluctuating environment. Although organisms adapt to their environment, that is, react to it in a manner calculated to promote their survival, the materials of which organisms are composed cannot escape from the consequences of the second law of thermodynamics. There is an inevitable cycle of death and decay, in which the bodies of plants and animals are broken down into inorganic materials with an increase of entropy. To this material is added the continuous discharge of waste resulting from the activities of living organisms. As long as solar energy is available, however, organization can be transmitted to new generations. Individual organisms will die, but the living systems of this earth will continue to survive; this is the potential immortality mentioned earlier.

The energy stored in living systems by endergonic reactions is released by oxidation, and it is because of this that a supply of oxygen is needed by all organisms, except the small number adapted for anaerobic life. Oxidative metabolism results in the production of carbon dioxide, so that there is a gaseous exchange between the organism and its environment. Such an exchange, involving an input of oxygen and an output of carbon dioxide, forms part of the process of respiration which may be referred to as external respiration. In man, as in terrestrial vertebrates in general (at least from reptiles upward), the exchange takes place in the lungs. The gases are transmitted between the lungs and the rest of the body by the blood stream —oxygen in loose combination with hemoglobin, and carbon dioxide mainly in solution as bicarbonate. This transport, together with the oxidative reactions taking place in the tissues, constitute internal aspects of respiration. The following section examines, as an example of adaptive organization, the ways in which some animals maintain continuity in their external gaseous exchanges and modify these exchanges in relation to alterations in the environment and in their own levels of activity.

■ NERVOUS CONTROL OF EXTERNAL RESPIRATION IN MAN

The general course of external respiration in man is familiar. During the process called inspiration, air is drawn into the lungs by suction. This intake of air is the result of increased negative pressure in the chest caused by expansion of the thoracic cavity. Expansion is effected by contraction of the diaphragm and the muscles which move the ribs; while discharge of the respired air (expiration) is brought about largely by elastic recoil of the lungs, as the diaphragm and intercostal muscles relax, and the ribs return to their resting position. These movements, termed the ventilation movements, result in a flow of air (the tidal flow) into and out of the bronchial passages and cavities of the lungs. Since it is impossible to expel all air from the lungs, as some degree of negative pressure always remains within the thoracic cavity, air remains which is termed residual. Part of this, the alveolar air, is contained within the alveoli, the ultimate cavities of the lung tissue where the gaseous exchange takes place between the air and the blood stream. As may be seen from the accompanying data (Table 1-1), the alveolar air, which thus stands intermediate between the atmosphere and the blood, differs in composition from both the inspired and expired air.

TABLE 1-1

Composition of Respiratory Air in Man (in Volumes Per Cent)[a]

	Inspired Air	Expired Air	Alveolar Air
Oxygen	20.71	14.6	13.2
Carbon dioxide	0.04	3.8	5.0
Nitrogen	78.00	75.4	75.6
Water vapor	1.25	6.2	6.2

[a] Data from Frank R. Winton and Leonard E. Bayliss, *Human Physiology*, 2nd ed. (Philadelphia: Blakiston Co., 1937).

The extent to which animals can survive a temporary loss of their oxygen supply varies a great deal, depending partly on the level of complexity of their organization, and partly on the degree to which their respiration may be adapted in specific ways to peculiarities of their normal environment. In man the supply must be maintained virtually without interruption, although not all tissues stand in equal need. The arm or leg can be isolated from respiratory exchange for at least an hour, but the heart, and to a greater extent the nervous system, are immensely more sensitive. If the brain is cut off from its oxygen supply in the blood stream for as little as five minutes, it will normally be damaged beyond possibility of repair, although this need not be so if the body is artificially cooled (Chap. 6). Not only must the ventilation movements be continued without a break when the body is at its normal temperature, they must also be modifiable in relation to changing demands, if the steady state is to be maintained. These requirements are met by a complex of interrelated physiological devices which show some of the fundamental characteristics of adaptive organization.

It is theoretically conceivable that external respiration might be maintained by a reflex mechanism. For example, a reduction in the oxygen circulating in the blood stream might stimulate specialized sensory receptors somewhere in the body. Nerve impulses from these structures could then be propagated through predetermined pathways in the peripheral nerves and central nervous system to bring about contraction of appropriate respiratory muscles. It will be seen later in this chapter that reflex pathways are important in the control of respiration in the flea *Xenopsylla*. They also have a part to play in man's respiration, but they are not the primary source of the respiratory ventilation movements. These are evoked not by reflex action but by the more or less regular discharge of volleys of nerve impulses

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through certain spinal nerves, i.e., the phrenic nerves, running to the diaphragm, and the intercostal nerves, running to the muscles of the ribs (*Fig. 1-1*). The impulses arise in the medulla of the brain in a localized region called the respiratory center. The rhythmicity of the respiratory movements is in large measure a direct consequence of spontaneous rhythmic activity in that center. Within certain limits, therefore, the supply of air to the lungs is ensured by an essentially automatic process that does not arise from any special sensitivity to oxygen lack.

A medullary respiratory center occurs not only in mammals but also in fish. Indeed, the fact that rhythmic respiratory activity can be autonomous and independent of stimulation from peripheral sensory receptors was first demonstrated clearly in a pioneer study of the goldfish brain by E. D. Adrian and F. J. J. Buytendijk.

Since the original observations of Caton various workers have recorded changes of electrical potential in the brain. It has been established that active parts become negative to inactive, but it is difficult to say what elements of the central nervous system are responsible for the effect. The action potentials of the nerve fibres will presumably contribute something, though Bablioni's experiments with strychnine favoured the nerve cells as the most important factor. The structures involved are so complex, however, that in recent years very little has been added to our knowledge of the central nervous system by the investigation of its potential changes.

The present experiments fall into line with earlier work in showing changes which can be localized and related to the normal activity of the brain, and the same difficulty arises when we attempt a further analysis. But a tentative analysis is possible and its results are of some interest. They suggest a type of electrical activity which differs from that of the nerve fibre in its much more gradual rise and decline, and this agrees with what we might expect from entirely different lines of work on the central nervous system.

METHOD

The preparation employed was the isolated brain stem of the goldfish removed from the skull and placed on a glass slide. Complete isolation may seem an unnecessary precaution, and the damage occurring through manipulation and from loss of the circulation must have accounted for many failures to observe any sort of activity. But in making a preliminary survey we were anxious to avoid all extraneous electric changes such as those due to the heart and the skeletal muscles. With a sensitive amplifying system, electrodes placed on the brain surface may record changes developed in almost any part of the body, and it seemed best to begin with a preparation in which this source of confusion could be definitely excluded.

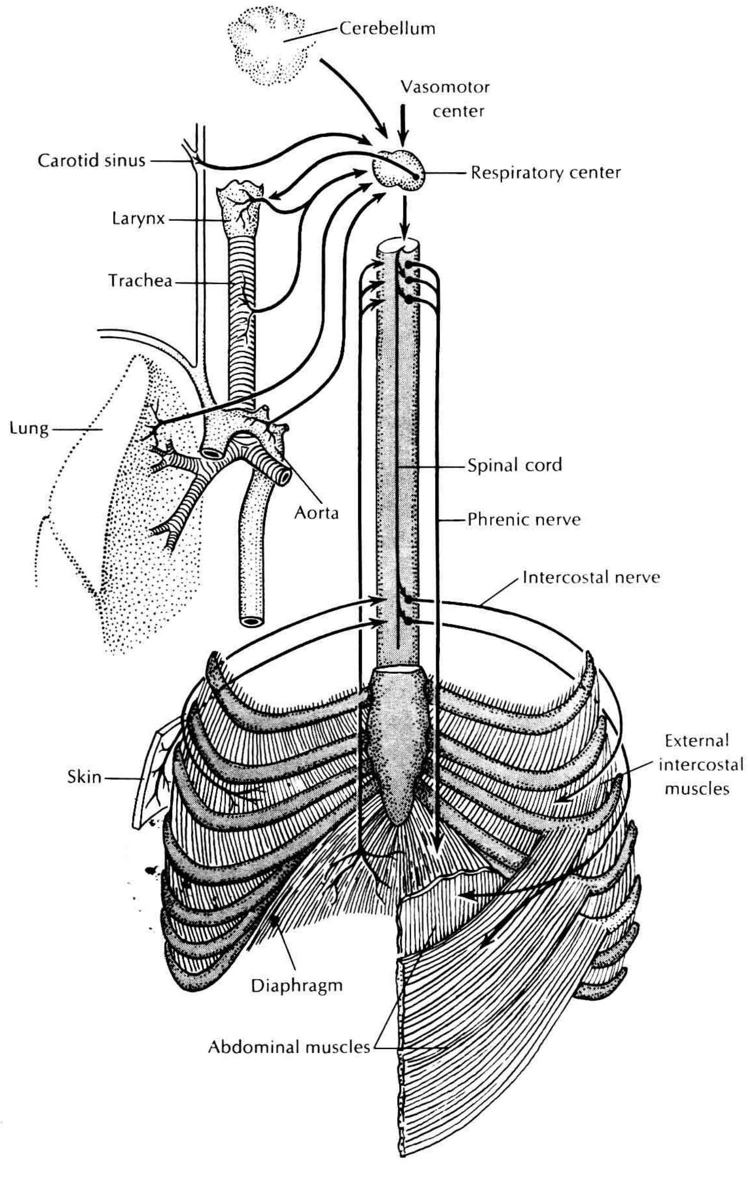

Fig. 1-1. Diagram of the respiratory muscles and the influences acting upon them. (Partly after Best and Taylor, from J. Z. Young, *The Life of Mammals*, Oxford: The Clarendon Press, 1957, p. 304.)

The goldfish was chosen because of the large size of its brain stem compared with that of the frog, but there is also the outstanding advantage that the respiratory centres are far more active. The importance of this will appear presently.

A diagram of the brain is shown in *Fig.* [*1-2*]. In making the brain stem preparation the fish was decapitated and the cerebrum destroyed by crushing. The brain stem was then carefully exposed, and after the roots of the cranial nerves had been cut, it was lifted or rolled out of its bed on to a glass microscope slide moistened with Ringer's fluid (containing 0.6 p.c. NaCl). In some preparations the base of the skull was removed with the brain stem. The preparation includes the medulla with the large vagal lobes on either side, the cerebellum which forms a rounded protrusion in the mid-line in front of the vagal lobes, and the mid-brain with its paired optic lobes (equivalent to the corpora quadrigemina in mammals). The primitive cerebrum is so placed that it can be destroyed by crushing the skull without much risk of damage to the lower part of the mid-brain.

The brain stem on its glass slide was placed on a stand carrying two non-polarizable electrodes (Ag, AgCl) ending in moist threads. The recording system was a valve amplifier leading to a Matthews oscillograph and a loud-speaker. The particular arrangement in use has been described recently, but as the experiments advanced, the coupling arrangements in the amplifier were progressively modified to give faithful records of slower and slower changes. The only other addition has been the provision of an alternative loud-speaker which gives prominence to sound waves of low frequency. This was installed for work on impulses of the slow type (*e.g.*, in sympathetic fibres), and it has been of great use in the present research where it is important to be able to detect potential fluctuations over the widest possible range of wave-lengths.

RESULTS

(1) RESPIRATORY WAVES: Unless the brain stem has suffered gross injury in the process of removal, it is nearly always possible to detect small and rapid potential oscillations which vary with the position of the electrodes and cease after an hour or more. As a rule they do not exceed about 0.005 millivolt. In many preparations, however, a much more striking effect appears, for the oscillograph records a succession of large, slow waves, occurring fairly regularly at intervals of 1 to 3 seconds. . . .

[These] potential changes have varied from 0.02 to 0.15 millivolt. If they occur at all they can usually be detected with any arrangement of the electrodes, provided that they are not placed symmetrically on either side of the brain stem. The waves may be evident as soon as the preparation is set up, or there may be a delay of some minutes before they begin: in some preparations they have only appeared for a few minutes, and in many they have never appeared at all. There is

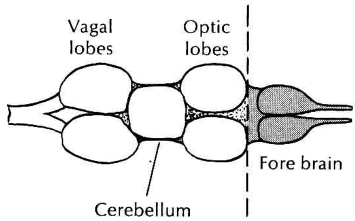

Fig. 1-2. Diagram of brain of goldfish *(Carassius auratus).* The preparation consists of the brain stem, the cerebral [forebrain] hemispheres (shaded) being destroyed. (From E. D. Adrian and F. J. J. Buytendijk, *Journal of Physiology*, 71 (1930), 122.)

usually some irregularity of the rhythm at the start, and a progressive slowing before the waves disappear.

These changes must indicate some kind of rhythmic activity, and the frequency at which they recur makes it almost certain that the activity is connected with respiration, for the respiratory movements in the goldfish occur at intervals of from 1 to 3 seconds and the motor nerves concerned take origin in the brain stem. The resemblance between the two rhythms is illustrated in *Fig.* [*1-3*]. The upper record is made from [an isolated brain], and the lower was made from an intact goldfish, breathing quietly in a tank of water, by throwing a shadow of the gills on to the slit of the recording camera.

The absence of rhythmic waves in many preparations is not surprising. Accidental damage to the brain stem must often be responsible, but in many fish the respiratory movements become irregular or cease when the fish is at rest in well-aerated water; and these fish are the least likely to furnish brain stem preparations with regular potential waves. The best preparations have been made from fish which breathe vigorously, and it is usually a favourable sign if rhythmic gill movements continue after decapitation and the destruction of the fore brain. . . .

LOCALIZATION: The waves are due to changes in the potential of the vagal lobes relative to the rest of the brain stem. If one electrode is on the mid-brain and the other on the caudal end of the medulla, either electrode may show negativity to the other. But if one is on the cephalic end of one of the vagal lobes, the deflection indicates negativity at this electrode wherever the other may be. . . . In agreement with this it is found that the maximum deflection occurs where one electrode is on the vagal lobe and the other at some distance either in front or behind, and also that the mid-brain can be extensively damaged without stopping the waves.[1]

Adrian and Buytendijk thought it likely that these slow potential waves were not due to nerve fiber discharges but were brought about by slow and continuous potential changes in a group of nerve cells in the brain stem. Moreover, they emphasized that these observations, regardless of the underlying cause, were a clear example of rhythmic activity in the absence of afferent impulses. Given an appropriate medium, the nervous tissue could beat as spontaneously as heart muscle.

The importance of the respiratory center of mammals can be demonstrated by cutting through the brain of experimental animals at carefully predetermined levels. A useful landmark is the pons Varolii on the underside of the cerebellum. If the cut is made at a level anterior to the pons (a process called decerebration), the normal respiratory movements continue. If, however, the cut is made at the hind end of the medulla, respiratory movements cease, for impulses from the center can no longer reach the spinal roots of the phrenic and intercostal nerves. The animal can now be kept alive only by some form of artificial respiration. The respiratory center is thus shown to be the power house of the ventilation movements, but to say this is to state only a small part of the story.

The functioning of the mammalian center has been explored further by applying electric stimulation to its different parts. This has shown that the center is differentiated into two regions (*Fig. 1-4*), one of which, lying ventrally, is an inspiratory center. Electric stimulation of this region in an experimental mammal brings about inspiratory movements. The more dorsal and lateral region of the respiratory center constitutes an expiratory center; stimulation of this results in an interruption of the movements of inspiration. In addition, there are cells in the pons which are functionally related to both the inspiratory and expiratory centers and which constitute a distinct center of their own, the pontine or neurotaxic center.

The interrelationship between these centers is complex, and it is here that reflex mechanisms have a part to play (*Fig. 1-4*). In the walls of the lungs are receptors that are sensitive to stretch. It has been shown by records of electrical activity in the vagus nerves that these receptors discharge nerve impulses along the sensory fibers of vagus nerves into the expiratory center. The lungs become expanded during inspiration; this stimulates the stretch receptors to increase their rate of discharge of nerve impulses. Consequently, such an increase is thought to stimulate the expiratory center which then discharges

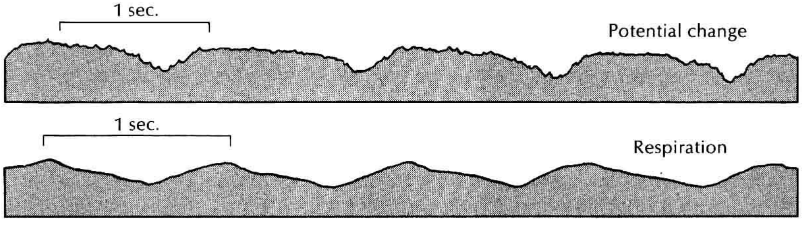

Fig. 1-3. Upper record: potential wave rhythm from the isolated brain of a goldfish. Lower record: rhythm of respiratory movements of intact fish. (From E. D. Adrian and F. J. J. Buytendijk, *Journal of Physiology*, 71 (1930), 125.)

impulses that arrest the activity of the inspiratory center. With the resulting advent of expiration, there is an accompanying reduction in tension of the lung walls leading to a decline in the discharge of nerve impulses from the stretch receptors. Thus at a certain stage expansion of the lungs effects a reflex inhibition of the inspiratory movements.

The significance of this reflex (the Hering-Breuer reflex) was not understood fully when it was first discovered. It seemed possible that it might be the primary factor in promoting the rhythmicity of the ventilation movements, but it is now known that this is not so. If both vagi of an experimental animal are cut, so that the impulses from the stretch receptors cannot reach the medulla, the animal will still continue to breathe, although the rhythm of the ventilation movements will be slower than normal. The Hering-Breuer reflex does not, therefore, initiate the rhythm, but it does exert some control over it. Although the significance of this reflex is obscure, one of its advantages may be that it can safeguard the lungs from overdistension.

While the respiratory rhythm continues in the absence of vagal inhibition, it ceases if the brain is cut immediately anterior to the medullary respiratory centers, separating the respiratory centers from the pontine center which is essential for the maintenance of their rhythmic activity. It is suggested that the inspiratory center, in addition to evoking the respiratory movements, acts also on both the expiratory and pontine centers. When these two areas are stimulated adequately by the respiratory center, they discharge inhibitory impulses into the inspiratory center and thus bring inspiration to an end. All the centers thus interact as a functional unit. Such, at least, are the lines along which the nervous control of respiration in man has traditionally been explained, although full understanding of how the respiratory rhythm is generated cannot be claimed.

■ CHEMICAL CONTROL OF EXTERNAL RESPIRATION IN MAN

So far mammalian ventilation movements have been described as dependent primarily upon an inherent neural rhythm, with some contribution also from reflex pathways. There is the further possibility of voluntary and conscious control from man's higher nervous centers. Human beings can control by their own volition both the depth of respiration (i.e., the volume of the tidal flow) and also the rate of ventilation. There are, however, strict limits to this control. A continuation of forced deep breathing, which amounts to overventilation of the lungs, soon results in a temporary cessation of breathing (apnoea). Conversely, breath can be held for only a limited time; the body soon takes control and restores normality by undergoing a period of increased ventilation (hyperpnoea). These lim-

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