reduced blood takes up larger amount of CO_2 than oxygenated blood. So that in the body, reduction of blood in the tissue capillaries increases the degree of CO_2 uptake from the tissues. (3) Oxygenation of blood causes evolution of CO_2. This happens in lungs. (4) As the CO_2 tension is increased, the total amount of CO_2 taken up by blood also rises. As the CO_2 tension falls CO_2 content also diminishes.

8.13. CONTROL OF RESPIRSTION

The normal rate of respiration in an adult is 14 to 18 per minute with a tidal volume of about 500 ml. The rate and depth of respiration (pulmonary ventilation per minute) is adjusted according to requirement of the body. For instance during muscular exercise metabolic activities are increased and the demand for oxygen by the working muscles is increased. At the same time a large amount of carbon dioxide is produced by the muscles and it becomes necessary to eliminate it. Thus in muscular exercise the respiration is increased both in rate and depth. In fact the increase in minute ventilation is directly proportional to the magnitude of muscular exercise. n the other hand, respiration is depressed during sleep when the metabolic rate is low. Since the rate and depth of respiration can be accurately adjusted to metabolic needs of the body there must be an efficient mechanism for its regulation.

Like other physiological functions of the body the act of respiration, too, is controlled by a special group of nerve cells in the brain stem, which constitutes the 'respiratory centre'. The activity of this centre is controlled by many factors which may be classified under two headings, viz.

I. Nervous factors and II. Chemical factors.

Respiratory entre

Respiratory centre consists of a widely scattered group of nerve cells in the reticular formation of the pons and medulla (Fig 271) which may be divided into 3 major areas :—

(1) Pneumotaxic area—located in the upper pons. It controls the activity of the two lower centres. Section at 'M' produces apneustic type of respiration characterised by prolonged inspiratory

cramps. It has subsequently been established that section of vagal afferents together with section at 'M' is necessary for typical apneustic respiration.

(2) Apneustic area located in the lower pons—so named because when isolated from the influence of 'pneumotaxic centre it leads to apneustic type of respiration mentioned above. Section at 'N' leads to gasping type of respiration from the medullary respiratory centre isolated from the influence of other parts of respiratory centre.

(3) Section at 'O' produces stoppage of respiration because the connection between the medullary respiratory centre and the motoneurones of the phrenic and intercostal nerves are severed.

Medullary respiratory centre located near the lower part of the floor of the fourth ventricle (Fig. 272) consists of two parts.

(1) Inspiratory centre—ventromedially placed and (2) Expiratory centre—dorsolaterally placed.

The above conclusions were based on stimulation experiments. Subsequent caretul studies with microelectrodes confirmed the existence of two sets of neurones (viz. inspiratory and expiratory) but they are comingled with each other, so that all the inspiratory or expiratory neurones are not collected together to form a 'centre' in the way it is usually understood. However for the sake of simplicity in description existance of such centres bilaterally may be postutated.

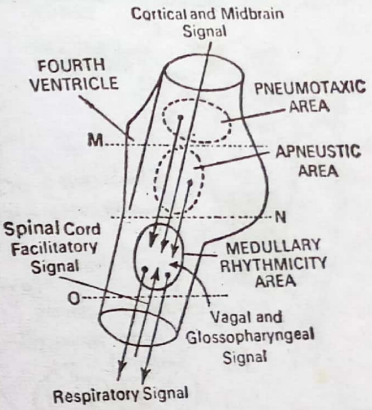

Fig. 271. The three parts of respiratory centre located in the brain stem (after Guyton).

(a) It has been further postulated that inspiratory centre of one side has got connec ion with inspiratory centre of opposite side. Same type of connection exists between the expiratory centres of two sides. So that stimulation of inspiratory centre of one side will have excite-inspiratory effect on the contralateral side. Same remark is true for expiratory centre.

(b) Second postulation is that homolateral inspiratory and expiratory centres have got 'to-and-fro' connection and reciprocally inhibits the activity of each other, so that stimulation of the inspiratory centre is attended simultaneously with inhibito-expiratory effect, though the neurophysiological basis for this connection between inspiratory and expiratory centres has not been established.

(c) The third postulation is that the medullary respiratory neurones have got an intrinsic rhythmicity of their own. If the medullary respiratory centre are isolated from impulses of higher

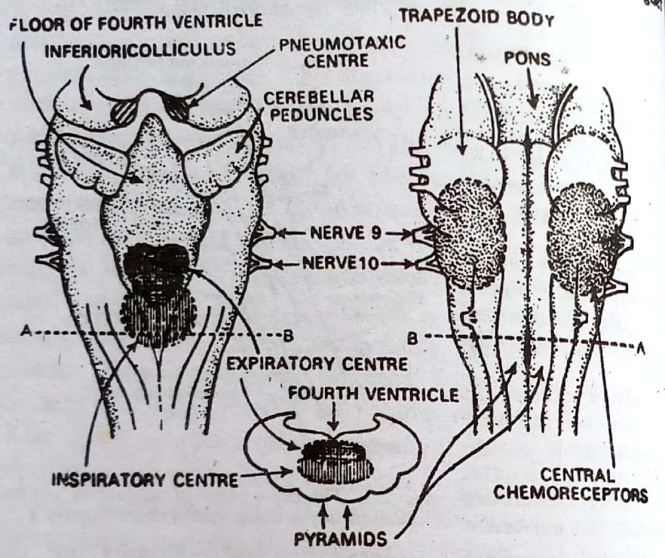

Fig. 272. Diagram of the medulla and pons in the cat's brain stem showing areas involved in control of respiration after electrical stimulation with microelectrodes connected to an amplifire (after Pitts and Burns).

parts by rostral transection 'gasping' type of respiration occurs (hence the name 'gasping centre'). Further transection more caudally will cause complete isolation of the medullary centre which nevertheless exhibits some spontaneous rhythmic discharge at least in the inspiratory nerve calls. The inspiratory centres, therefore, have got a basic rhythmicity of their own (c. f. cardiac muscle). This area, however, by itself is not capable of giving a normal smooth type of respiration. The exact mechanism by which

normal rhythmic respiration is maintained is not yet properly understood. It is probable that normal respiration occurs due to co-ordinated activity of the 3 parts of the respiratory centres mentioned above.

Machanism of rhythmic respiration (Fig. 273)

Inspiration commences by discharge of impulses from apneustic centre to the inspiratory centre. Apneustic centre at the same time sends impulses to the pneumotaxic centre of upper pons. This centre sends excitatory impulses to the expiratory centre which inhibits the inspiratory centre. The inspiratory centre at the same time receives inhibitory impulses from the vagal stretch afferents

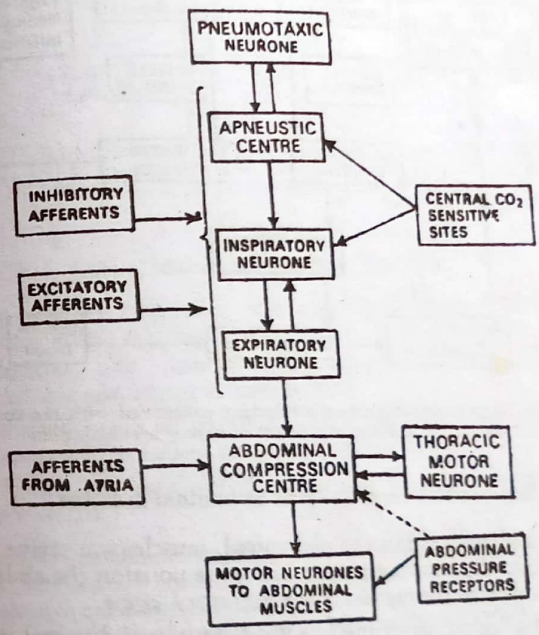

Fig. 273. Schematic representation of respiratory mechanism in the brainstem of a cat.

stimulated by lung inflation during inspiration. Being influenced by the double negative 'feedback' mechanism—the activity of the nerve cells of the inspiratory centre stops and expiration commences passively. The cycle is repeated automatically at the end of expiration because the vagal stretch afferents are no longer active and

the reciprocal inhibition of inspiratory centre from expiratory centre comes to an end after the stoppage of activity of the expiratory centre (Fig. 274).

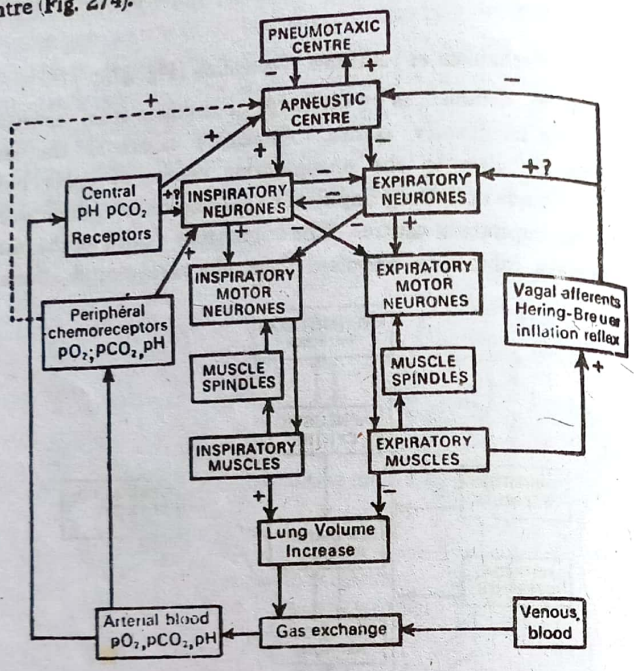

Fig. 274. Diagram depiting major mechanism concerned with the control of respiration and the regulation of alveoria-ventilation.

Reflex effect on activity of abdominal muscles

In the standing position the abdominal muscles are active during expiration but in a resting person in supine position the abdominal muscles are inactive throughout the respiratory cycle.

1. During rapid breathing, e.g. exercise, the abdominal muscles become active during early expiration.

2. Positive intrapulmonary pressure elicits reflex contraction of abdominal muscle. The response is abolished by vagotomy. Positive intrapulmonary pressure elicits contraction of abdominal muscles in a closed chest dog but fails to do so if the chest is opened though in this case the the lung distension is greater. The afferent fibres responsible for contraction of abdominal muscles, therefore, are separate from those concerned in Hering-Breure Reflex.

the reciprocal inhibition of inspiratory centre from expiratory centre comes to an end after the stoppage of activity of the expiratory centre (Fig. 275).

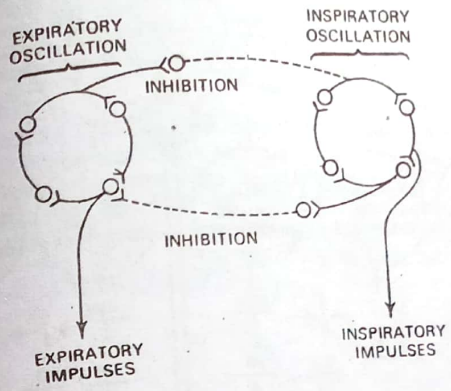

Fig. 275. Diagram depiting the dotted inter-neuronal connection between the expiratory and inspiratory centres responsible for alternate excitation and inhibition of inspiratory and expiratory centres.

Role of abdominal muscles (Fig. 276)

During normal respiration the abdominal muscles are inactive. They become active during

(1) exercise and other conditions leading to hyperpnoea (increase in rate and depth of respiration).

(2) positive pressure breathing (for example during anaesthesia when a pump is attached to an intra-tracheal tube).

(3) diminution in blood volume in certain low pressure areas of circulatory system.

The atrial mechanoreceptors (and probably receptors in other parts of circulatory system) normally maintain reflexy the tone of the abdominal muscles. The afferent fibres run in the vagus and are separate from those concerned in Hering-Breuer reflexes. Centre for these reflexes is a group of nerve cells separate from those of respiratory centre and has been named as abdominal compression centre (ACC). This centre is influenced by the adjoining respiratory centre in reflexes (1) and (2) and in reflexes from the sino-aortic zone, but is affected directly by reflexes from low pressure areas of cardio-vascular system. Amongst the latter the atrial mechanoreceptors have been extensively studied. Fall in pressure in the atria causes increased tonicity of abdominal muscles thereby diminishing the blood volume

in the capacitance vessels of the abdomen and increasing the blo volume in the atria. Rise in atrial pressure has got opposite effect.

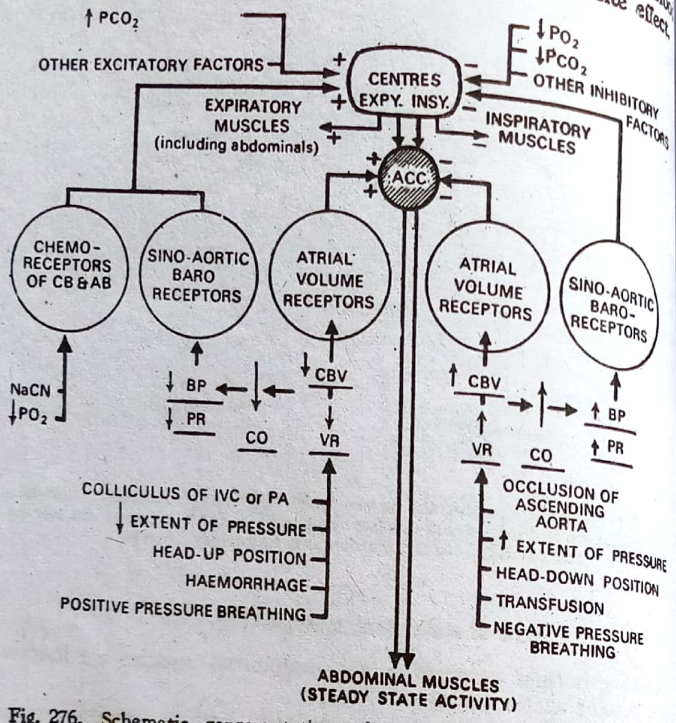

Fig. 276. Schematic representation of main factors and mechanisms concerned with altering the level of activity of abdominal muscles in respiratory to cardiorespiratory changes. The left side of the diagram depicts excitatory influences which affect the action of abdominal muscles either through the respiratory centre or more directly. The right side illustrates inhibitory changes which promote a decrease in the activity of abdominal muscles. EXPY = expiratory centre; INSY = inspiratory centre; ACC = abdominal compression centre (abdominal muscle tonus centre); BP = (arterial) blood pressure; PR = peripheral resistance; CO = cardiac output; CBV = central blood volume; VR = venous return; IVC = inferior vena cava (postcaval vein); PA = pulmo nary artery; —, inhibitory effect, + excitatory effect (after Best and Taylor's Physiological Basis of Medical Practice, 9th edn.)

The existence of ACC (abdominal muscle tonus centre) separates from respiratory centre but acting in collaboration with it makes it probable that the activity of the abdominal muscles in respiration is in part determined by reflexes through this centre. This centre, like respiratory centre, is sensitive to P_{UO_2}.

Besides respiration the ACC also reflexly modifies the tone of the abdominal muscles in such a way that the intrathoracic blood volume remains unaltered and an effective cardiac output is maintained.

I. NERVOUS CONTROL OF RESPIRATION

The Hering-Breuer Reflexes :

These reflexes prevent overdistension of the lungs during inspiration and collapse of the lungs during expiration. The former reflex is known as Hering-Breuer *inflation* reflex and the latter is Hering-Breuer *deflation* reflex.

1. Inflation reflex :

The receptors for these reflexes are 'stretch receptors' located in the lungs, mainly the bronchi and bronchioles. They are stimulated during inspiration when the lungs become stretched. The afferent impulses travel in the vagi and are relayed in 'tractus solitarius' before they reach the respiratory centre where they exert an inspiration-inhibiting effect. The inspiration is thus cut off in time and expiration commences (Fig. 277).

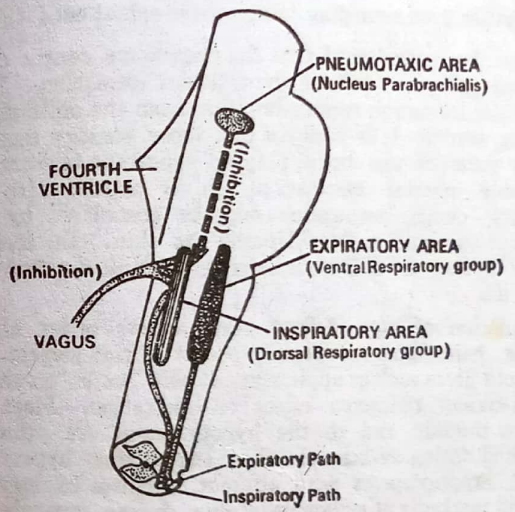

Fig. 277. Oversimplified diagram showing organisation of the respiratory centre.

Section of the vagi abolishes the inflation reflex when the inspiration gets unduly prolonged and the chest is held up in inspiratory position at a time when no air is entering the lungs.

II. Deflation reflex :

The respectors may be described as compression respectors located probably in the alveolar septa. They are stimulated during expiration and reflexly inhabits expiration and reciprocally stimulates inspiration. The afferent fibres are carried in the vagi. The

deflation is thus mediated by a separate set of receptors and
by a separate set of fibres in the vagi.

It may be mentioned that during normal expiration the
receptors become unstretched resulting in cessation of inhib
impulses to the inspiratory centre. Since this centre is
active inspiration commences as soon as inspiration-inhib
impulses resulting from lung inflation ceases.

The inspiration-exciting effect of 'deflation reflex' bec
obvious in condition, such as, pneumothorax, hydrothorax,
where the degree of collapse of the lungs is more severe and re
in stimulation of the respiratory process.

The physiological effect of Hering-Breuer reflexes is to mai
the extent of lung inflation so that the tidal volume tends to
within a useful range. Indirectly the respiration rate is
adjusted so as to maintain adequet level of pulmonary and alve
ventilation.

Impulses from ascending tracts of the spinal cord (Fig. 278)

It has been mentioned that the respiratory centre consists
specialised group of cells in the reticular formation. The cells
the reticular formation receive impulses from the collaterals of
ascending tracts. It is believed that those sensory impulses fr
different parts of the body play an important facilitatory role
maintaining normal respiration. In a patient with depres
respiratory centre respiration may be stimulated by periphe
stimulus of any kind, such as slapping the skin. In fact, it is
practice to slap the new-born baby to establish the first respirat
cycle of life.

Stimulation of any afferent nerve causes reflex alteration
breathing, pain fibres are specially potent in this respect. Stimu
tion of cold fibres such as application of cold water on the face
got well-known excitatory effect on respiration. Heat recepto
located on the skin and in the hypothalamus are stimulated
warm blood during exercise and fever and produce hyperventilatio
Muscular proprioceptors send afferent impulses to the respirato
centre and markedly stimulate respiration during muscular exerci
Proprioceptors of the respiratory muscle profoundly modify
respiratory movement of the next cycle.

Rise in pressure in right atrium and the great veins reflex
augments respiration during muscular exercise and cardiac failure.

Glossopharyngeal nerve contains afferent fibres which inhib
respiration during second stage of deglutition.

Hiccough is due to reflex spasm of the diaphragm associat
with spasm of the laryngeal muscles arising from irritation of sens
nerve endings of the gastrointestinal tract.

Stimulation of somatic sensory nerves of the nose inhibi
respiration and may cause reflex sneezing.

Coughing is a reflex phenomenon caused by irritation of the mucous membrane of the respiratory tract. It is an important protective reflex in which the irritant material is got rid off from the respiratory tract. At the beginning of the act a deep inspiration is

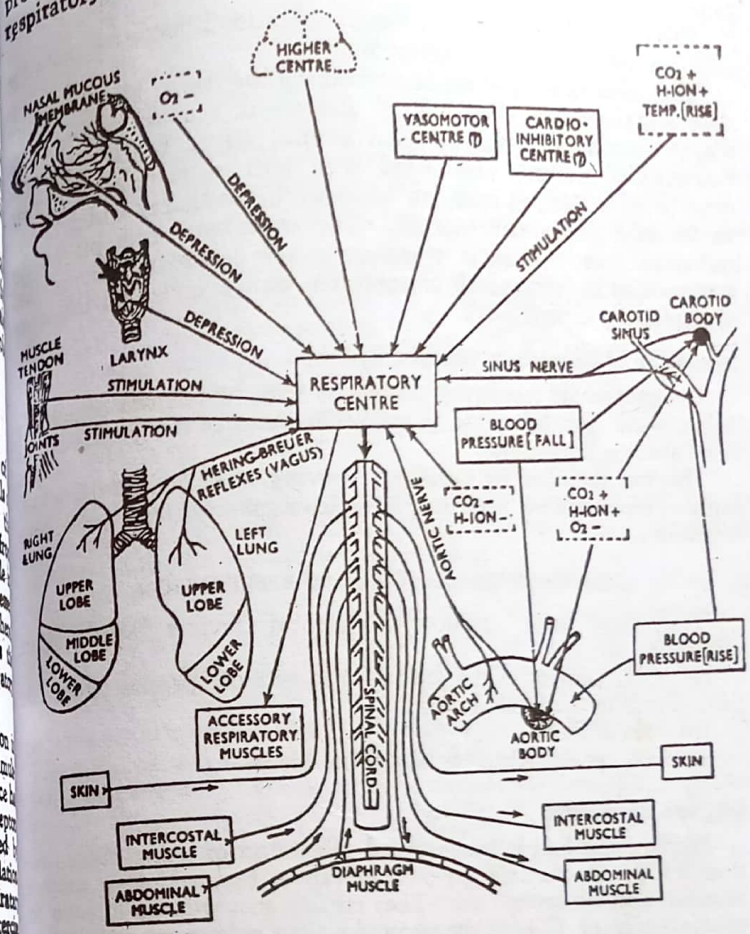

Fig. 278. Schematic representation of regulation of the respiratory centre. + means excess ; – means less.

taken, the glottis is then closed and violent expiratory effort is made against a closed glottis causing great rise in intrathoracic pressure. The glottis is then opened suddenly causing expulsion of the 'cough'—the droplets are ejected with the velocity of a jet plane.

Reflexes from sino-aortic zone

A sudden rise of pressure in this area causes reflex slowing in the rate and amplitude of breathing. If the pressure rise is considerable

in experimental animals, apnoea may result (adrenaline apnoea) the rise in blood pressure is maintained for some time an' occurs and respiration commences again. This is due to (i) adapta of the receptors and (ii) rise in P_{CO_2} during apnoea stimula respiratory centre.

Fall in blood pressure stimulates respiration reflexly through chemoreceptors of the sino-aortic zone.

The reflex slowing of respiration during the rise of blood pres depresses the 'pump' effect on the abdominal venous reservoir that less blood enters the heart and cardiac output is also depre Fall of blood pressure is associated with hurried respiration so more blood is pumped from the abdomen to the thorax which c an increase of cardiac output. The important role played abdominal muscles in these responses can be easily understood is controlled by 'abdominal compression centre' under the influe of respiratory centre.

Distension of Pulmonary Vascular Bed

In experiments where the pulmonary vascular bed was comple isolated but for its nerve supply—distension of the vessels ca rapid shallow breathing.

This was abolished by vagotomy proving its reflex nature. explains rapid shallow breathing in patients suffering from pulmon congestion.

II. CHEMICAL CONTROL OF RESPIRATION

The three most important chemical factors which af respiration are

(i) CO_2 content of the blood or to be more precise tension CO_2 (P_{CO_2}) in the arterial blood.

(ii) pH of blood.

(iii) O_2 tension (P_{O_2}) of the arterial blood.

CO_2 and Respiration

Haldane and Smith demonstrated the effect of rising concentr tion of CO_2 in inspired air on respiration by making a subj rebreath his own expired air. They noticed that with an increase concentration of CO_2 in the inspired air the pulmonary ventilati increased remarkably and that respiration increased both in rate a in depth. Atmospheric air normally contains a negligible amou of CO_2 (0·03%). The concentration of CO_2 in the inspired air m be increased up to 1% without any noticable effect on pulmon ventilation (respiratoay minute volume, RMV). If 4% of CO_2 inhaled, the RMV in approximately doubled and the subj becomes conscious of his respiration. At concentrations above the cardiac and respiratory functions are depressed and subject symptoms like confusion and headache occurs. In fact the RM does not increase significantly when more than 10% CO_2 is inhale

About 20% CO_2 in inspired air produce depression of respiration associated with convulsive seizures.

The RMV and alveolar P_{CO_2} (P_{A,CO_2}) are interdependent upon each other and further P_{A,CO_2} increases as the CO_2 of the inspired air increases. In the experiments of Haldane and Smith the alveolar P_{CO_2} was increased gradually by making the subjects rebreath his own expired air over a period of time. It was demonstrated that within the physiological range increase in P_{A,CO_2} is attended with a linear increase in the RMV.

The purpose of this respiratory stimulent effect of CO_2 will be obvious by looking at the simple model shown below. 'A' is a compressible bulb represents the lungs with a tube attached to it (the airways). Fig. 279 shows that 'A' is filled with some quantity of smoke (CO_2).

There is also a device fitted at 'A' through which smoke can be injected. It will be understood that it more and more smoke is injected into the bulb and at the same time the bulb is pumped more and more vigourously the amount of smoke injected in will be equal to the amount of smoke ejected out of the bulb and the concentration of smoke within the bulb will not rise, provided the amount of smoke injected is not excessive.

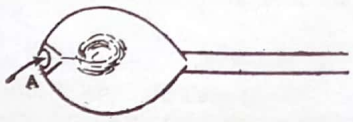

Fig. 279

Increased P_{A,CO_2} stimulates respiration and thereby drives out increasing amount of CO_2 from the lungs with each expiration so that an attempt is made to keep the P_{A,CO_2} at its resting level. This compensation, of course, fails when the concentration of CO_2 in the inspired air exceeds 5%. The table illustrates the point.

EFFECT OF GRADUAL INCREASE IN CO_2 CONTENT OF INSPIRED AIR

CO_2 % in inspired air	Average depth of respiration	Average rate of respiration per minute	CO_2 % in alveolar air
0·04	673 ml	14	5·6
0·79	739 ml	14	5·5
2·02	864 ml	15	5·6
3·07	1216 ml	15	5·5
5·14	1771 ml	19	6·2
6·02	2104 ml	27	6·6

Site of action of CO_2

The powerful stimulant action of CO_2 on respiration has been well established. CO_2-sensitive cells (chemoreceptors) are located in two places, viz. (1) centrally in the medulla and (2) peripherally in the carotid and aortic bodies.

(1) **Central Chemoreceptors :**

These cells are located bilaterally on the ventral aspect of the

medulla and are placed superficially anterior to the point of entry of the glossopharyngeal and vagous nerves. They are highly sensitive to CO_2 change and to change in pH of the blood and also of cerebrospinal fluid (CSF). Rise in P_{CO_2} or fall in pH stimulates these chemoreceptors primarily which again stimulates secondarily the cells of the respiratory centre increasing the volume and frequency of respiration.

In an elaborate series of experiments Pappenheimer and his co-workers perfused the ventriculo-cisternal systemts of goats with HCO_3^- solution of different concentration and measured their ventilatory response to CO_2. They concluded that CO_2 acts as a respiratory stimulus by increasing [H^+] in the interstitial fluid of the chemo-receptor cells scattered in the vicinity of the capillaries of bulbar reticular formation. These cells are not placed superficially and do not come in direct contact with the CSF.

Mode of action :

CO_2 by itself has little direct stimulant action on respiration. The most potent source of stimulation is rise in H^+ concentration which occurs whenever there is a rise in P_{CO_2} according to the equation $CO_2+H_2O \rightleftharpoons H^+ + HCO_3^-$. H^+ cannot diffuse easily from blood to the brain or to CSF but CO_2 can diffuse freely in either direction. A rise in H^+ concentration of the blood, therefore, will have a delayed access to the chemoreceptor cells whereas a rise in CO_2 concentration of the blood will be followed very soon by rise in CO_2 concentration of the CSF and tissue fluid in the brain. The H^+ liberated in CSF by dissociation of H_2CO_3 will have immediate and direct access to the medullary chemoreceptors with consequent stimulation of respiration. The H^+ liberated in brain tissues will be 'buffered' in the first instance by the acid-base buffers of the brain and its action on the chemoreceptors will consequently be delayed (Fig. 280). It may be noted that there is no significant amount of 'buffers' in the CSF.

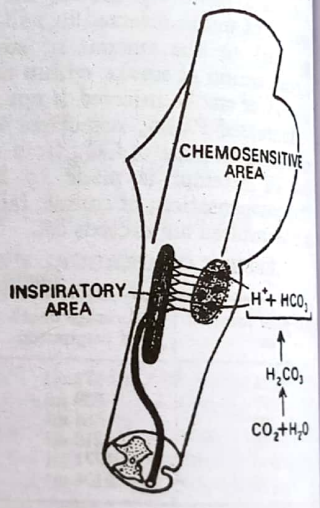

Fig. 280. Stimulation of inspiratory area by the chemosensitive area located bilaterally in the area lying only a few microns beneath the ventral medullary surface. Note that hydrogenions stimulate the chemosensitive area, which mainly CO_2 in the fluid gives rise to the hydrogen ions.

The initial-stimulating effect of CO_2 on respiration declines after a few minutes. This is due to the fact that HCO_3^- is transported activity from the blood to the CSF and thus the H^+ of the CSF is neutralised to a considerable extent. This explains the diminution of stimulant effect on respiration of CO_2 which is prompt at the onset but declines to about one-fifth of the original effect after about 2 days.

From the quantitative point of view CO_2 is more potent a respiratory stimulant than H^+ and further the action of both these factors is very conspicuous in the neighbourhood of their normal value. Thus the respiratory stimulant effect of CO_2 is most prominent in the neighbourhood of P_{CO_2} range of 40 to 45 mm Hg and that of H^+ in the range of pH 7·45 to 7·35.

(2) Peripheral Chemoreceptors :

Chemoreceptor cells are located in carotid and aortic bodies and reflexly stimulate respiration when the concentration of CO_2 of the blood flowing through them is increased. Arguments have been raised regarding the relative importance of the central *versus* peripheral chemoreceptors in normal respiratory drive. It appears that the central receptors are more important in this respect—the peripheral receptors playing a secondary supporting role in conditions of emergency. In animals after chronic denervation of the carotid and aortic bodies the resting minute volume (RMV) of respiration falls to 80% of normal and consequently the arterial P_{CO_2} rises by 10 mmHg.

It is, therefore, reasonable to conclude that 80% of the resting respiratory drive of respiration is due to central chemoreceptors and 20% due to peripheral chemoreceptors.

Oxygen tension and breathing :

This has been studied by making the subject breath O_2 and N_2 mixture containing different proportion of oxygen. Normal atmospheric air contains 20·93% of O_2. The amount of oxygen in the inspired gas mixture can be reduced to about 12% in many individuals without any appreciable change in ventilation. However at levels of 10% of O_2 in the inspired air the respiration is stimulated with simultaneous reduction of P_{A,CO_2} as a result of hyperventilation. The low P_{A,CO_2} has a depressant action on respiration. It is clear, therefore, that respiration-stimulating effect of O_2 lack will be enhanced if suitable measures are taken to prevent the fall of P_{A,CO_2} by adding appropriate amount of CO_2 to the inspired air.

Further a subject breathing low concentration of O_2 will have a low P_{A,O_2}, a condition analogous to the situation of a subject at high altitude where the low P_{A,O_2} is due to fall in barometric pressure. It can be calculated that the P_{A,O_2} of a subject at 5·5 km 18,000 feet is the same as that of a subject at sea-level breathing 10·5% of O_2. In both the resultant hyperventilation will lead to fall in P_{A,CO_2} and alkalosis, which is corrected later by the kidneys. It is

known that fall in P_{A,CO_2} by 4 mm Hg. causes apnoea and alkalosis depresses respiration. The respiration under these condi ions is maintained entirely by O_2 lack or a re-adjustment of sensitivity of respiratory centre to CO_2. In acute exposure to high altitud, respiratory drive is maintained by O_2 lack only whereas in persons residing at high altitude for some time the respiratory centre becomes sensitive to low P_{CO_2}.

Mode of action of oxygen lack

The respiration stimulating effect of O_2 lack is seen only in intact animals. In an animal with denervated carotid sinus O_2 lack will depress breathing. It has been proved by various workers and is an universal'y accepted fact that direct action of O_2 lack on respiratory centre is depression of respiration—the respiration-stimulating effect of O_2 lack is a reflex one through the sino-aortic chemoreceptors. The discharge of impulses from the chemoreceptor cells increases with the fall in oxygen tension of the arterial blood—the maximu n effect is observed between arterial P_{O_2} of 60 mmHg and 30 mmHg. This is range in which percentage saturation of blood with oxygen falls almost perpendicularly (dissociation curve) and consciousness is lost very soon.

The carotid and aortic bodies are most highly vascular structures in the body. Consequently, the arterio-venous oxygen content difference is very low. In hypotension with blood pressure near about 60 mmHg the blood flow through these structures becomes very slow and sluggish and the arterio-venous O_2 content difference becomes high indicating low P_{O_2} within the chemoreceptor cells. Under these conditions there occurs reflex stimulation of respiration (and also vasoconstriction) which tends to restore the blood pressure to near normal value.

In conclusion it may be said that under normal conditions the level of pulmonary ventilation is controlled by three chemical agencies, viz.

(1) Rise in arterial P_{CO_2}.
(2) Fall in arterial P_{O_2}.
(3) Increase in arterial cH.

Any one of these factors may play a major role in driving respiration. It seems that above a certain range approximately 75 mmHg. P_{O_2} of inspired air) O_2 lack has no eflect on respiration, similarly below a certain range approximately 33 mmHg P_{CO_2})—CO_2 has no effect on respiration. Under ordinary circumstances the effect of above three factors are additive but one of three factors is enough to augment ventilation in the absence of other two. For example in metabolic acidosis there is great increase in H^+ concentration of the blood, the P_{O_2} being normal and P_{CO_2} below normal. However, the RMV is greatly augmented in this condition.

Reference:—

Human Physiology

Dr. C.C. Chatterjee.