PERIODIC BREATHING IN THE PRESENCE OF HIGH ALVEOLAR OXYGEN TENSIONS IN NORMAL INDIVIDUALS

by

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INTRODUCTION

During the past century, the phenomenon of periodic breathing has received increased clinical and experimental attention particularly in its relationship to various patho-physiological processes.

Hippocrates (1) was the first writer to suggest the clinical observation of irregular or periodic breathing. "The respiration throughout like that of a man recollecting himself, and rare, and large....."

Haldane (2) feels that John Hunter described periodic breathing before Cheyne and Stokes but give no references. Also the French school lays claim to early observation (3) of this phenomenon. Rabé in a thesis in 1891 claimed that a French physician of Grenoble named Nicolas in 1789 described periodic breathing which he observed in an 81 year old man.

"Ce qui était plus extraordinaire que cette irrégularité du pouls, c'était un suspension absolue, une sériation des mouvements respiratoires pendant vingt-cinq secondes. Alors le jeu des organes se rétablissait peu à peu et par une gradation très sensible, il reprenait son énergie pour cesser à nouveau à l'instant marqué."

John Cheyne, in 1818, published a paper (1) giving a complete description of what is now called Cheyne-Stokes respiration.

"..... On the 10th of April he was found in bed flushed, speechless, and hemiplegic. How long he had been in that state could not be ascertained..... The only peculiarity in the last period of his illness, which lasted eight or nine days, was in the state of the respiration. For

For several days his breathing was irregular; it would entirely cease for a quarter of a minute, then it would become perceptible, though very low, then by degrees, it became heaving and quick, and then it would gradually cease again. This revolution in the state of his breathing occupied about a minute, during which there were about thirty acts of respiration." He also makes note of seeing similar breathing in a relative of the patient just before death (1).

His equally famous pupil, William Stokes, made a more complete description (1) of this both interesting and startling phenomenon.

"..... It consists in the occurrence of a series of inspirations, increasing to a maximum, and then declining in force and length, until a state of apparent apnoea is established. In this condition the patient may remain for such a length of time as to make his attendants believe that he is dead, when slow inspiration, followed by one more decided, marks the commencement of a new ascending and then descending series of inspirations... ..... I do not know any more remarkable or characteristic phenomena than those presented in this condition, whether we view the long-continued cessation of breathing, yet without any suffering on the part of the patient, or the maximum point of the series of inspirations, when the head is thrown back, the shoulders raised, and every muscle of inspiration thrown into the most violent action: yet all this without rale or any sign of mechanical obstruction. The vesicular murmur becomes gradually louder, and at the height of the paroxysm is intensely puerile.

The decline in the length and force of the respirations is as regular and remarkable as their progressive increase. The inspirations become

each one deeper than the preceding, until they are all but imperceptible, and then the state of apparent apnoea occurs. This is at last broken by the faintest possible inspiration; the next effort is a little stronger, until, so to speak, the paroxysm of breathing is at its height, again to subside by a descending scale." (1)

Since these descriptions the interest and the observations of this phenomenon have greatly increased until today every medical student is familiar with Cheyne-Stokes respiration. By definition, Cheyne-Stokes breathing is a particular form of periodic respiration. Haldane (2) points out that there must be a period of apnea of a definite length with regular periods of dyspnea interposed. Exactly how many seconds of apnea are necessary to make regular periodic breathing Cheyne-Stokes breathing has never been defined. It can be stated that any periodic breathing with a definite period of apnea occuring at definite intervals and with a gradually increasing then declining respiratory effort, is Cheyne-Stokes respiration.

Various types of periodic breathing have been observed clinically and have been produced experimentally. A few conditions in which Cheyne-Stokes respiration has been reported as occuring are:

Typhoid fever	Nephrosis (Type?)
Cerebral hemorrhage	Catalepsy
Tubercular meningitis	Anesthesia
Cerebral embolism	Cardiac failure
Newly born child	Coronary occlusion
Morphine administration	

Experimentally, periodic breathing has been observed under several conditions:

1-following hyperpnea at high altitudes;

2-following exercise while breathing artificial gas mixtures;

3-by use of anesthetic agents alone or in combination with other drugs;

4-by mechanical devices such as Haldane's soda-lime tube and concertina; and

5-by increasing intracranial pressure.

Many factors are involved in controlling respiratory rate, depth, and rhythm. Each of these may be involved in modifying and controlling respiration under conditions which may produce irregularities or alterations in rate, depth, and/or rhythm.

Role of carbon-dioxide:

Since the work of Lavoisier and Laplace indicating that the amount of carbon-dioxide produced approximately equals the oxygen consumed there has been a series of discoveries with regard to the mechanism of the stimulatory action of carbon-dioxide on respiration.

Henderson developed and stressed the acapnoic theory of irregular breathing associated with improper maintenance of circulation. The accepted site of action of excess carbon-dioxide is on the respiratory center. Although Schmidt and others believe that it is direct stimulatory action, there is still some question of pH being an important consideration.

There is no adequate information concerning pH changes in the respiratory center itself under conditions producing increased or decreased respiratory drive. Pembry and Allen (4) and later others (3,5,6) demonstrated that the addition of carbon-dioxide to inspired air readily abolishes Cheyne-Stokes respiration. From 1% to 5% concentrations of

carbon-dioxide were used. Haldane (2) has made the statement that the chief fly-wheel of the respiratory center is the great storage capacity of the body tissues (not the respiratory center) for carbon-dioxide. He points out that this "buffer-capacity" is lost in forced hyperpnea.

Role of Oxygen Tension:

Haldane and later Schmidt have shown clearly the role of the aortic and carotid bodies in producing respiratory drive at low oxygen tensions. Except for recent studies by workers in Schmidt's laboratory (7) it has been accepted that oxygen tensions must fall to 91-106 mm. of Hg. as compared to normal tensions of 153 mm. Hg. (20%) in the inspired air before any stimulation of respiration occurs. Any continuous oxygen drive at normal tensions has been overlooked or discounted.

State of Acid-Base Balance:

The common knowledge of effect of pH changes on respiratory drive will not be discussed, since great changes in acid-base balance must occur before appreciably affecting pH.

Reflexes:

The relationship of a rise in blood pressure initiating a decrease in respiratory activity, and vice-versa, is extremely important. The importance of the Hering-Breuer reflexes may be of some importance in initiating respiration after hyperventilation with 100% oxygen. Gradual collapse of the lungs will occur as the oxygen is absorbed from the alveoli and viscero-somatic reflexes to produce respiratory effort will be initiated.

EXPERIMENTAL

While recording respiratory minute volume under various conditions, a periodic type of breathing was accidentally produced (9). Since this phenomenon could not be readily explained according to the usual theories of Cheyne-Stokes respiration, it was investigated further.

METHOD

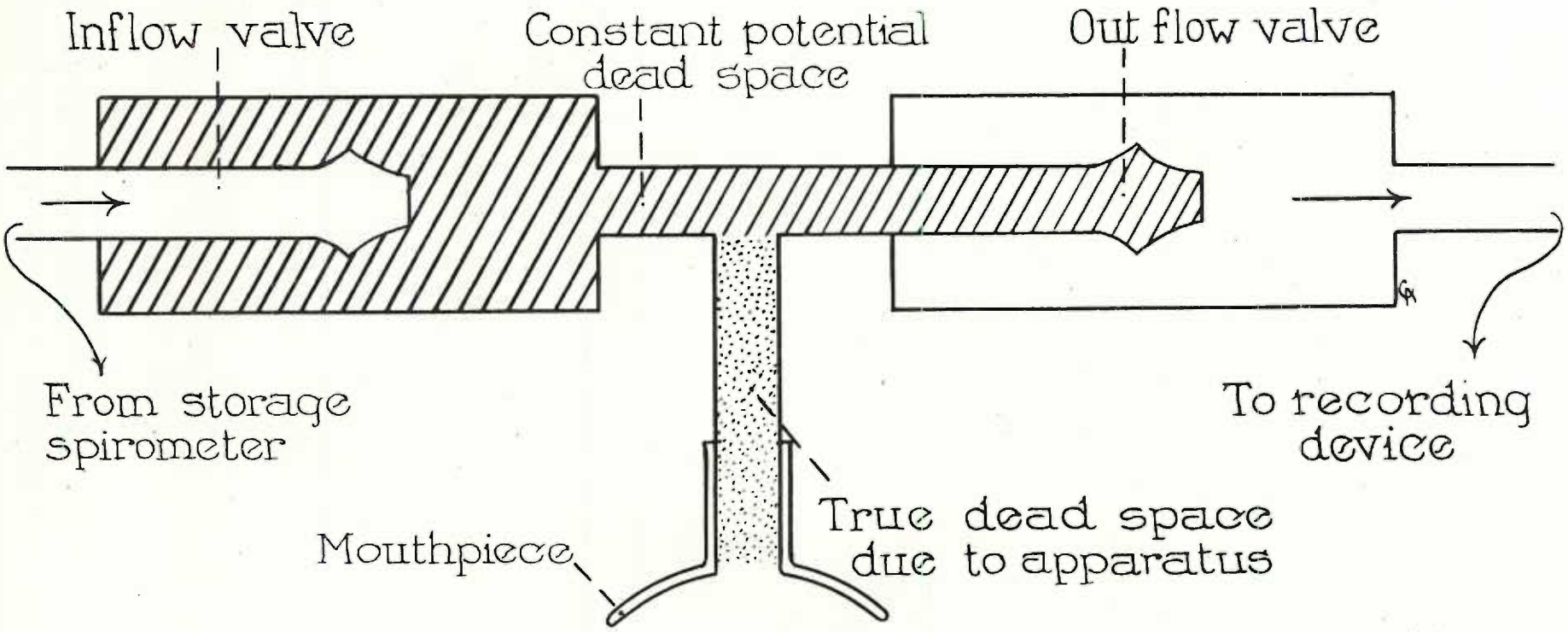
Men of ages 23-35 years, with no known cardiac or respiratory diseases, acted as subjects. The entire experiment was conducted with the subject resting comfortably in the supine position. He was allowed 5-7 minutes to reach a stable level before being attached to the apparatus. A mouth piece was used because face masks were found to increase the respiratory minute volume as much as 250%. The nose was clamped. The gas flowing into the spirometer which served as a reservoir was washed through two consecutive water bottles which were in a water bath at room temperature. In this way the inspired air was saturated with water vapor from 95-100 percent at room temperature (23 3°C). Valves maintained unidirectional flow from the storage spirometer into the lungs and from the lungs into either a flow meter or recording spirometer or both. The recording spirometer was manipulated so that at the end of each expiration it was immediately and rapidly emptied in preparation for receiving the volume of the next expired breath. By this method a record was taken on a drum of the volume and time of each expiration.

RESULTS

Periodic breathing was observed under the following conditions.

FIGURE 1

This illustration shows the mechanism of maintaining the unidirectional flow of the gases. Rebreathing occurs in the tube entitled "True Dead Space Due to Apparatus". A small but undetermined quantity of rebreathing occurs in the "Constant Potential Dead Space".


Inflow valve
Constant potential dead space
Out flow valve
From storage spirometer
To recording device
True dead space due to apparatus
Mouthpiece

1-True dead space of the apparatus as illustrated in diagram was between 30-40 cc.

2-Use of gas from a tank containing 100% oxygen.

3-Individuals having greater than average respiratory stimulation as a result of low oxygen tension.

All three of the conditions had to be in effect simultaneously. Six subjects were studied. No periodic breathing was observed in six experiments on four of these subjects. Two of the subjects were known to show a minimal respiratory stimulation in response to low oxygen tensions (9). The responses of the other two subjects to low oxygen tension were not studied. Periodic breathing was produced in every case of six experiments on two other individuals known to show a greater than average respiratory stimulation in response to low oxygen tension (9). No periodic respiration occurred in these two subjects when the dead space was removed or doubled.

An analysis of the records in which periodic breathing developed revealed the following sequence of events. First there was a decrease in the respiratory minute volume when the shift was made from atmospheric air to 100% oxygen. This decrease occurred within 30-90 seconds. Subsequently there developed periodic breathing the difference between the periods of hyperpnea and apnea becoming more and more marked until 75-80% of the vital capacity of the subject was utilized in each respiration in contrast with only 7% of the vital capacity with hypopneic breathing. The greatest respiratory rates occurred during the middle of developing respiratory effort and during the middle of decreasing respiratory effort. This result indicates that the periodic breathing could not be on a

FIGURE 2

This record is obtained from a subject sensitive to oxygen lack who is breathing 100% oxygen through a small dead space. The upward deflection is the record of the expired air being blown into a recording spirometer, while the downward deflection to the record of manual emptying of the spirometer.

The time and volume can be read directly from the record, each horizontal line representing 100 cc. The record reads from left to right beginning with the lower line. An alveolar air sample was taken at the end of record noted by "#sample".

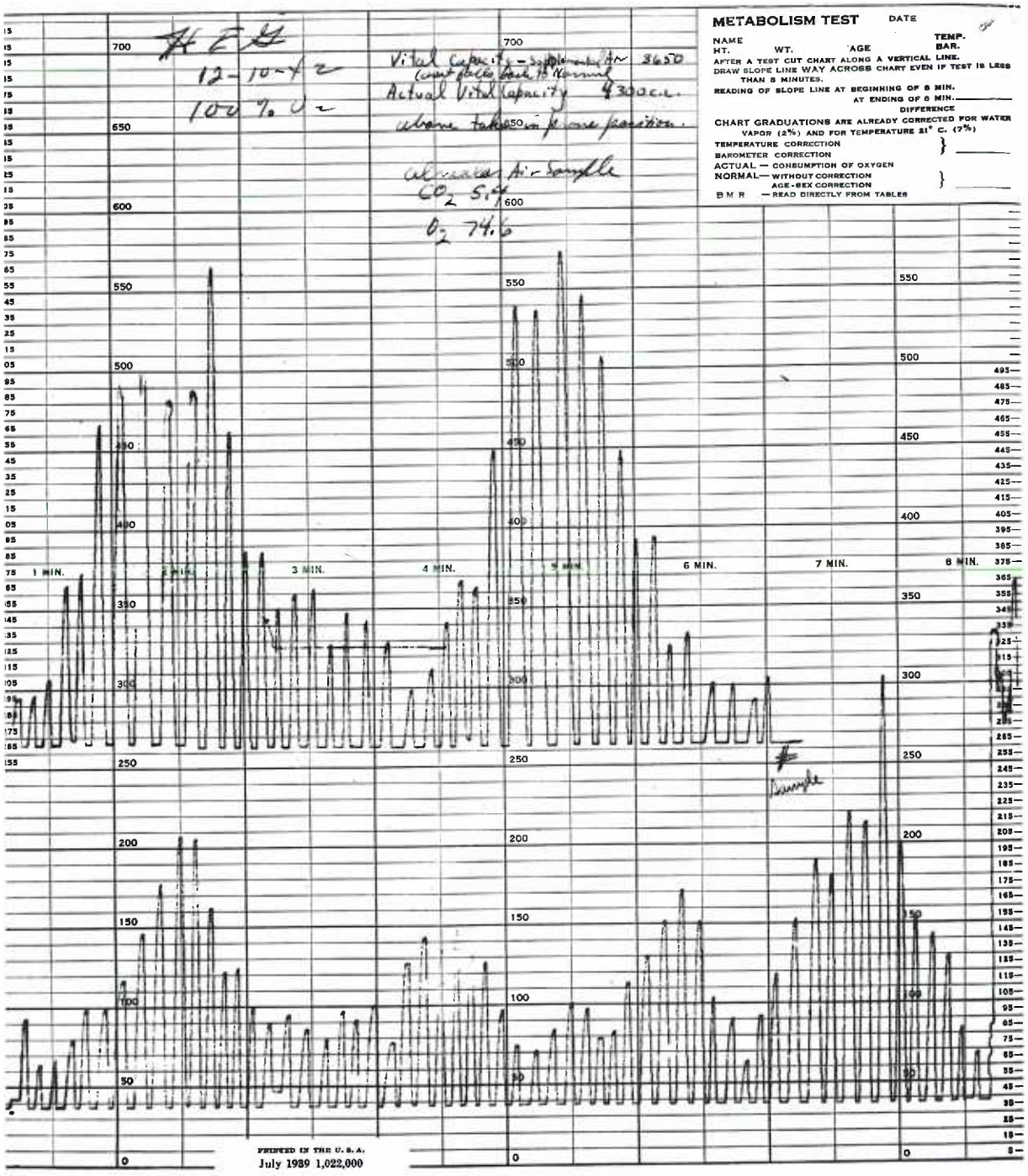
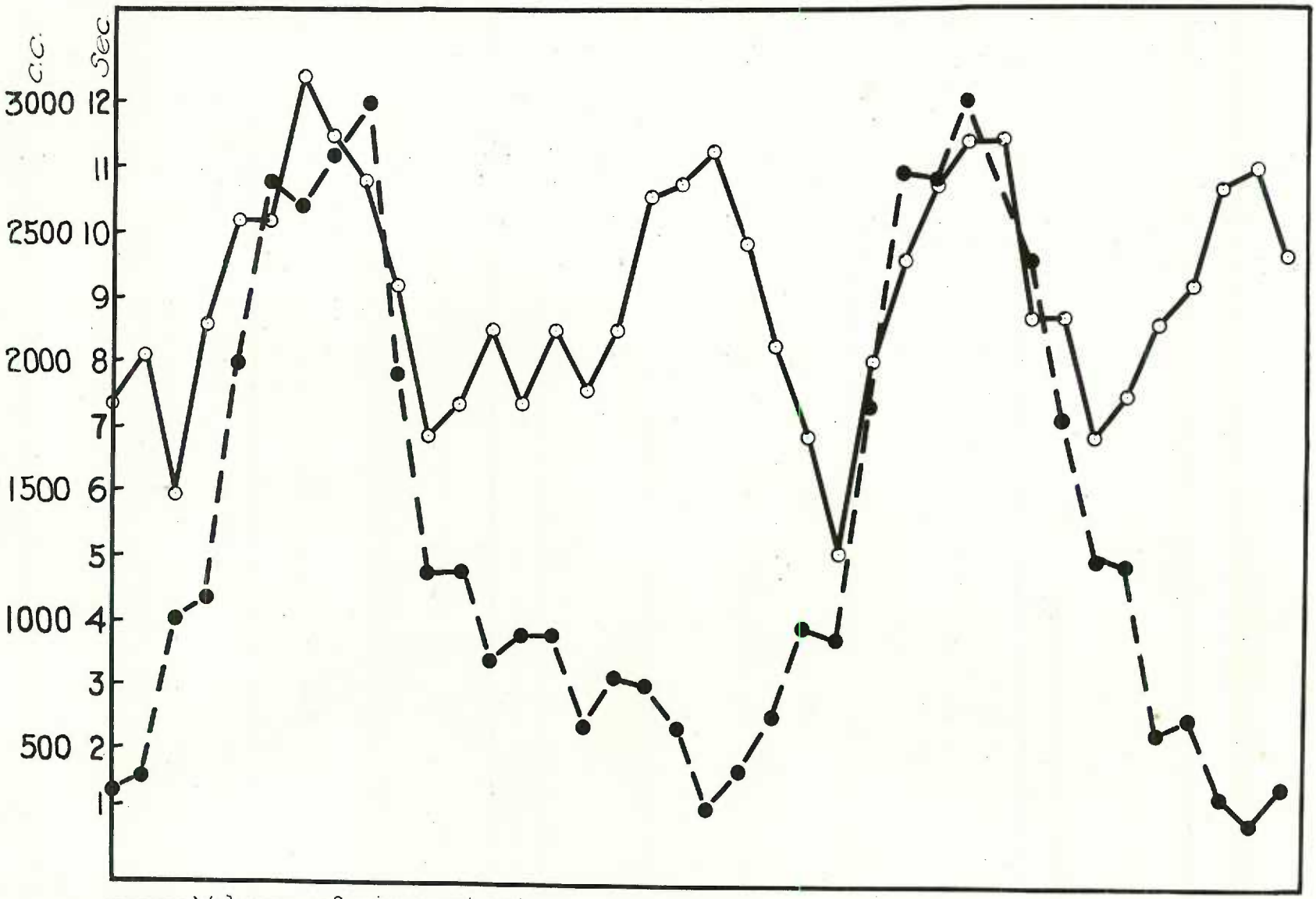

METABOLISM TEST
DATE
NAME
HT.
WT.
AGE
TEMP.
BAR.
AFTER A TEST CUT CHART ALONG A VERTICAL LINE.
DRAW SLOPE LINE WAY ACROSS CHART EVEN IF TEST IS LESS THAN 8 MINUTES.
READING OF SLOPE LINE AT BEGINNING OF 8 MIN.
AT ENDING OF 8 MIN.
DIFFERENCE
CHART GRADUATIONS ARE ALREADY CORRECTED FOR WATER VAPOR (2%) AND FOR TEMPERATURE 21° C. (7%)
TEMPERATURE CORRECTION
BAROMETER CORRECTION
ACTUAL — CONSUMPTION OF OXYGEN
NORMAL — WITHOUT CORRECTION
AGE-SEX CORRECTION
B M R — READ DIRECTLY FROM TABLES
H E G
12-10-42
102 % O2
Vital Capacity - Supplemental Air 3650
(must plateau last 15 seconds)
Actual Vital Capacity 4300 c.c.
above taken in prone position.
Alveolar Air Sample
CO2 5.4
O2 74.6
1 MIN.
2 MIN.
3 MIN.
4 MIN.
5 MIN.
6 MIN.
7 MIN.
8 MIN.
Sample
PRINTED IN THE U. S. A.
July 1939 1,022,000

FIGURE 3

These figures were calculated from the upper line of record 1. The time was determined from the beginning of expiration to the beginning of the next expiration, the volumes of each expiration being noted. The shortest lengths of the respiratory cycles, that is the fastest respiratory rates, occur at the low points in the time line. There are two low points per cycle, one occuring during developing respiratory effort, and one during decreasing respiratory effort.



——Volume of air expired.

——Length of respiratory cycle from beginning expiration to beginning expiration.

FIGURE 4

A record similar to record 1 is taken five months later on the same subject with similar results. The initial drop in respiratory minute volume when the gases breathed are changed from atmospheric air to 100% oxygen is striking. Periodic breathing then gradually develops.

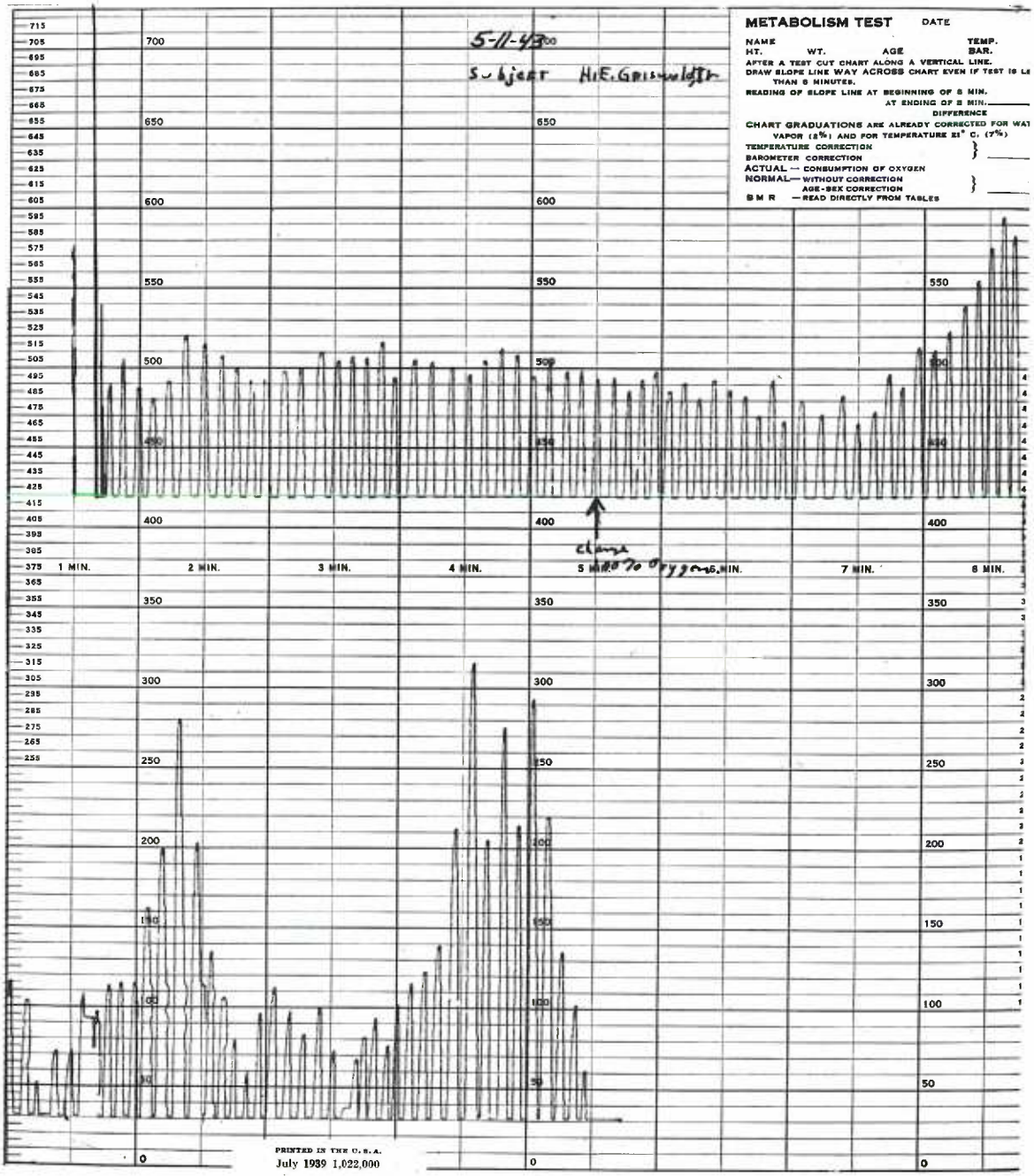
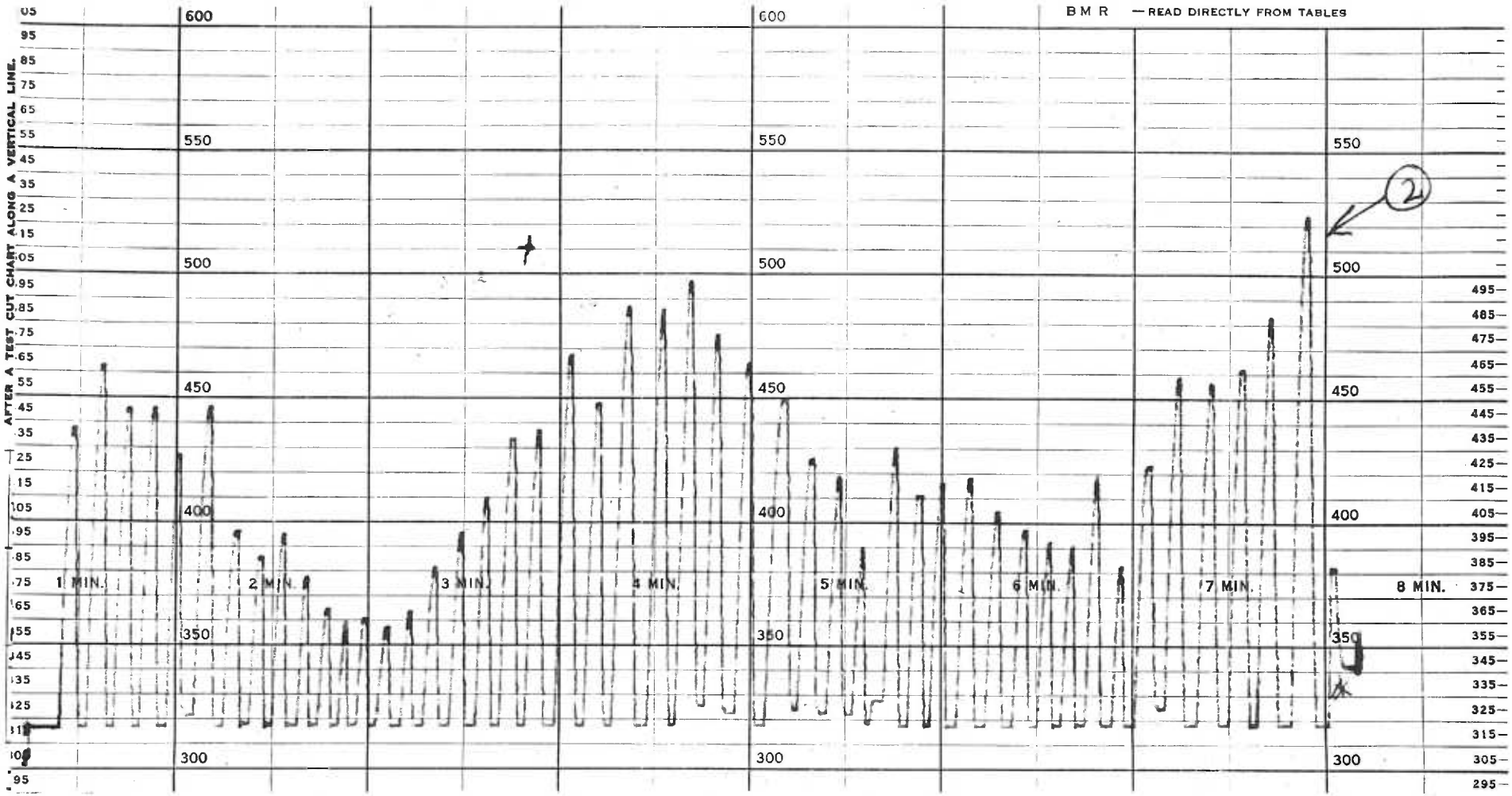

METABOLISM TEST
DATE
NAME
HT.
WT.
AGE
TEMP.
BAR.
AFTER A TEST CUT CHART ALONG A VERTICAL LINE.
DRAW SLOPE LINE WAY ACROSS CHART EVEN IF TEST IS LE
THAN 6 MINUTES.
READING OF SLOPE LINE AT BEGINNING OF 6 MIN.
AT ENDING OF 6 MIN.
DIFFERENCE
CHART GRADUATIONS ARE ALREADY CORRECTED FOR WAT
VAPOR (2%) AND FOR TEMPERATURE 21° C. (7%)
TEMPERATURE CORRECTION
BAROMETER CORRECTION
ACTUAL — CONSUMPTION OF OXYGEN
NORMAL — WITHOUT CORRECTION
AGE-SEX CORRECTION
B M R — READ DIRECTLY FROM TABLES
5-11-43
Subject H.E. Griswold Jr.
change to Oxygen
1 MIN.
2 MIN.
3 MIN.
4 MIN.
5 MIN.
7 MIN.
8 MIN.
PRINTED IN THE U. S. A.
July 1939 1,022,000

FIGURE 5

This is part of a record of periodic breathing with a different subject. Here the periodic breathing was maintained for over fourteen minutes, a sample of alveolar air being taken at (2).


BMR — READ DIRECTLY FROM TABLES
AFTER A TEST CUT CHART ALONG A VERTICAL LINE.
600
550
500
450
400
350
300
1 MIN.
2 MIN.
3 MIN.
4 MIN.
5 MIN.
6 MIN.
7 MIN.
8 MIN.
495
485
475
465
455
445
435
425
415
405
395
385
375
365
355
345
335
325
315
305
295

psychic basis. Another fact ruling out the psychic element is the extreme regularity of the phases of the respiratory effort and the manner in which they develop.

Alveolar air samples taken at specific times indicated no possibility of hypoxia.

	CO_2	O_2
Beginning of apnea #1	4.6	81.4
Maximum hyperpnea #1	4.6	70.4
End of apnea #2	5.4	74.6

DISCUSSION

Clinically, periodic breathing occurs in two distinct types of cases with various combinations of these types. There are 1) those conditions associated with definite increase in the pressure of the cerebrospinal fluid and 2) those conditions which may cause anoxia of the respiratory center. John Cheyne's description was that of a patient suffering from a cerebro-vascular accident with probable increase in cerebrospinal pressure and brain edema. Wyster (10) has faithfully duplicated periodic breathing in dogs by techniques designed to increase intracranial pressure. In contrast, cases of coronary occlusion and myocardial infarction may show periodic breathing. Here it is felt that there is anoxia of the respiratory center because of deficient circulation. In morphine poisoning with marked depression of the respiratory center, periodic breathing has been observed. Again the question of respiratory center sensitivity enters into the picture. Actually, Haldane has been the chief advocate of the anoxic theory of Cheyne-Stokes respiration. He based his

conclusions primarily on the fact that Pembry and Allen (4) observed that the addition of oxygen (100%) to the inspired air abolished the period of apnea. It has been overlooked however that in their original paper they state (4) that diminished as well as increased oxygen supply would abolish the apnea. Also carbon-dioxide, 1% or more, produced regular breathing.

Anthony, Cohn and Steele (5) in 1932 truly correlated the saturation of arterial blood with the apneic and hyperpneic stages of Cheyne-Stokes respiration. Using a 9-way stopcock and radial artery puncture, they were able to secure separate, immediately successive samples as rapidly as desired. They found that the oxygen varied between 15.1 and 18.5 volumes percent (79.9%-98.2 saturation); and the carbon-dioxide varied between 42.2 and 50.1 volumes percent. The greatest oxygen tension concentration occurred during the first half of apnea the minimum during the first part of the return of respiratory effort. The carbon-dioxide concentrations were highest during the return of respiratory effort and lowest just before the beginning of apnea.

They do not agree with Klein's explanation that Cheyne-Stokes respiration is a result of increased circulation time. If this is the true explanation then changes in flow from lung to the respiratory center should alter length of the respiratory cycle; this does not exist for cases have also been shown of increased circulation time with no Cheyne-Stokes respiration and vice versa. They observed, like Pembry and Allen (4), that addition of carbon-dioxide or oxygen to the respired air produced cessation of Cheyne-Stokes respiration. Five percent carbon-dioxide stopped the apneic phase usually within five minutes, the apneic phase

becoming shorter and shorter. The hyperpnoic phase gradually leveled off.

In contrast, oxygen causes lengthening of the hyperpnoic phase with equalization of the respirations. They observed that some patients show Cheyne-Stokes respiration only when asleep and others only when awake.

Recently Christie and Hayward (11) have demonstrated two types of periodic breathing in anesthetized cats which they interpret as being:

1-associated with changes in respiratory centre activity, and

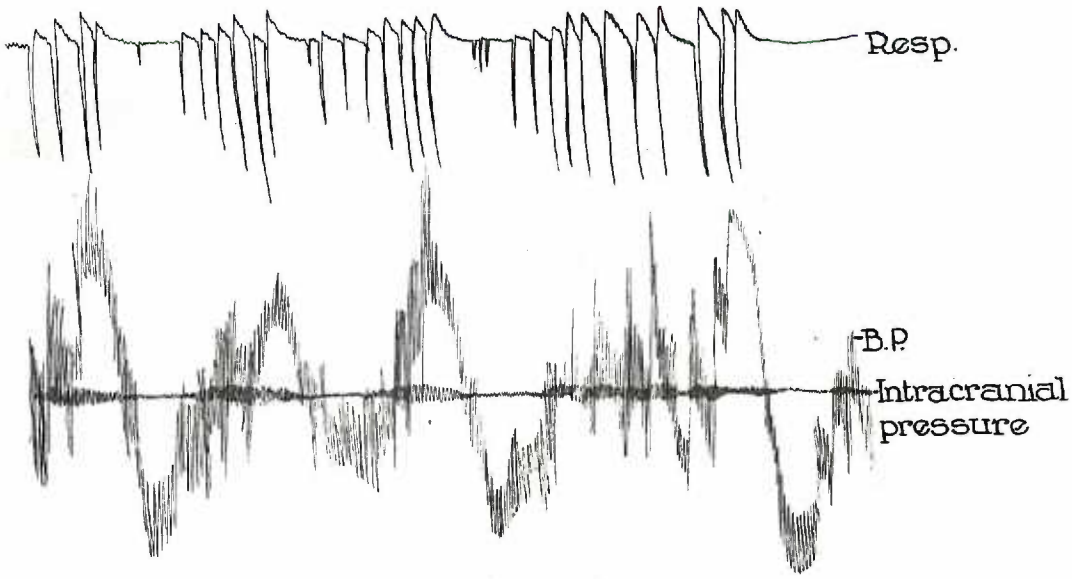
2-associated with changes in the distensibility of the lungs only. They feel, as did Greene (6) that the two types of records indicate two distinct processes, a cardiac and cerebral type of periodic breathing. In the cardiac type of Cheyne-Stokes respiration, there is a fluctuating expiratory position plus a longer cycle. Also they feel that their experimental work, which shows an association of Traube-Hering waves in the systemic circuit with the periodic respiratory effort, suggests the possibility of pulmonary vascular changes. However, it must not be forgotten that changes in the volume of the pulmonary vascular bed will cause Hering-Breuer reflexes resulting in periodic reflex stimulation of the respiratory center. This, as well as associated periodic anoxia that always occurs during the end of the apneic phase, certainly does not eliminate the possibility of waxing and waning respiratory center activity.

Barbour (12) in producing Cheyne-Stokes respiration by morphine administration to anesthetized cats also found a cardiac and cerebral (Oyster) type. He emphasized the differences in blood pressure changes coincident with the apneic and hyperpneic phases. All workers have found in the cerebral (Barbour) type of respiration that apnea occurs with a

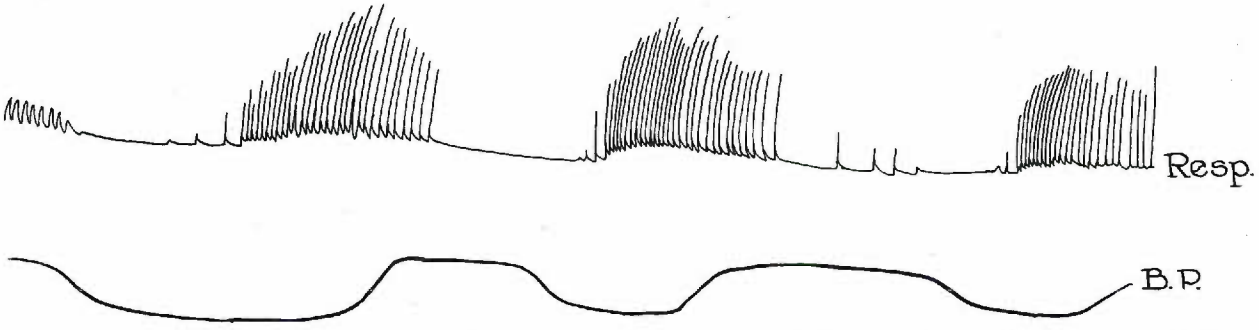
FIGURE 6

Tracings of the two clinical types of periodic breathing are shown in this illustration. In both cases, the upper line is respiratory activity. In the record after Eyster, intracranial pressure is being maintained at a constant pressure. The irregular line is blood pressure which is taken from the same zero-pressure line as the intracranial pressure. Therefore, when the blood pressure tracing is above the intracranial pressure tracing, the blood pressure actually is greater than the intracranial pressure. In the illustration after Barbour, the lower line illustrates fluctations in mean arterial blood pressure.

It is clearly evident that in the nervous type of periodic breathing, apnea occurs when the blood pressure falls below the intracranial pressure. The opposite occurs in the circulatory type of periodic breathing, as apnea occurs when the blood pressure is at its highest level.



NERVOUS TYPE PERIODIC BREATHING after Eyster (10)



CIRCULATORY TYPE OF PERIODIC BREATHING after Barbour (12)

fall of blood pressure and hyperpnea with a rise. In the cardiac type, the fall in blood pressure initiates the onset of respiration, and the rise just precedes the apneic stage.

Careful analysis indicates a similarity of the two types of periodic breathing, namely, reflex stimulation of the respiratory centre associated with hypoxia. In the cardiac type, the drop in blood pressure may possibly be associated with initial hypoxia which would produce a reflex hyperpnea. As the hypoxia is corrected and the blood pressure rises, apnea ensues. The source of this overcompensation lies in some degree with cardiac embarrassment and/or respiratory activity changes, the exact role of each being undetermined.

In contrast, in the intracranial type, apnea occurs when the vasomotor centre fails and blood pressure falls below intracranial pressure with true ischemia of the brain and respiratory center.

In our experiments there was no chance for hypoxia. Alveolar oxygen was over 70%, and there was no vasomotor or cardiac failure. It was noted however, and latter more clearly shown, that there was an initial decrease in respiratory minute volume during the first 30-120 seconds of breathing 100% oxygen. This seemed to be similar to findings of Schmidt's laboratory (7) in which it was concluded that oxygen may normally be causing respiratory drive in dogs. In our experiments in which there was a drop of 30-40% in the respiratory minute volume initially, there was a return to the control level. This suggested that a new equilibrium of respiratory drive was established the carbon-dioxide being built up during the initial period of decreased respiration, the final result being sufficient to maintain normal gaseous exchange.

SUMMARY

While recording respiratory minute volume under various conditions, a periodic type of breathing was accidentally produced (9). Since this phenomenon could not be readily explained according to the usual theories concerning the causes of Cheyne-Stokes respiration, it was investigated further.

The historical observations of periodic breathing, particularly with reference to John Cheyne and William Stokes, are quoted. The vividness and exactness of the description of clinical periodic breathing by Cheyne and Stokes (1) has never been equaled.

A description of the technique to record respiratory tracings and respiratory minute volumes under uniform conditions is given. Periodic breathing was found to occur only when all three of the following conditions were present simultaneously:

1-True dead space of the apparatus as illustrated in diagram was between 30-40 cc.

2-Use of gas from a tank containing 100% oxygen.

3-Individuals having greater than average respiratory stimulation as a result of low oxygen tensions.

A careful analysis of the records demonstrated several points. First, that when the shift from atmospheric air to 100% oxygen was made, there was a drop in the respiratory minute volume during the first 30-90 seconds. Second, there was a gradual development of periodic breathing. Third, the periodicity was very regular. Fourth, the greatest respiratory rates occurred during the middle of developing respiratory effort and during the middle of decreasing respiratory effort. The regularity and

continuity of the cycle indicates that this type of breathing could not be duplicated voluntarily.

It is generally assumed that periodic breathing does not occur except when there is a strong probability of anoxia of the respiratory center. In these experiments the oxygen percentages of the alveolar samples taken at maximum hyperpnea, beginning of apnea and end of apnea were always above 70%. It is felt that a lower than normal oxygen tension in the respiratory center plays no part in the production of this periodic breathing.

Fluctuations in the oxygen tension of the blood above normal levels is considered to be a factor since the periodic breathing is more apt to occur in individuals who are unusually sensitive to a lowering of oxygen percentage of inspired air from 20.95 to 12%. It is considered that, in this case, the respiratory drive is a combination of oxygen and carbon dioxide drive, a certain carbon dioxide tension being necessary as demonstrated by the fact that increase or decrease of dead space eliminates the periodic breathing. In these cases, there is a removal of part of the oxygen drive by shifting from 21-100% oxygen. The new conditions are such that a fluctuating oxygen and carbon dioxide tension exists, producing a periodicity of respiration.

A discussion of the two main types of clinical Cheyne-Stokes respiration is given.

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