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THE RESPIRATORY EFFECTS OF THERAPEUTIC DOSES OF CYCLOBARBITONE, TRICLOFOS AND ETHCHLORVYNOL

BY

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The use of barbiturates as hypnotics is sometimes limited by the fear of respiratory depression, and in patients with respiratory embarrassment the choice of hypnotic usually falls on a nonbarbiturate drug such as chloral hydrate or paraldehyde. It has never been clearly demonstrated that barbiturates, when used in ordinary doses, depress respiration more than do other hypnotics. There is, however, ample evidence that normal sleep is accompanied by a fall in ventilation, a rise in arterial and alveolar carbon dioxide tension (P_{CO_2}) and a reduced ventilatory response to inhaled carbon dioxide mixtures (Robin, Whaley, Crump & Travis, 1958; Bülow, 1963).

It is therefore necessary, when considering the action of hypnotic drugs, to answer two questions. Is the depression of breathing, during drug-induced sleep, greater than that which would have resulted from sleep alone? Secondly, is breathing depressed by a hypnotic drug when the subject is kept awake? We have attempted to answer these questions by means of experiments on healthy volunteers to whom cyclobarbitone, triclofos (a chloral derivative) and ethchlorvynol (a carbinol) were administered.

METHODS

The subjects were healthy male volunteers, aged 21 to 30 years, and were either members of the staff or medical students, well accustomed to physiological apparatus. They were studied in the afternoon, after fasting for 3 hr and in a semirecumbent position on a " cardiac " bed.

Gas mixtures were supplied to the subjects, ventilation ($\dot{V}$) was measured, and alveolar carbon dioxide pressure (P_{A,CO_2}) was recorded, continuously by methods previously described (Cunningham, Cormack, O'Riordan, Jukes & Lloyd, 1957; Anderton & Harris, 1963; Austin, Harris & Slawson, 1963). Samples of alveolar gas were taken during steady states for analysis of oxygen and carbon dioxide content by the Haldane method.

Measurement of response to carbon dioxide

Inspired gas mixtures contained 50% oxygen in order to minimize the hypoxic stimulus. The technique used in almost all cases was that of Anderton & Harris (1963), in which $\dot{V}$ and P_{A,CO_2} are measured continuously while inspired P_{CO_2} is raised 2 mm Hg every 30 sec gradually from a steady state at 20 mm Hg to another at 40 mm Hg. A plot of corresponding $\dot{V}$ and P_{A,CO_2} values forms a half-loop which is converted into a straight line by applying a time-lag to ventilation. In this way steady-state $\dot{V}/P_{A,CO_2}$ relationships

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may be inferred from values obtained during a changing state. This technique is essential is studying sleep, since true steady states are difficult to achieve. Bülow (1963) used a similar method; he applied a time-lag of about 25 sec. By the loop technique the lag is longer, between 2 and 3 min. This estimate is shorter than our previous one of 4 min (Anderton & Harris, 1963) which was made with a less responsive analyser. It agrees with that of Riley, Dutton, Fuleihan, Nath, Hurt, Yoshimoto, Sipple, Permutt & Bromberger-Barnea (1963).

The time-lag necessary to make the pre-drug $\dot{V}/P_{A,CO_2}$ line straight was applied to the subsequent measurements made after the drug was given. This step involves the assumption that the stimulus–response interval is the same during sleep as in the waking state. This can only be determined by direct experiments which have not yet been done. However, the greater part of the 2- to 3-min delay is probably due to blood–cell–cerebrospinal fluid transfer-mechanisms and it seems improbable that these are altered in sleep.

Mathematical treatment of results

All values of $\dot{V}$ and P_{A,CO_2} obtained in any one experiment were standardized in such a way that the slope (D) and the P_{A,CO_2} intercept (B) of the pre-drug $\dot{V}/P_{A,CO_2}$ line, in the absence of hypoxia, had the arbitrary values of 3.5 l./min/mm Hg and 36 mm Hg respectively. Post-drug observations in different subjects could then be directly compared with each other, differences in body-size and innate sensitivity to carbon dioxide having been eliminated. The standardization procedure has been described in detail (Anderton, Harris & Slawson, 1964).

Ventilatory responses after giving a drug cannot properly be evaluated by comparison with the responses before giving the drug; it is necessary to compare them with an estimate of what the responses would have been had no drug been given. We have used the data on repeatability collected by Anderton *et al.* (1964). Fig. 1 shows the pooled results on response to carbon dioxide, without hypoxia, from Programmes 2, 3a

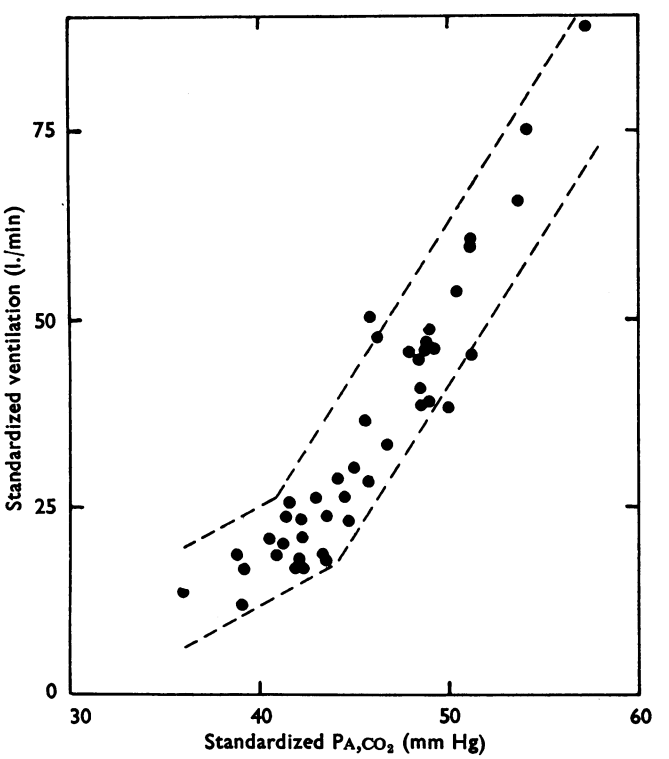

Fig. 1. Standardized $\dot{V}$ and P_{A,CO_2} values for the second periods of test-retest experiments, in the absence of hypoxia. Dotted lines indicate two standard deviations of $\dot{V}$-estimate above and below regression.

and 3b of their paper. $\dot{V}/P_{A,CO_2}$ points for the " repeat " periods are shown, all having been standardized according to the respective " initial " periods. Their distribution suggests a linear relationship above a ventilation of 15 l./min and a P_{A,CO_2} of 40 mm Hg. The four points below 40 mm Hg were therefore excluded and a regression line was calculated for the remaining forty points. The right upper pair of dotted lines represent two standard deviations of the $\dot{V}$-estimate above and below this regression line. Inspection of Fig. 1 shows that it would not have been justifiable to continue the lower of these limits below $\dot{V}=15$ l./min, because none of the values used in the calculation fell below this level. Limits for the lowest points (left lower dotted lines) were therefore set by calculating regression and standard deviation from regression for the twenty-one points with a P_{A,CO_2} below 45 mm Hg. Both sets of 95% limits have been drawn to their points of intersection, and the same sets of lines incorporated into subsequent Figures showing the response to carbon dioxide after the drugs.

The ventilatory response to hypoxia has been assessed in terms of the change, induced by hypoxia, in the " sensitivity " to carbon dioxide. If the $\dot{V}/P_{A,CO_2}$ line in the absence of hypoxia is known, a single $\dot{V}/P_{A,CO_2}$ point at a low alveolar oxygen tension (P_{A,O_2}) is enough to characterize the $\dot{V}/P_{A,CO_2}$ line at that P_{A,O_2}, since Lloyd, Jukes & Cunningham (1958) have shown that hypoxia causes no significant change in the P_{A,CO_2} intercept (B). According to Lloyd *et al.* (1958), the slope (S) of the $\dot{V}/P_{A,CO_2}$ line during hypoxia is expressed by the equation:

$$S=D\{1+A/(P_{A,O_2}-C)\}$$

where D is the slope of the $\dot{V}/P_{A,CO_2}$ line in the absence of hypoxia and A and C are constants. From this equation:

$$(S-D)/D=A/(P_{A,O_2}-C)$$

This expression represents the response to hypoxia at a given P_{A,O_2}. If it be determined at the same P_{A,O_2} before and after the administration of a drug (determinations 1 and 2), then the change in the hypoxic response is given by:

$$(S_2-D_2)/D_2-(S_1-D_1)/D_1, \text{ or } S_2/D_2-S_1/D_1$$

This has been calculated from the present data and plotted in Fig. 6 against the mean of the two values for P_{A,O_2} determined before and after the drug. As in the case of the response to carbon dioxide, we have compared the changes in hypoxic response, observed after giving a drug, with those calculated from the repeatability studies of Anderton *et al.* (1964). These authors showed that there is a systematic increase in hypoxic responsiveness on retesting after a short interval. Only the data of Programme 3b of Anderton *et al.* (1964) have been used for the present purpose, and are shown in Fig. 6.

Procedure

When sleeping responses were measured, results were obtained before the drug was given, again while sleeping 30 to 90 min after taking the drug, and then after being wakened and kept awake by being made to read a book. Some experiments did not include a sleeping phase. In one experiment (with triclofos) a final sleeping phase was studied. In the remainder, it may be questioned whether the effect of the drug lasted to the end of the experiment. However, most subjects had some difficulty in staying awake after the drug; also, the results were the same in experiments which included no sleeping phase and in which the post-drug waking period occupied the same time as the sleeping phase in other experiments.

In three experiments we recorded two electroencephalographic leads, one frontal and one occipital. Records were classified according to Loomis, Harvey & Hobart (1937) into five stages, from A to E. No attempt was made to correlate the electroencephalographic pattern closely with respiratory behaviour. Our aims were, first, to confirm that ordinary observation was adequate to assess sleep and gain a rough idea of its depth and, secondly, to establish the time at which the deepest sleep level was reached.

RESULTS

Response to carbon dioxide without hypoxia

Ethchlorvynol. Fig. 2 shows the results in three experiments, in one of which a sleeping period was not included. Of the other two subjects, one fell asleep and his sleeping values are shown by the joined solid circles. The remaining subject tried to sleep but only dozed;

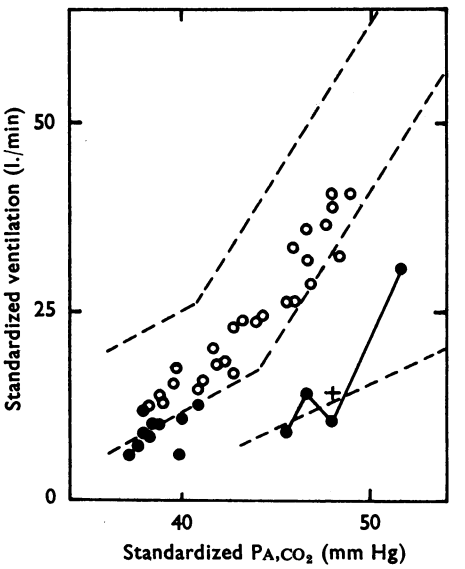

Fig. 2. Ventilatory response to carbon dioxide without hypoxia after 500 mg of ethchlorvynol: ●, sleeping; ○, awake. In this and Figs. 3 to 5 the 95% limits shown in Fig. 1 are indicated. The lower dotted line shows the $\dot{V}/P_{A,CO_2}$ line for Stage E of natural sleep, calculated from Bülow (1963). + shows a single $\dot{V}/P_{A,CO_2}$ point obtained during sound natural sleep by ourselves.

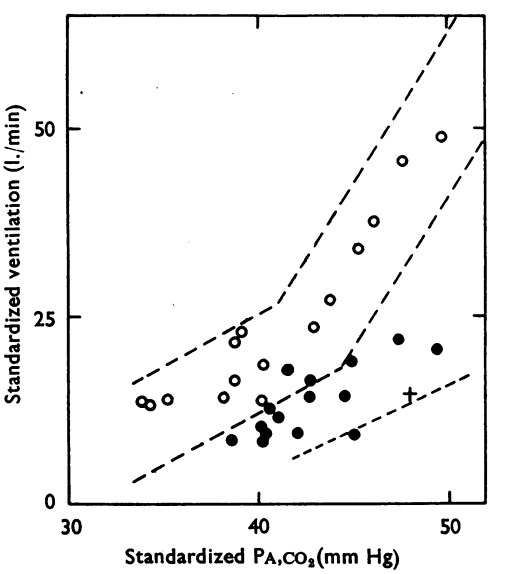

Fig. 3. Ventilatory response to carbon dioxide without hypoxia after 200 to 300 mg of cyclobarbitone: symbols as in Fig. 2.

his sleeping points are shown unjoined. Depression of the response to carbon dioxide is shown by the position of the solid circles below and to the right of the repeatability range, and the degree of depression reflects the depth of sleep. The post-drug, waking points (open circles) fall within the repeatability range.

Cyclobarbitone. Fig. 3 shows the results obtained in three experiments in which conventional doses of cyclobarbitone (two of 200 mg, one of 300 mg) were administered. All three subjects achieved a satisfactory sleep; one in whom the electroencephalogram was recorded showed stage D or E patterns at the time of his maximum respiratory depression. Most of the sleeping points in Fig. 3 lie below and to the right of the expected range. All the post-drug, waking points lie within it.

Fig. 4 illustrates the findings in three subjects given larger doses (two of 500 mg and one of 600 mg) of cyclobarbitone. In one of the subjects given 500 mg the experiment did not include a sleeping period, though he had great difficulty in staying awake. The other two subjects were allowed to sleep, and slept deeply; stage D or E patterns were seen in the electroencephalogram throughout the sleep of the subject whose data are shown as the left-hand set of joined solid circles. In the subject given 600 mg, the respiratory depression was greater, as shown by the right-hand set of circles. On being wakened this subject found great difficulty in staying awake and his first two " waking " points, shown by the half-filled

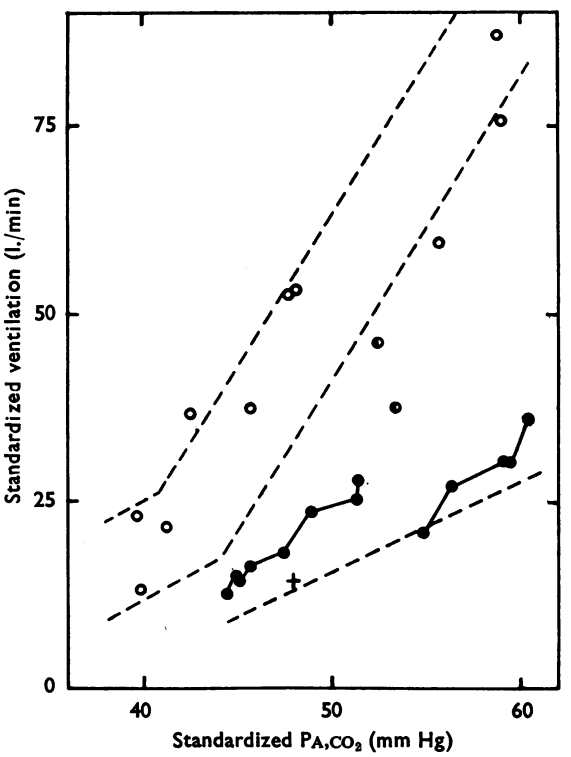

Fig. 4. Ventilatory response to carbon dioxide without hypoxia after 500 to 600 mg of cyclobarbitone; ◐, drowsy; symbols otherwise as in Fig. 2.

circles, really represent dozing. As inspired carbon dioxide pressure was raised he became more alert and the highest three open circles show a transition into the repeatability range. Waking points for the other two subjects all lie within this range except for one point which lies above it.

Triclofos. Results from two subjects given 1 g and from one subject given 3 g are plotted in Fig. 5. Sleep in all three subjects was light; the electroencephalogram of the subject given 3 g did not progress beyond stage A. Almost all " sleeping " points for these subjects lie just below the repeatability range. All waking points lie within this range.

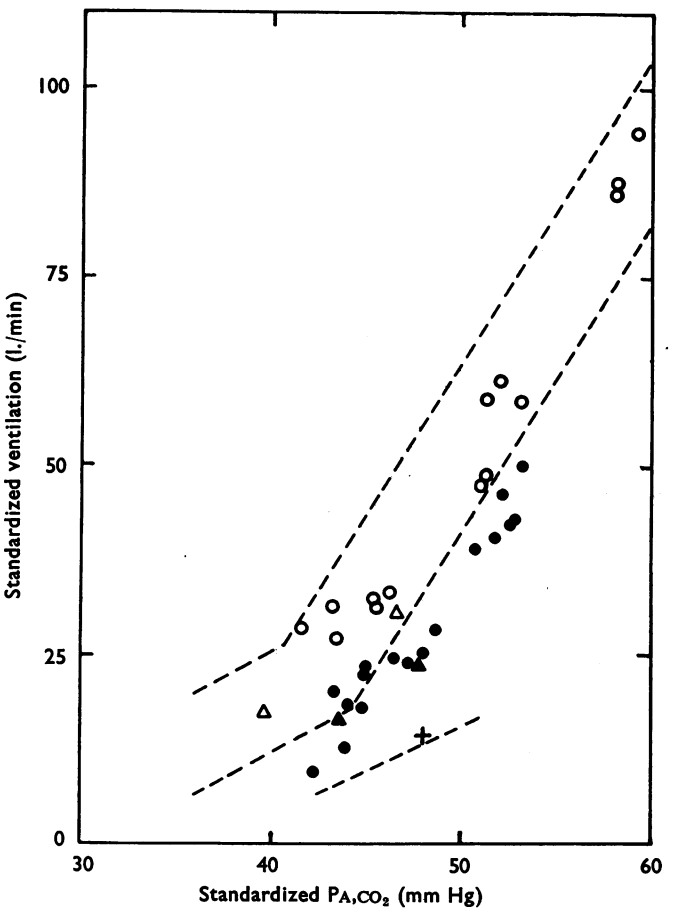

Fig. 5. Ventilatory response to carbon dioxide without hypoxia after triclofos; △▲, awake and " sleeping " after 3 g; ○●, awake and sleeping after 1 g; symbols otherwise as in Fig. 2.

Response to hypoxia

The changes in response to hypoxia, at various levels of oxygen pressure, observed after 500 mg of ethchlorvynol (one subject), 200 mg of cyclobarbitone (one subject), 500 mg of cyclobarbitone (two subjects) and 600 mg of cyclobarbitone (one subject) are shown in

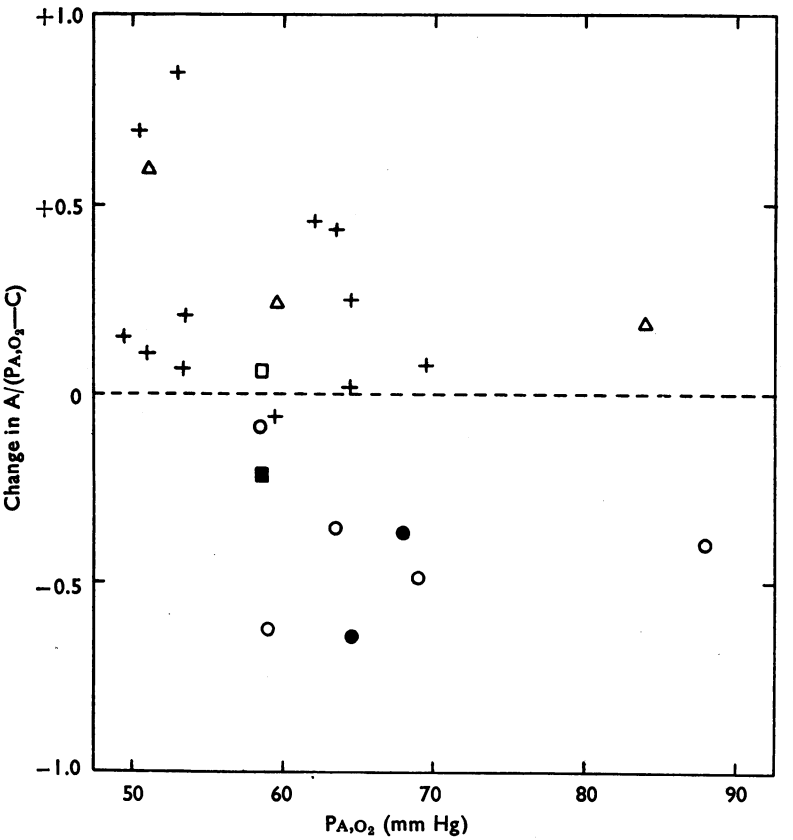

Fig. 6. Ventilatory response to hypoxia after 500 mg of ethchlorvynol (△, awake), 200 mg of cyclobarbitone (□, awake; ■, sleeping), 500 to 600 mg of cyclobarbitone (○, awake; ●, sleeping) and after no drug had been given (+, awake). For calculation of hypoxic response, see text.

Fig. 6. Results from the repeatability study of Anderton *et al.* (1964) have also been plotted. When awake after 500 mg of ethchlorvynol the response to hypoxia was normal, as it was in the waking subject after 200 mg of cyclobarbitone. Sleeping hypoxic responses were depressed after both conventional and higher doses of cyclobarbitone, as were waking responses after the higher doses.

DISCUSSION

Ventilatory response to carbon dioxide

The results show that the response to carbon dioxide was depressed during sleep after conventional doses of these hypnotics, but in no case was the depression greater than that found during natural sleep (Figs. 2 to 5). The same is true even of the quantitatively greater depression after a thrice-normal dose of cyclobarbitone. After waking, and while the drugs were still acting, the response to carbon dioxide returned to normal. We conclude that the drugs we have studied do not, of themselves, depress the response to carbon dioxide but that depression does occur when the administration of the drug is followed by sleep. The degree of such depression is apparently no greater than that found in natural sleep.

Keats & Kurosu (1957) reported significant stimulation of the response to carbon dioxide after 100 mg of pentobarbitone. This finding has not been confirmed by our experiments; apart from one waking point after 500 mg of cyclobarbitone (Fig. 4) no post-drug waking response was above the repeatability range.

Ventilatory response to hypoxia

Until the finding of Anderton *et al.* (1964) that the response to hypoxia is increased on retesting has been confirmed, and until the reasons for it are known, responses to hypoxia before and after drugs can be a matter for only tentative conclusions. Our present results suggest that after cyclobarbitone the response to hypoxia may be diminished while the response to carbon dioxide is unaltered. This result is at variance with the widely held view that the response to hypoxia is more durable than is that to carbon dioxide and is less affected by drugs. We are not aware that the problem has been properly investigated in man. The technique devised by Cunningham *et al.* (1957), and used by us, seems admirably suited to further study of this question. In order to demonstrate differences in respiratory action between various hypnotics—differences which have long been accepted by clinicians —attention may have to be given to the responses to hypoxia rather than to carbon dioxide.

It remains uncertain how far the results of this study in healthy young men can be applied to the treatment of patients with respiratory failure. Certainly any method of inducing sleep will depress the response to carbon dioxide; the effect of sleep, *per se*, on the response to hypoxia has hardly yet been studied. We have not shown that any of the hypnotics we have investigated have a specific action on the response to carbon dioxide. Cyclobarbitone, however, seems to depress hypoxic responsiveness irrespective of sleep, and this may be of clinical importance.

SUMMARY

1. The ventilatory response to excess of carbon dioxide was investigated in twelve healthy young adult subjects awake before, and both asleep and awake after, therapeutic doses of cyclobarbitone, triclofos and ethchlorvynol. In five subjects responses to hypoxia were similarly studied.

2. P_{A,CO_2} and P_{A,O_2} were used as indices of the carbon dioxide and hypoxic stimuli, and ventilation as the response. Conventional methods were used to supply inspired gas mixtures and to sample alveolar gas. Gas analysis was performed by the Haldane method.

3. No significant change in the response to carbon dioxide occurred after any of the three hypnotics while the subject was awake. During sleep the response was depressed in proportion to the depth of sleep and was never greater than the depression induced by natural sleep. The same result was obtained even after a dose of cyclobarbitone three-times the conventional therapeutic dose.

4. The response to hypoxia was depressed in the waking and sleeping states after the larger dose of cyclobarbitone. It was normal in the waking state after conventional doses of cyclobarbitone and ethchlorvynol.

5. The widely accepted distinction between barbiturate and nonbarbiturate hypnotics in respect of ventilatory depression is not borne out so far as the response to carbon dioxide is concerned; none of the three drugs tested appears specifically to depress this response.

However, evidence was obtained of specific depression, unassociated with sleep, of the response to hypoxia by a thrice-normal dose of cyclobarbitone.

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REFERENCES

ANDERTON, J. L. & HARRIS, E. A. (1963). The changing state of breathing during inhalation of CO_2, studied with an inexpensive, recording CO_2-analyzer. *Quart. J. exp. Physiol.*, **48**, 1–12.

ANDERTON, J. L., HARRIS, E. A. & SLAWSON, K. B. (1964). The repeatability of ventilatory responses to excess of CO_2 and lack of oxygen. *Quart. J. exp. Physiol.*, **49**, 43–51.

AUSTIN, W. T. S., HARRIS, E. A. & SLAWSON, K. B. (1963). A simple, rapid, recording carbon-dioxide analyser. *Lancet*, **ii**, 984–985.

BÜLOW, K. (1963). Respiration and wakefulness in man. *Acta physiol. scand.*, **59**, suppl. 209, 1–110.

CUNNINGHAM, D. J. C., CORMACK, R. S., O'RIORDAN, J. L. H., JUKES, M. G. M. & LLOYD, B. B. (1957). An arrangement for studying the respiratory effects in man of various factors. *Quart. J. exp. Physiol.*, **42**, 294–303.

KEATS, A. S. & KUROSU, Y. (1957). Increased ventilation after pentobarbital in man. *Fed. Proc.*, **16**, 311.

LLOYD, B. B., JUKES, M. G. M. & CUNNINGHAM, D. J. C. (1958). The relation between alveolar oxygen pressure and the respiratory response to carbon dioxide in man. *Quart. J. exp. Physiol.*, **43**, 214–227.

LOOMIS, A. L., HARVEY, E. N. & HOBART, G. A. (1937). Cerebral states during sleep, as studied by human brain potentials. *J. exp. Psychol.*, **21**, 127–144.

RILEY, R. L., DUTTON, R. E., FULEIHAN, F. J. D., NATH, S., HURT, H. H., YOSHIMOTO, C., SIPPLE, J. H., PERMUTT, S. & BROMBERGER-BARNEA, B. (1963). Regulation of respiration and blood gases. *Ann. N.Y. Acad. Sci.*, **109**, 829–851.

ROBIN, E. D., WHALEY, R. D., CRUMP, C. H. & TRAVIS, D. M. (1958). Alveolar gas tensions, pulmonary ventilation and blood *p*H during physiologic sleep in normal subjects. *J. clin. Invest.*, **37**, 981–989.