RESPIRATORY EFFECTS UPON THE VISUAL THRESHOLD

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In a completely dark adapted individual the absolute threshold of vision remains constant within narrow limits indefinitely. The photochemical systems of the receptors are at rest; and this state is not disturbed appreciably by the minimal exposures to light needed to determine the threshold. Under such circumstances various types of physiological stress cause marked changes in threshold which must originate at levels central to the photochemical system itself. In this sense the threshold of the dark adapted eye is an indicator of central nervous imbalance.

It has already been shown that lowering the oxygen tension of the inspired air to about 10 per cent, while it does not affect the course of visual adaptation, raises the threshold 2 to 4 times (Bunge, 1936; McDonald and Adler, 1939; McFarland and Forbes, 1940–1941). Lowering the blood sugar with insulin has been reported to induce a similar response (McFarland and Forbes, 1940–41).

The present paper is concerned with the effects upon the threshold of low oxygen tensions, applied gradually or suddenly, and of short and long duration; and of changes in the rate of breathing and in the composition of the inspired gases. All thresholds have been measured in the periphery of the dark adapted eye and involve the function of the rod apparatus alone.

I

Apparatus and Methods

Visual thresholds were measured with an adaptometer which has already been described (Wald, Jeghers, and Arminio, 1938). In this instrument the intensity of the test field is regulated with a pair of circular neutral wedges, superimposed in reverse so as to compensate each other. The full white radiation from a tungsten filament lamp was employed.

The subject faced circular test fields which subtended visual angles of 1° or 2° and were centered respectively 13° or 10° below a red fixation star. A shutter controlled by the subject exposed the field for flashes 1/50 second in duration. The fixation point remained on at all times. All observations were monocular, usually on alternate eyes. During most experiments each subject wore a pair of spectacles in which the lenses had been replaced with thin brass discs pierced with circular

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openings 1.6 or 2 mm. in diameter. These served as artificial pupils to guard against the possibility that any of the recorded changes in threshold were due to fluctuations in pupil area.

Gas mixtures were prepared in large cylinders, and for short term experiments were transferred to a Douglas bag. The subject wore a nose clip and breathed through a mouthpiece communicating with a two-way valve, so that only the mixtures could be inhaled and all expired gases escaped into the room.

II

Low Oxygen Tensions

Our first experiments on the effects of low oxygen tensions, performed in 1937, confirm in general the observations of Bunge, of McDonald and Adler, and of McFarland and Forbes. The discussion which follows is restricted primarily to aspects of the experiments which amplify and extend these previous reports.

In this series of experiments no attempt was made to regulate the rate or depth of breathing with the thought that in this way automatic compensatory mechanisms would be given free play to meet the anoxia. A 1° test field was used, centered 13° below the fixation point. Artificial pupils were worn in some of the experiments; beyond raising the general level of the threshold they did not appreciably modify the results.

Two types of experiment were performed, one in which the anoxia was of short duration and began and ended abruptly; and another conducted in a gas chamber in which the anoxia was established gradually and maintained for a number of hours.

In the first type of procedure completely dark adapted subjects, breathing through a mouth-piece, were switched instantaneously from room air to air-nitrogen mixtures containing 8 to 11 per cent oxygen. After 20 to 30 minutes the subject was returned abruptly to room air.

The simplest and most usual type of response to this procedure is shown in Fig. 1 A. In almost all cases the threshold rose within 1 to 10 minutes of anoxia to new levels 0.2 to 0.5 log unit above normal. In repeated experiments with 6 subjects this change averaged 0.35 log unit or a rise of about $2\frac{1}{4}$ times. Occasionally after reaching the anoxic level the threshold fluctuated widely, rising for short intervals to as much as 0.7 to 1.0 log unit above normal. On returning to room air the threshold ordinarily fell within a few minutes to the normal level.

Certain subjects yielded results which departed from this pattern in characteristic ways. In Subject J. B. the threshold behaved in an orthodox way during the anoxia, but on the return to room air it fell rapidly to far below the normal level and remained subnormal for 10 to 15 minutes (Fig. 1 B). This subject also described vivid visual hallucinations during this period,

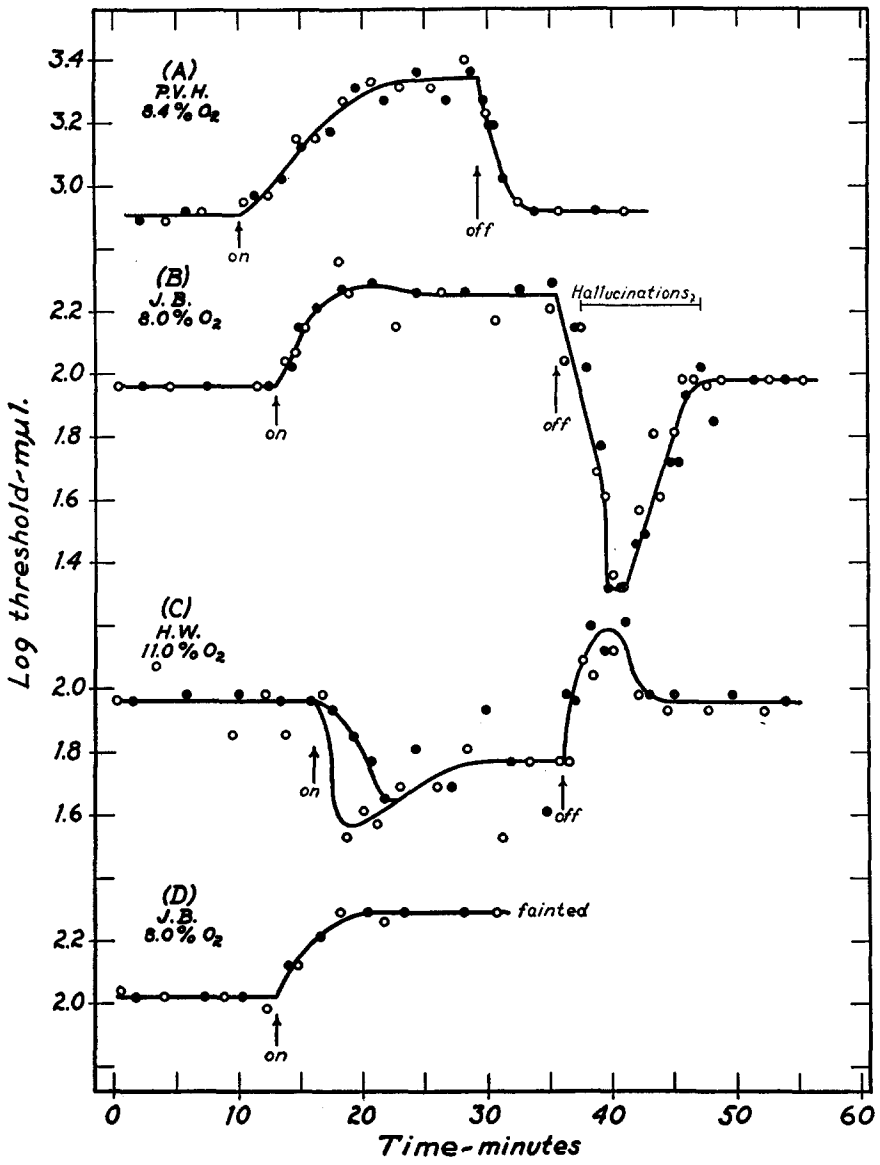

FIG. 1. Changes in the visual threshold on sudden exposure to and release from low oxygen tensions with breathing uncontrolled. Each point represents a single measurement of the threshold. In Experiment A artificial pupils were worn; B–D were performed with natural pupils. Open circles show measurements on the right eye, solid circles those on the left eye. Thresholds in millimicrolamberts ($=10^{-6}$ millilamberts).

replacing one another rapidly and with no apparent continuity of subject, for as long as 12 to 15 minutes. Subnormal thresholds appeared in 4 and hallucinations in 6 out of 7 completed experiments with this subject. The hallucinations did not depend therefore on visual hypersensitivity; yet when both phenomena appeared together they coincided roughly in time.

Another subject yielded a pattern of threshold changes the mirror image of that just described (Fig. 1 C). In 2 out of 3 experiments his threshold *fell* during the anoxia. The records of these experiments contain the significant notation, "Puffs very hard; breathes gas up very rapidly." In all experiments with this subject the threshold rose sharply on the return to room air and remained for a time well above the normal level.

These wide variations in response may be ascribed primarily to characteristic differences in breathing pattern among the subjects. They did not appear in later experiments with 2 subjects in which the rate and depth of breathing were controlled. As shown below such supersensitivity as appears in Fig. 1 B and 1 C may be produced at will by hyperventilation; and the sequence of changes in Fig. 1 C was apparently due to the hyperventilation actually observed during the anoxia followed by a period of apnea on the return to room air.

The magnitude of the observed changes seems to represent the limit to which the visual threshold can be displaced by these means. It did not vary consistently with the oxygen tension between 8 and 11 per cent; nor was the rise in threshold obviously related to the distress experienced by the subjects. During anoxia subjects frequently reported sensations of dizziness, numbness, and cold in the extremities, feelings of restlessness, and flickering "subjective" light and color sensations, in no apparent relation with the behavior of the threshold. All subjects reported red "subjective" light starting about 15 to 30 seconds after the return to room air and lasting 2 to 3 minutes. One experiment ended when the subject fainted with his threshold established at a stable level 0.27 log unit above the norm (Fig. 1 D). It may be concluded from these observations that the visual threshold reflects only a restricted segment of the central nervous changes in anoxia.

Through the courtesy of Dr. D. B. Dill we were permitted to participate in anoxia experiments at the Fatigue Laboratory of Harvard University in 1937. These were conducted in a gas chamber in which the air was diluted with nitrogen without change in total barometric pressure. Oxygen contents of 11 to 12 per cent, simulating altitudes of 15,000 to 17,000 feet, were attained within 30 to 90 minutes after the first introduction of nitrogen, and were maintained thereafter for about 5 hours. Data from two such experiments, performed with natural pupils, are shown in Table I and in Figs. 2 and 3. A third experiment in which artificial pupils were worn yielded similar results.

These experiments indicate that the visual threshold rises with the first

dilution of oxygen (Fig. 2). The scatter of individual measurements is such that from 20.9 to about 14 per cent oxygen (10,000 to 11,000 feet) there is some overlap of thresholds with the norm; yet the average threshold rises slowly throughout this interval. As the oxygen is diluted below about 14 per cent the threshold increases rapidly, in the present subject to a level about 0.35 unit or $2\frac{1}{4}$ times above normal, at about 11 per cent oxygen (17,000

TABLE I

Data of two experiments performed in a gas chamber in which the air was diluted with nitrogen at sea level atmospheric pressure. Subject P. V. H. Thresholds in millimicrolamberts (10^{-6} millilamberts).

Oxygen	"Altitude"	Time	Average log threshold		No. of readings averaged	Remarks
			Right eye	Left eye		
per cent	*feet*	*min.*				
20.9	0	0	2.02	2.03	12	
18.1	4000	3–12	2.07	2.07	5	
16.8	6000	18–32	2.14	2.09	5	
16.1	7000	33–40	2.08	2.09	4	Uncomfortable; puffing
15.6	7800	42–53	2.08	2.10	4	
14.0	10500	56–67	2.11	2.13	4	
12.3	13800	76–96	2.18	2.16	6, 7	Dizzy; periodic breathing
11.8	15000	98–115	2.21	2.17	5	
11.3	16000	120–139	2.25	2.25	5	Sick; yawning
11.3	16000	147–177	2.29	2.27	7	Sick
11.3	16000	262–292	2.30	2.29	7	Sick
20.9	0	299–320	2.01	2.00	6, 5	
20.9	0	0	2.05	2.03	4	
10.9	17000	58–120	2.34	2.34	15, 16	
11.3	16000	240	—	—	—	Arterial saturation 74.5 per cent
10.9	17000	316–333	2.34	2.32	4	
10.9	17000	373–391	2.38	2.38	5	
20.9	0	398–405	2.06	2.07	3	

feet). The form of this relation suggests that with still further decrease in oxygen tension the threshold might rise much higher. Actually, however, this is close to the limiting tolerance of unacclimatized subjects. As Table I indicates the present subject experienced serious distress even at these levels and probably could not have continued the experiment at still lower oxygen pressures.

Some time after the anoxic threshold had been well established in each of these experiments the subject was highly light adapted and his complete dark adaptation curve was measured. All thresholds, rod and cone, were found to be about equally elevated on a logarithmic scale, *i.e.*, multiplied by an

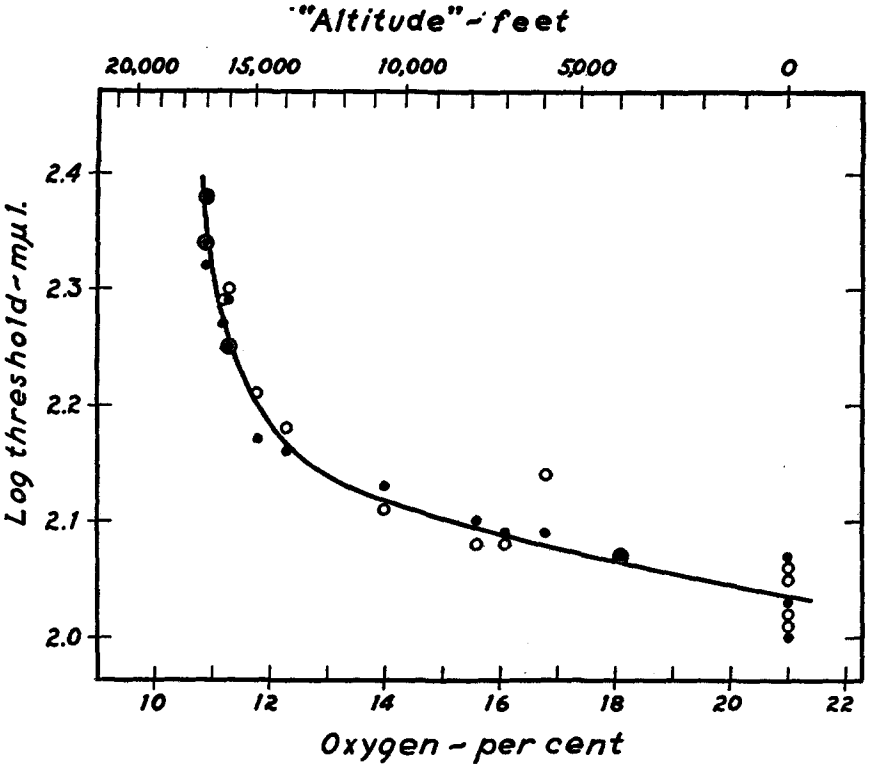

FIG. 2. The variation of visual threshold with decrease in oxygen tension or rise in simulated altitude. Data from Table I. Open circles, right eye; solid circles, left eye. Subject P. V. H.

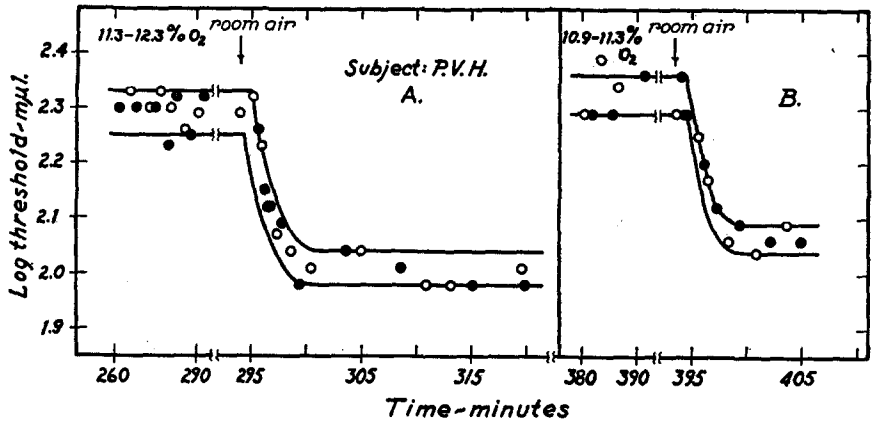

FIG. 3. Descent of the threshold to normal following 5 to 6.5 hours exposure to low oxygen tensions. Open circles, right eye; solid circles, left eye.

approximately constant factor. The speed of rod and cone dark adaptation appears to be entirely unaffected by anoxia (*cf.* Bunge; McDonald and Adler; McFarland and Forbes).

At the close of each experiment the subject was returned abruptly to sea level atmosphere. The details of the descent of his visual threshold are shown in Fig. 3. After exposures of 5 and 6.5 hours to diminished oxygen tensions the threshold returned to its normal level within 5 to 6 minutes, and without incident.

The changes recorded in these long term experiments agree in magnitude with those obtained with the same subject on sudden and short exposure to anoxia (Fig. 1 A). The adjustment of central nervous structures to low oxygen tensions appears to be a rapid process. Anoxias of several hours duration cause changes in the threshold which neither exceed those recorded during the first few minutes nor persist longer after the return to room air.

III

Acid-Base Imbalance

The following experiments are concerned with the effects of respiratory acid-base imbalance on the threshold. The subjects breathed to the beat of a metronome, so far as possible without change in amplitude; and the rate and depth of respiration were recorded by pneumograph. Thresholds were measured in a 2° field centered 10° below the fixation point, and artificial pupils 2 mm. in diameter were worn at all times. As in previous experiments the subjects were kept completely dark adapted throughout. The results of these experiments are shown in Fig. 4 (Subject H.C.G.) and Fig. 5 (Subject H.P.K.).

On increasing the rate of breathing room air by 50 to 100 per cent the threshold fell, usually within 5 to 10 minutes, to about half its normal value (Figs. 4 *a* and 5 *a*). In 22 experiments with 2 subjects this decrease ranged from 0.13 to 0.41 log unit and averaged 0.27 log unit or a decline of 47 per cent. On returning abruptly to the normal rate of breathing the threshold rose to normal usually within 2 to 3 minutes.[1]

Oxygen tensions of 32 to 36 per cent do not appreciably affect these results (Fig. 4 *b*; Fig. 5 *b*, *c*). The hypersensitivity induced by rapid breathing is not due therefore to increased oxygenation of the blood.

It is, however, due to the alkalosis associated with hyperventilation, and can be abolished or reversed by adding carbon dioxide to the inspired gases. The presence of 2 per cent carbon dioxide in mixtures containing 32 to 36 per cent oxygen does not affect the threshold when breathed at the normal

[1] Gellhorn (1936 *a*) has reported that rapid breathing *raises* the threshold for brightness discrimination. The relation of these to the present experiments is obscure.

rate, but completely abolishes the fall in threshold otherwise associated with rapid breathing (Fig. 4*c*; *d*; Fig. 5*d*). When the carbon dioxide content is raised to 5 per cent the threshold rises 0.2 to 0.5 log unit at both normal and rapid rates of ventilation (Fig. 4*e*, *f*; Fig. 5 *e*, *f*).

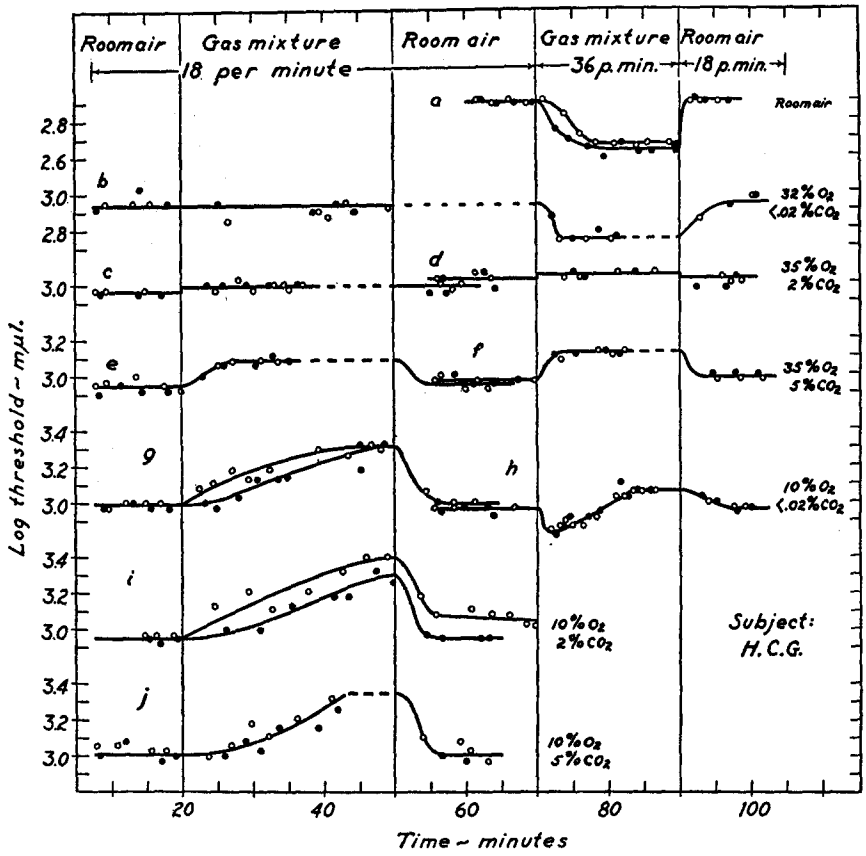

FIG. 4. Effects on the visual threshold of variations in the rate of breathing and in the composition of the inspired gases. Rates of breathing are shown at the top of the figure, gas composition to the right of each experiment. In this subject the normal uncontrolled rate of breathing in room air was 18 per minute. Open circles, right eye; solid circles left eye.

Respiratory alkalosis and acidosis therefore exert opposed effects upon the visual threshold. The former depresses, the latter raises the threshold in about equivalent degree, averaging in the present experiments about 0.3 log unit or a factor of about 2.

IV

Anoxia and Acid-Base Imbalance

These experiments are concerned with the interaction of acid-base imbalance and low oxygen tensions upon the visual threshold. The rate and depth of breathing were controlled and artificial pupils were worn at all times.

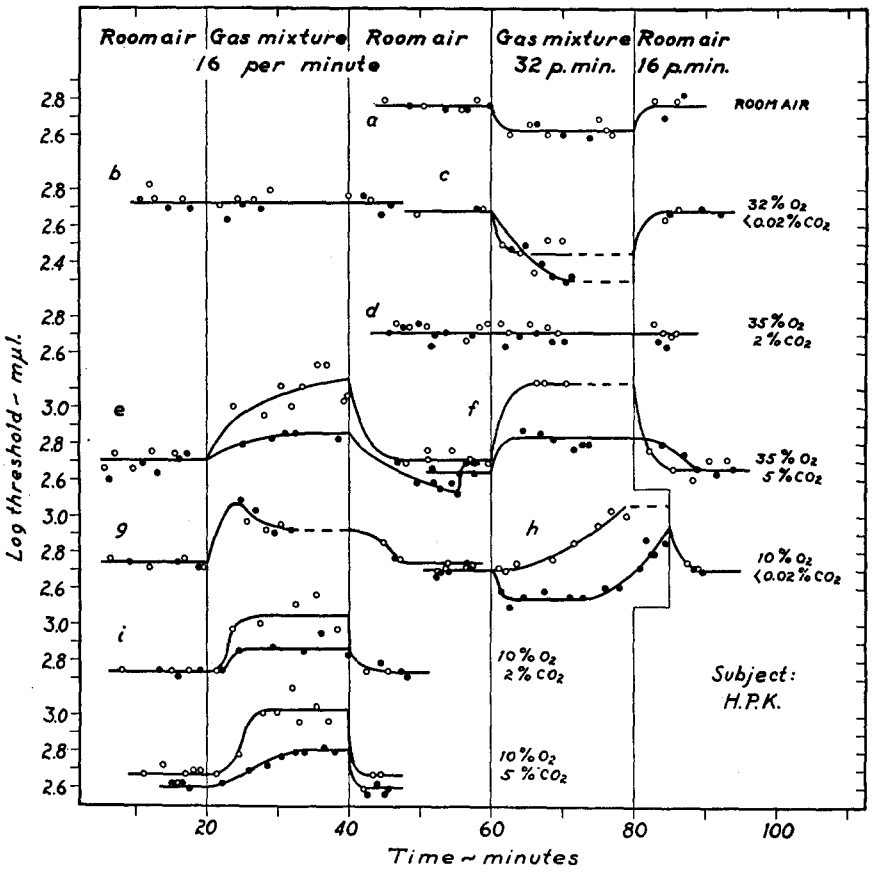

FIG. 5. Effects on the visual threshold of variations in respiratory rate and in the composition of the inspired gases. In this subject the uncontrolled rate of breathing in room air was 16 per minute. Symbols as in Fig. 4.

The reaction to 10 per cent oxygen breathed at the normal rate (16 to 18 per minute) was essentially like that shown in Fig. 1 A in which the breathing had been uncontrolled, but was obtained invariably in the present experiments (Figs. 4 *g* and 5 *g*). The threshold rose in anoxia and fell promptly to normal

at its close with no appearance of the individual peculiarities and incidents which marked the earlier experiments.

A particularly interesting situation results when low oxygen is breathed at twice the normal rate (Figs. 4 *h* and 5 *h*). Usually the threshold falls at first; always it at least fails to rise for several minutes. Finally it always does rise, eventually to values above the normal level; though it may remain, as in Fig. 4 *h*, well below the level attained at lower rates of breathing. The effects of rapid breathing therefore usually at first predominate over those of simple anoxia. After a time some of this advantage is lost. It is very likely that further manipulation of the breathing rate might maintain a much more effective compensation of anoxia than is evident in the present procedure.

Breathing rapidly apparently also ameliorates the subjective symptoms of anoxia. When 10 per cent oxygen was breathed at the normal rate the subjects invariably reported such symptoms—"subjective" light, difficulty in concentrating, lassitude, and so on. Rapid breathing of the same mixtures elicited no comments whatever, except in one instance "feels O.K."

The addition of 2 per cent carbon dioxide to mixtures containing 10 per cent oxygen, when breathed at the normal rate, contributed no notable differences in behavior (Figs. 4 *i* and 5 *i*). Mixtures containing 5 per cent carbon dioxide and 10 per cent oxygen also produced no extraordinary changes in the threshold beyond those occasioned by low oxygen alone (Figs. 4 *j* and 5 *j*); but with these mixtures the subject usually was unable to regulate his respiration effectively. The pneumograph records showed large increases in the depth of breathing in almost all cases; and frequently the subject was unable also to keep the rate of breathing down to that set by the metronome. Panting, sweating, and general distress usually cut these experiments short. The subjects were unable to complete experiments in which either 2 or 5 per cent carbon dioxide in 10 per cent oxygen was breathed rapidly.[2]

V

DISCUSSION

The changes in visual threshold observed in the present experiments are due to changes in structures central to the photochemical system of the rods. It is not possible to locate them at present with greater precision. They may originate at any loci along the visual pathways from rod outer limbs to cortex. It is known that nerve cell bodies and synapses in contrast with axones are highly sensitive to oxygen want. Recently it has been shown also that in the

[2] These procedures should not be confused with experiments in which CO_2 is added to the inspired gases without control of breathing (*cf.* Gellhorn, 1936 *b*). In the latter case 2 to 3 per cent CO_2 may aid in compensating the anoxia by stimulating the respiration.

cat hyperventilation increases the pH of the cerebral cortex and simultaneously lowers its threshold for neural or electrical excitation; hypoventilation or any other means of decreasing the cortical pH raises the threshold (Dusser de Barenne, McCulloch, and Nims, 1937). Lehmann (1937) has made comparable observations on peripheral nerve; in the phrenic nerve of the cat the threshold for induction shocks falls linearly as the pH rises from 7.2 to 8.1.

It is beyond the scope of the present paper to discuss extensively the blood and tissue changes which accompany anoxia and changes in respiratory rate. It should at least be noted, however, that these stresses do not act independently, but are involved in a complex pattern of interrelationships. Anoxia usually stimulates rapid breathing, in part due to the acidosis which results from incomplete oxidation of metabolic products. Hyperventilation in turn tends to compensate initially for anoxia; by raising alveolar oxygen and lowering alveolar carbon dioxide tensions it promotes the oxygenation of hemoglobin in the lungs. Hyperventilation, however, also induces alkalosis which may intensify the anoxia in either of two ways: by inhibiting the discharge of oxygen from blood to tissues, and by provoking a period of apnea.

In our initial experiments all these potentialities were permitted free play and resulted in a great variety of reaction patterns (Fig. 1). On exposure to anoxia the threshold rose or fell; on return to room air it rose, or fell to normal or subnormal levels. Simple regulation of the rate and depth of breathing in later experiments brought all these phenomena under control. But it may be assumed that the latter experiments no less than their forerunners involved the continuous interaction of internal changes in both oxygen and hydrion concentration.

These experiments raise a possibilty which should be explored further. Since the threshold may vary in either direction in anoxia depending upon the breathing pattern, it should be possible to regulate the latter so as to obtain virtually no change in threshold, and hence an optimally compensated response. It is clear from our observations that subjects left to their own devices do not automatically establish optimal behavior.

In general these experiments support the thesis that the visual threshold offers a practicable quantitative index of physiological imbalance. It is more sensitive and reliable for this purpose than subjective awareness of distress or sensory change; and has the advantage over certain other types of physiological measurement that it provides an index of net change in the central nervous system itself, usually the first to fail in physiological stress (Barcroft, 1934).

This is probably the principal importance of such measurements. During light and dark adaptation the visual threshold varies through a range as great as 1:1,000,000. In contrast the variations induced by even extreme central nervous imbalance are relatively small. In the present experiments

they average about 1:2. In subjects exposed to about 10 per cent oxygen Bunge found the average rise of threshold to be about 3; McFarland and Forbes about 4; and McDonald and Adler (1939) about 2.5 times. These seem to represent the extreme limits of variation which disturbances central to the photochemical system can contribute to the visual threshold.

SUMMARY

Measurements are reported of the effects of respiratory stresses upon the absolute threshold of peripheral (rod) vision. Since subjects were kept wholly dark adapted and the photochemical system of the rods therefore stationary, the changes recorded may be assumed to have originated more centrally. To this degree the measurements provide a quantitative index of central nervous imbalance.

Breathing room air or 32 to 36 per cent oxygen at about double the normal rate causes the visual threshold to fall to approximately half the normal value within 5 to 10 minutes.

This change is due primarily to alkalosis induced by the hyperventilation, and can be abolished or reversed by adding carbon dioxide to the inspired mixtures. Normal or rapid breathing of 2 per cent carbon dioxide causes no change in threshold; with 5 per cent carbon dioxide the threshold is approximately doubled.

Breathing 10 per cent oxygen at the normal rate also approximately doubles the threshold. This effect is compensated in part by rapid breathing. When 10 per cent oxygen is breathed at twice the normal rate the threshold usually falls at first, then slowly rises to supernormal levels.

Due primarily to variations in their breathing patterns subjects yield characteristically different responses on sudden exposure to low oxygen tensions with breathing uncontrolled. The threshold may either rise or fall; and on release from anoxia it may rise, or fall to normal or subnormal levels. The threshold adjusts to anoxia rapidly; exposures lasting 5 to 6 hours do not produce greater or more persistent changes than those of much shorter duration.

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