OCULAR EFFECTS OF CHANGES IN OXYGEN AND CARBON DIOXIDE TENSION

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RESPIRATION is a characteristic common to living tissue. The respiration of ocular tissues, as compared with that of other vertebrate tissues, is unique. Retinal energy requirements are such that this tissue has the highest rate of oxygen consumption in the body. In man, an elaborate dual circulatory system meets these needs. Immediately adjacent lies the largest avascular collection of tissues in the body: the vitreous, lens, and cornea. The integrity of these tissues depends upon an unceasing expenditure of energy largely generated by local intracellular oxidation of organic substrates with molecular oxygen. Carbon dioxide is a product of such oxidation. Most ocular diseases are associated with local or distant cellular derangements leading to impaired organ function. Respiration is a basic cell function and oxygen and carbon dioxide are basic elements of this function. A thorough knowledge of the ocular effects of changes in the concentrations of these gases is therefore fundamental to an understanding of ocular disease. It is our purpose to describe a series of experiments in which the ocular effects of manipulating oxygen and carbon dioxide tension are examined.

These experiments, performed during the last three years, have aimed at the problems of acute and chronic ischemic ocular disease. It is now clinically possible to obtain blood oxygen tensions as high as 2500 mm Hg (normal, 100 mm Hg) by hyperbaric oxygenation. Initial attempts to oxygenate an acutely ischemic retina by elevating the oxygen tension in the adjacent intact choroidal circulation met with little success.[1-3] An experimental program has therefore been undertaken to learn more about the responses of the normal retina to ischemia, hyperoxia, hypercapnia, and hypocapnia. The results of these studies will, we hope, establish a more rational basis for improving oxygen delivery to the retina in patients with both chronic and acute ischemic retinal disease.

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METHODS

Our experimental method of producing intraocular ischemia involves raising intraocular pressure above ophthalmic pressure long enough for blackout to occur. Experimentally this situation can be produced by positive G acceleration,[4] by pressing on the eyeball with the finger,[5] by use of an ophthalmodynamometer,[6] by means of a plethysmographic goggle,[7] or by a suction cup.[8] We used the transducer ophthalmodynamometer supplied with the Mueller tonography apparatus. This

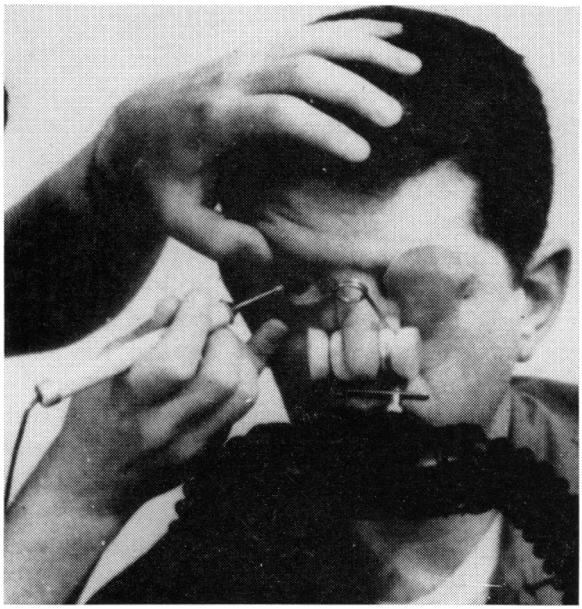

FIGURE 1
Technique of pressure application and gas delivery.

instrument continuously records the pressure exerted by the dynamometer. Following the instillation of one drop of proparacaine (Ophthaine) hydrochloride as a topical anesthetic, the instrument is applied to the temporal sclera and the pressure is rapidly increased until the reading exceeds ophthalmic systolic pressure by 20 to 50 Gm.* The pressure level attained is continuously recorded on an Esterline-Angus kymograph. Although the deformation of the eye produced by

*Although ophthalmodynamometers are calibrated in grams, this is not a pressure unit but refers to the method used to calibrate the instruments. Methods for conversion to pressure units have been devised.[9]

ophthalmodynamometry might seem injurious, wide diagnostic use of the technique has proved it to be quite safe. A small subconjunctival hemorrhage at the site of application is the only complication we have observed. Although ophthalmic systolic pressure is exceeded by a wide margin, the technique is not painful.

In our experiments, the end point for loss of visual function is blackout. It is important to realize that visual function under such conditions of elevated intraocular pressure is not lost instantaneously. Loss begins in the peripheral field and the island of remaining vision becomes progressively smaller until central vision is lost and the subject "sees black." Jaeger *et al.*[10] and Duane[11] have described this phenomenon in detail. At high oxygen pressures with oxygen breathing, the entire process is temporally expanded and the end point becomes less definite since central vision may rapidly fade in and out a few times before blackness persists. For this reason, after occluding the untested eye, the subjects are asked to view an 8 × 88-mm vertical black line on a matt white surface 1.8 m distant. This line is illuminated by a spotlight in the hyperbaric chamber. When this line first disappears completely, the subject signals and the ophthalmodynamometer is rapidly and smoothly removed from the eye. The time to blackout is measured on the kymograph tracing between the up-trace of rapid pressure application and the down-trace of pressure release (Figure 2).

The arterial oxygen tension of the subjects is controlled over wide ranges by changing the environmental atmospheric pressure and the concentration of oxygen in the inspired gas. Environmental pressure is controlled by conducting the experiments in a chamber in which atmospheric pressure can be adjusted to any level between 0 and 100 psi (pounds per square inch gauge). In this work we have, for reasons of safety, elected not to exceed an atmospheric pressure level of 45 psi (3,087 mm Hg). The desired atmospheric pressure can be maintained in the hyperbaric chamber with an accuracy of ±0.5 mm Hg. Gases are delivered to the subjects through a hose with demand valve regulator. A scuba mouthpiece of the Cousteau type is used in conjunction with a nose clip. Expired gas is exhaled into a hose and bag which is then vented through the chamber wall using a system of the respiratory gas partitioner type. In this system a small excess of pressure over that within the chamber (0.1 mm H_2O) triggers a pneumatic amplifier which vents the bag to the outside. An oxygen atmosphere in the chamber is never used because of the extreme hazards of such an environment. The concentrations of oxygen, nitrogen, and carbon dioxide are manipulated as desired by feeding the gas mixture

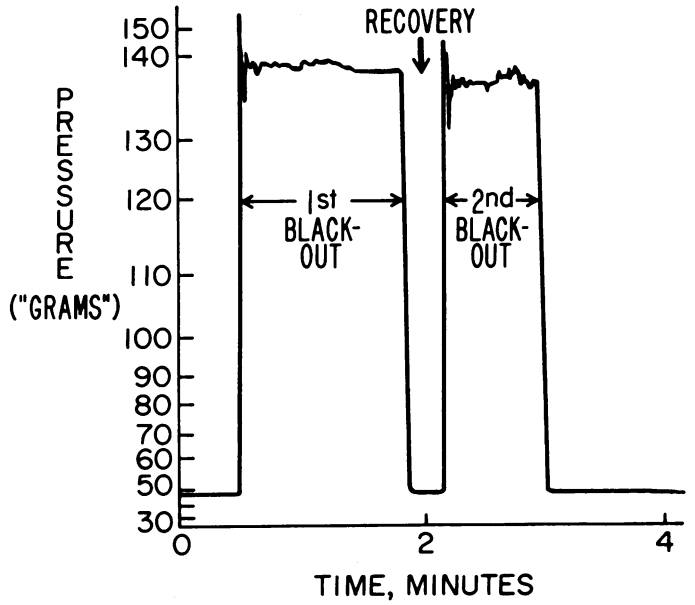

FIGURE 2
Method of measuring time to blackout.

to the inspiratory gas regulator from high pressure tanks with reduction valves. Gas mixtures can be switched back and forth outside of the chamber without the knowledge of the subject.

Blood gas measurements are made from brachial or radial arterial samples drawn from indwelling Teflon catheters with stopcocks. The samples are immediately analyzed in the hyperbaric chamber using an Instrument Laboratories blood gas analyzer. This instrument consists of an electrometer with constant temperature bath, Severinghaus pCO_2 electrode, and modified Clark platinum microcathode oxygen electrode. Calibrations are checked during the measuring period with gases analyzed on the Scholander apparatus and tonometered blood.

Measurements of blood-vessel diameter are made from fundus photograph negatives taken with Zeiss fundus cameras in the chamber. Camera power supplies are located outside of the chamber and the area about the camera bulbs is nitrogen purged to reduce the hazard of fire. Geometry of the photographs is controlled by attempting to keep the position of the optic disk constant in both control and experimental photographs.[12] The subjects' pupils are dilated 20 to 60 minutes

prior to photography with one drop of 1 per cent tropicamide (Mydriacyl) and one drop of 10 per cent phenylephrine (Neosynephrine). Measurements are made microscopically from the negatives with an eyepiece graticule or from tracings of density scans made by a modified Jarrell-Asch recording microdensitometer (spectrophotometer) (Figure 3).

FIGURE 3

Blood vessel diameter measurements made from densitometer recording. Note negative in track ready for scanning, slit aperture over photomultiplier tube below, and synchronized recorder to the right.

All of the studies were performed on human volunteers who were informed of the known risks and paid for their participation. Appropriate and extensive safety precautions were taken to prevent injury to both subjects and experimenter. To our knowledge, no subject has experienced any ill effect from the experiments described.

THESES

A sound defense of the propositions set forth below depends upon a step by step construction of the experimental evidence validating each conclusion. We therefore urge the reader to bear with us if the earlier steps seem to require no discussion or to be self-evident. A careful appreciation of these earlier steps is essential for evaluation of the later propositions. Each of the sections to follow is titled by the

proposition to be defended in that section. The pertinent data are summarized in tables and plotted in graphic form in each section. To avoid unnecessary obfuscation and burdensome repetition, more detailed compilations of the data are included in an Appendix. Useful tables of equivalents and conversion factors may also be found there.

1. PREOXYGENATION IS EFFECTIVE IN PROLONGING VISION AFTER OCULAR CIRCULATORY IMPAIRMENT PRODUCED BY PRESSURE ON THE EYEBALL

Sixteen years ago Lambert and Bjurstedt[13] noted that increasing the oxygen tension in inspired air prolonged the latency of blackout produced by pressure on the eyeball. This brief report was apparently never expanded or followed by other work in the area. In 1964 Carlisle *et al.*[5] and Anderson and Saltzman[14] confirmed that preoxygenation prolonged the interval between the application of pressure to the eyeball and blackout. Furthermore, they showed that persistence of vision was roughly proportional to the theoretical blood oxygen tension existing prior to the application of pressure to the eyeball. Since hemoglobin under normal conditions is 96–98 per cent saturated in its passage through the lungs, the protection against ischemia afforded by preoxygenation is related to the additional oxygen which is dissolved in the blood and carried to the ocular tissues. The oxygen dissolved in the plasma (more accurately, blood water) is increased by increasing the atmospheric pressure at which the oxygen is inhaled. This is conveniently expressed as an increase in arterial blood oxygen tension in millimeters of mercury (mm Hg). It is important to realize that blood oxygen tension is not linearly related to blood oxygen content. The hemoglobin molecule is such an efficient carrier of oxygen that, to equal the oxygen delivered by hemoglobin (blood arterial oxygen tension of 93 mm Hg), arterial oxygen tension of about 7000 mm Hg is necessary.[15]

At a tension of 2000 mm Hg a "blood" without hemoglobin could transport enough oxygen in solution for normal tissue needs. At such very high blood-oxygen tensions, hemoglobin may remain very largely saturated during its transit through the circulation. When this occurs, hemoglobin's buffering and CO_2 transport functions are diminished and local tissue pCO_2 may increase slightly.[15]

It was easy to confirm that increases in blood-oxygen tension protect against subsequent retinal ischemia (Table 1). Before proceeding further two questions required answers: How long must the subject or patient be oxygenated to achieve the maximum protective effect? Is retinal circulation actually occluded by pressure on the eyeball?

TABLE 1. EFFECT OF OXYGEN ON BLACKOUT TIME

Atmos. pressure (mm Hg)	Times to blackout (sec.)				Mean of last 3 columns
0760	12.3*	16.4	16.8	15.1	16.1
1277	13.2*	20.7	22.5	27.2	23.5
1794	15.4*	36.0	36.4	...	36.2
2311	15.6*	55.8	62.0	53.8	57.2

*Period of preoxygenation 10 seconds or less.

2. VERY NEARLY THE MAXIMUM PREOXYGENATION EFFECT IS OBTAINED WITHIN TWO MINUTES

The lungs are very efficient oxygenators of blood. Normally the arterial pO_2 closely reflects alveolar pO_2. A small amount of unsaturated blood does enter the arterial circulation through the thebesian veins and from the bronchial and pleural circulations but its effect in lowering the arterial pO_2 is quite small. When the subject or patient stops breathing air and begins breathing oxygen, the alveolar pO_2 does not, however, rise to its maximum value at once. Several factors act to slow this rise.

With the first breath of oxygen, the 500 ml of oxygen in the first tidal inspiration must mix with the 2500 ml of air remaining in the lungs at the end of expiration (volumes are approximate). The alveolar pO_2 rises rapidly within a few breaths as the nitrogen in this lung compartment is replaced with oxygen. The gas in the lungs must, however, equilibrate with that dissolved in the body tissue. The replacement of body nitrogen with oxygen is a much slower process and complete replacement may require up to twelve hours of oxygen breathing.[16] For experimental purposes it is neither practical nor possible to preoxygenate for twelve hours. Not only is the time prohibitive, but oxygen convulsions would occur at higher atmospheric pressures after periods as short as thirty or forty minutes.[17]

To clarify this problem it seemed worthwhile to investigate two factors. One, the rise in arterial pO_2 with oxygen breathing, was studied by drawing timed arterial blood samples after the start of oxygen breathing both at ambient pressure and at an atmospheric pressure of 1,794 mm Hg (20 psi). It can be seen from Table 2 that 95 per cent or more of the level reached at three minutes has been obtained after 105 seconds of oxygen breathing. This is perhaps more clearly seen from the plot of these results (Figure 4). Included in this plot are additional data on the rate of return of arterial oxygen tension to initial levels upon resumption of air breathing.

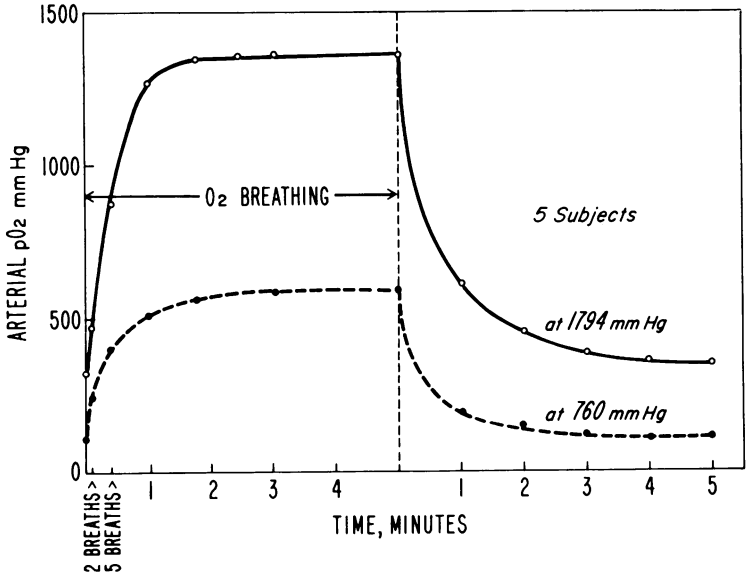

FIGURE 4

Rapidity of change in arterial oxygen tension at beginning of pure oxygen breathing and after resumption of air breathing.

TABLE 2. ARTERIAL pO_2 CHANGE WITH O_2 BREATHING*

Atmos. pressure (mm Hg)	Air	Arterial pO_2, mm Hg					
		2 breaths	5 breaths	60 sec.	105 sec.	180 sec.	300 sec.
760	105	241	402	514	557	587	583
1794	325	466	874	1268	1340	1361	1356

*Data from five subjects.

The second factor, the influence of the duration of preoxygenation on the time to blackout, was also investigated. One subject was studied at several different atmospheric pressures. A plot of the results obtained (Figure 5) illustrates that the greater part of the preoxygenation effect is obtained within one to two minutes. Similar data have been reported by Anderson *et al.*[18]

Because of the hazard of oxygen breathing at high atmospheric pressures and because of the penalty of decompression time for every minute of experimental time beyond standard exposure intervals, it is desirable to select the minimum preoxygenation time required for

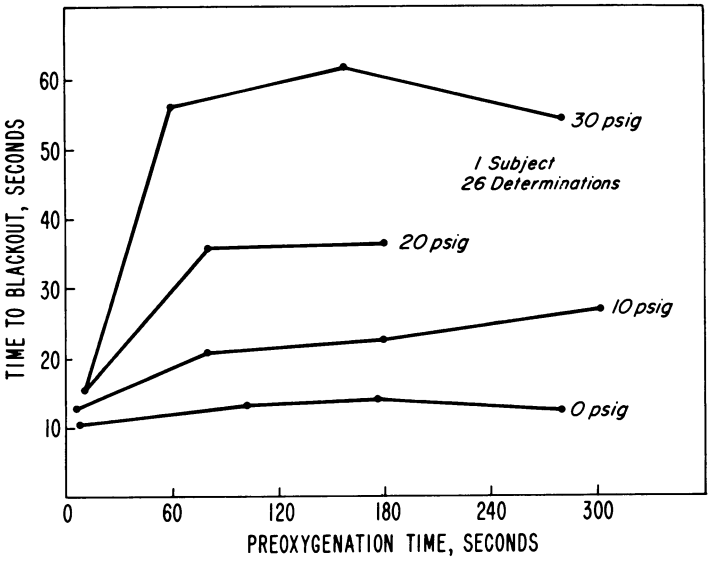

FIGURE 5

Duration of preoxygenation with 100 per cent oxygen compared with time to blackout.

meaningful results. Two minutes seemed to meet these criteria and this interval was selected as our standard preoxygenation time on the basis of the studies reported above and further experience to be detailed in later sections.

3. INCREASING THE INTRAOCULAR PRESSURE TO LEVELS ABOVE OPHTHALMIC SUPPLY PRESSURE BY OPHTHALMODYNAMOMETRY ELIMINATES THE RETINAL UPTAKE OF OXYGEN FROM THE EXTRAOCULAR CIRCULATION

It is possible that oxygen might leak into the eye in spite of the high intraocular pressures attained by ophthalmodynamometry. This might occur if the circulation were not completely occluded or if oxygen diffused through the ocular coats in significant amounts. Although diffusion through the cornea may occur, significant oxygenation of the macular area by this route is felt to be extremely unlikely. The cornea is not exposed to 100 per cent oxygen but to chamber air. The distances involved are long and the time for diffusion short. The resistance of the corneal stroma to diffusion of oxygen is so great that Heald and Langham[19] calculate that under normal conditions diffusion in the

reverse direction (endothelium to epithelium) could supply only one-fortieth of the respiratory needs of the epithelium. Friedenwald and Pierce[20] have also shown that aqueous pO_2 does not fall when the cornea is covered by a contact lens. When the circulation is occluded, oxygen utilization by the cornea, iris, ciliary body, and peripheral retina would deplete any oxygen that did traverse the corneal barrier. Oxygenation of the macular area by atmospheric oxygen must therefore be insignificant.

Another possible source of oxygen during the ischemic period might be the extraocular circulation. A direct method for testing for the possibility of a significant oxygen contribution from this source was devised.

At high atmospheric pressures the time to blackout, after pressure is applied to the eye, approaches one minute. In the usual experimental blackout procedure, the subject continues to breathe 100 per cent oxygen during this interval. If there were a significant leak of oxygen into the eye, the time to blackout should be shortened by switching the subject to breathing air immediately after the experimental intraocular pressure level was attained, since arterial pO_2 would be markedly reduced. If there were no significant leak and circulation were completely occluded, it should make no difference whether the subject breathed air or oxygen after pressure had been applied to the eyeball. The times to blackout with the subject breathing air and oxygen during the ischemic interval were therefore compared (Table 3). It would seem from these data that there is no significant leak of oxygen into the eye after pressure is applied to the eye by our technique. For this reason we feel justified in assuming that the circulation to the eye is effectively occluded by such pressure elevations and that there is no significant oxygenation by diffusion from the extraocular circulation.

In ophthalmodynamometry the systolic pressure is ordinarily taken to be that intraocular pressure which first obliterates the central artery pulsation at the disk. This is often called "retinal artery pressure." A more accurate term is "ophthalmic artery pressure" since the intraocular pressure necessary to obliterate the central artery pulse is considerably higher than that normally existing in the central retinal artery.[21] In our experiments, care is taken to exceed this ophthalmic artery pressure by 20 to 50 ophthalmodynamometric grams. The retinal arterial system under these conditions is blanched and pulseless. Although the choroidal system is normally invisible, it too lies within

TABLE 3. EFFECT OF AIR BREATHING DURING THE ISCHEMIC INTERVAL ON THE TIME TO BLACKOUT (seconds)

Subject	Atmos. pressure (mm Hg)	Gas inhaled	Blackout time continuous O_2 (sec.)	Blackout time air breathing (sec.)
002	990	O_2	19.0	18.0
006	990	O_2	18.4	18.3
002	990	O_2–CO_2	27.0	26.0
006	990	O_2–CO_2	22.6	21.2
007	2828	O_2	63.9	59.5
002	2828	O_2	75.0	82.0
006	2828	O_2	81.7	84.0
002	2828	O_2–CO_2	87.0	91.0
006	2828	O_2–CO_2	89.8	100.3
001	2828	O_2–CO_2	53.4	59.2
MEAN			53.8*	56.0
012	2311	O_2	36.7	47.8
012	2311	O_2	53.7	37.8
012	2311	O_2	42.6	42.9
022	2311	O_2	37.1	43.9
022	2311	O_2	35.6	34.4
022	2311	O_2	33.4	34.1
022	2311	O_2	33.1	32.8
MEAN			38.9	39.1
GRAND MEAN (both data sets)			46.4	47.6

*The preoxygenation time for this group was 5 minutes while that of the group breathing air during the ischemic interval was 10 minutes. In the experiment with subjects 012 and 022, the preoxygenation times were identical (2 minutes).

the relatively rigid scleral envelope and it too is supplied by the ophthalmic artery. We have also performed ophthalmodynamometry while directly observing large choroidal vessels (part 14). The pressures obtained from these choroidal vessels were similar to those obtained by observing the central retinal artery.

Since the intraocular pressure attained by our techniques is higher than that in the middle third of the ophthalmic artery, there is a good theoretic basis for stating that this pressure completely occludes intraocular circulation. The experimental results confirm this belief.

4. OXYGEN LACK IS THE IMMEDIATE CAUSE OF LOSS OF OCULAR FUNCTION WHEN OCULAR CIRCULATION IS OCCLUDED

In the experiments described above, the times to blackout are longer when the arterial oxygen tensions are high and shorter when the oxygen tensions are low. During hyperbaric oxygenation other factors

such as hemoglobin concentration, blood pressure, blood glucose, and arterial pCO_2 seem to remain constant or vary over very small ranges.[22] Increases in the time to blackout of 1000 per cent are obtained at 2,828 mm Hg (40 psi) with oxygen breathing. If no other energy substrate (glucose, for example) increases proportionately as the arterial oxygen tension is increased, it is implicit that oxygen lack is the immediate cause of loss of ocular function when ocular circulation is occluded. If the amount of available oxygen at the time of circulatory occlusion is progressively increased, the time to blackout progressively increases. In terms of retinal function, oxygen is therefore the most flow-limited metabolite. Elevated blood glucose levels might nevertheless have an effect. To test for such an effect, a series of determinations of time to blackout during intravenous administration of 5 per cent glucose and saline was compared with a similar series during intravenous administration of saline alone (Table 4).

TABLE 4. EFFECT OF GLUCOSE ON TIME TO BLACKOUT

	Saline	5 per cent glucose and saline
Blackout times (sec.)	8.2	8.0
	12.2	8.0
	12.8	11.7
MEAN	11.0	9.2

Intravenous glucose did not seem to offer any protection against ischemic blackout in this pilot study. Although the statistics are not significant because of the small number of determinations, there seemed to be less protection with intravenous glucose and saline than with saline alone. The study does illustrate, however, that increases in blood glucose do not produce very large increases in blackout times. If oxygen breathing caused an elevation of blood glucose, this elevation could not alone account for the manyfold increase in the time required for ischemic blackout. Studies on a diabetic patient also gave no indication of any glucose-related effect on blackout (part 8). Studies on isolated retina with electrical recording of light-evoked retinal responses have shown that reduction of glucose to levels as low as 30 mg/100 ml was well tolerated with no apparent effect on the evoked response.[23] There is therefore both *in vivo* and *in vitro* evidence that marked changes in retinal glucose levels can be tolerated without loss of function.

5. CORRELATION OF THE TIME REQUIRED FOR ISCHEMIC BLACKOUT WITH THE ARTERIAL OXYGEN TENSION EXISTING JUST PRIOR TO CIRCULATORY OCCLUSION PERMITS AN IN VIVO ESTIMATE OF HUMAN RETINAL OXYGEN UTILIZATION

If 100 per cent oxygen is inhaled at increasing atmospheric pressures, arterial oxygen tension also increases. A correlation of blood oxygen tensions with the time required for ischemic blackout depends upon a knowledge of the arterial oxygen tension existing in normal individuals with oxygen breathing at various atmospheric pressures. The ideal alveolar oxygen tension may be calculated quite simply, assuming a normal pCO_2 of 40 mm Hg and a body temperature of 37° C. It is merely the atmospheric pressure minus the alveolar pCO_2 and minus the water vapor partial pressure of 47 mm Hg. At an atmospheric pressure of 1,794 mm Hg (20 psi) the relationship yields an alveolar oxygen tension of 1707 mm Hg, while at sea level the tension would be 673 mm Hg ($paO_2 = 760 - 40 - 47$). Although equilibration of

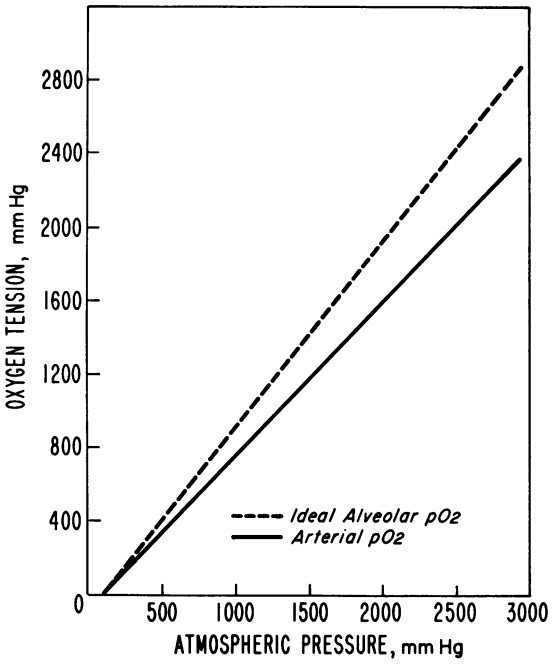

FIGURE 6

Difference between alveolar and arterial oxygen tension at various atmospheric pressures. Subjects breathing 100 per cent oxygen.

pulmonary blood with alveolar gas is rapid and the tensions are similar, measured blood arterial oxygen tensions do not reach alveolar levels.[24] The mean blood arterial oxygen tension found at 1,794 mm Hg atmospheric pressure after two minutes of oxygen breathing was 1,360 mm Hg (part 2). Similar studies at 2,311 mm Hg atmospheric pressure have yielded a value of 1,860 mm Hg. A comparison of alveolar pO_2 and experimental arterial pO_2 is plotted and the values are listed in Table 5. Some of these values are based upon extrapolations assuming a linear relationship.[22]

TABLE 5. ARTERIAL OXYGEN TENSIONS OF NORMAL MEN BREATHING 100 PER CENT OXYGEN

Atmos. pressure		Ideal alveolar pO_2 (mm Hg)	Actual arterial pO_2 (mm Hg)
psi	mm Hg		
0	760	673	550
4.45	990	903	740
10	1277	1190	985
20	1794	1707	1425
30	2311	2224	1860
40	2828	2741	2300

TABLE 6. MEAN TIMES TO BLACKOUT

Pressure (mm Hg)	760	990	1277	1794	2311	2828
Pressure (psi)	0	4.45	10	20	30	40
Time (sec.)	11.0	13.5	17.5	27.1	38.4	54.0

The times to blackout at atmospheric pressures of 760, 990, 1,277, 1,794, 2,311, and 2,828 mm Hg were measured in fourteen normal young men who were preoxygenated for two minutes. The mean times to blackout at these pressures are shown in Table 6. When these points are plotted (Figure 7) the curve is fairly linear. This curve also depicts the rate at which the retinal oxygen tension falls after the ocular circulation is occluded. This rate is a function of the slope of the line, not the absolute value of the time to blackout at any given point. This assumes that for each subject retinal oxygen utilization is constant, that blackout occurs when the oxygen tension declines to a given constant level, and that the amount of blood evacuated from the eye by the ophthalmodynamometric pressure is constant. It does not assume that these factors are the same for all subjects, only that for any given subject the factors are constant. To illustrate, one subject may have longer times to blackout at all pressure levels tested than

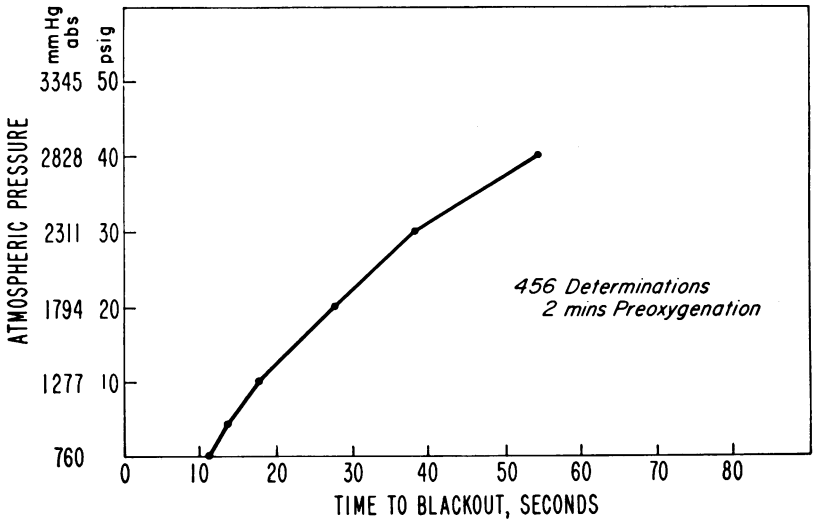

FIGURE 7

Increase in persistence of vision after circulatory occlusion with O_2 breathing at high atmospheric pressures.

another, but the oxygen utilization would be the same if the slopes of the two curves were similar. The subject with the longer time to blackout would have a greater metabolic reserve rather than a lower oxygen utilization.

With further assumptions, a calculation of the actual *in vivo* rate of oxygen utilization can be made. This calculation depends upon the solubility of oxygen in retinal tissue. Sendroy *et al.*[25] have calculated the solubility of oxygen in various biologic fluids and tissues. If their data are recalculated (assuming a body temperature of 37° C and that their actual atmospheric oxygen concentration was 20.938 per cent) the following tissue concentrations (in ml O_2/100 ml tissue) are obtained: white blood, 0.0031; plasma, 0.0028; water, 0.0031; 0.9 per cent saline, 0.0030; and red blood cells, 0.0035. We have selected 0.0030 as the solubility factor based upon the assumption that retinal tissue is of a highly vascular water-base type. The retinal oxygen concentration (ml O_2/100 ml retina) at any given pO_2 is therefore taken to be $0.0030 \times pO_2$. The change in tissue oxygen concentration in ml O_2/100 ml wet retina/min. can therefore be expressed as O_2 concentration $= pO_2 \times 0.0030 \times 60$. The oxygen uptakes for fourteen healthy subjects were computed from linear regressions of 462 times to blackout (Table 7). These data may be compared with the values

TABLE 7. OXYGEN UTILIZATION OF HEALTHY MEN

Subject	pO_2 rate of change (mm Hg/sec.)	O_2 utilization (ml O_2/100 ml/min.)	Q_{O_2} (ml/Gm dry/hr.)
001	53.4	9.6	39
002	33.7	6.1	25
003	52.3	9.4	39
004	30.6	5.5	23
005	26.2	4.7	19
006	32.1	5.8	24
007	40.9	7.4	30
012	19.4	3.5	14
013	40.5	7.3	30
016	48.4	8.7	36
017	39.2	7.1	29
018	50.7	9.1	37
019	42.5	7.7	31
020	32.9	5.9	24
MEAN±S.D.	38.8±10.2	7.0±1.8	28.6±7.5

obtained from smaller groups reported by Carlisle *et al.*[5] (three subjects) and Anderson and Saltzman[14] (four subjects). Their values were 8.7 and 9.7 ml O_2/100 ml wet retina/min., respectively. These high uptakes reflect the prodigious retinal capacity for energy production. Although in this experiment we are concerned primarily with respiration, the retina is also able to break down rapidly carbohydrate to lactic acid (glycolysis) with the production of energy. Glycolysis seems to proceed more rapidly under hypoxic conditions,[26] but, in the retina, lactic acid may be produced in quantity in the presence of oxygen (aerobic glycolysis).[27]

Oxygen utilization may be expressed in several ways. The most convenient for our purposes is the volume in milliliters of oxygen under standard conditions utilized in one minute by 100 ml of retina (wet tissue). A more classical method is the expression of oxygen uptake in terms of the volume in milliliters of oxygen utilized in one hour per gram of dehydrated retina (dry tissue). When expressed in these units, the notation Q_{O_2} may be used. The conversion of our data to this unit system depends upon the dry weight of 100 ml of wet retina and the specific gravity of wet retina. If values for cattle retina (see Appendix) are employed, Q_{O_2} may be obtained by multiplying the wet tissue values by 4.1.

The classical method of determining Q_{O_2} is by the use of excised tissue in a Warburg apparatus. The *in vivo* correlation is by no means exact since respiration (and glycolysis) of the excised tissue can be markedly influenced by changes in the medium bathing the tissue. It has been found for example that the rate of respiration is higher with

bicarbonate-buffered solutions than with phosphate-buffered solutions.[26,28] Some *in vitro* values for retinal Q_{O_2} are shown in Table 8. The retinal Q_{O_2} of 28.6 calculated from these oxygen uptake determinations is similar to many of the *in vitro* values in Table 8. There is, however, a basic difference between the two determinations. In the Warburg technique whole retinas are analyzed, while the loss of function in blackout may represent failure of but one link in the chain of

TABLE 8. IN VITRO DETERMINATIONS OF RETINAL Q_{O_2} (ML O_2/GM DRY/HR.)

Value	Year	Animal	Scientist	Reference
30.7	1926	Rat	Warburg	29
20.3	1933	Rat	Dickens & Greville	30
30.7	1935	Rat	Laser	31
34.0	1943	Rat	Craig & Beecher	26
16.2	1939	Cattle	Craig & Munro	32
22.4	1960	Rat	Graymore	28
12.4	1965	Cattle	Glocklin & Potts	33
14.0	1959	Cattle	Futterman & Kinoshita	34

visual cells. Duane[4] and Noell[35] maintain that the ganglion cell or its synapses are the most oxygen-sensitive cells in the visual chain. Whatever the sensitive cell, our values for oxygen utilization and Q_{O_2} apply to the tissue within oxygen diffusion distance of these cells. Furthermore, since the end point is loss of central vision, the cells are in the macular area.

The similarity of the values obtained with the two techniques suggests that the metabolism of the area of the retina responsible for blackout has respiratory characteristics similar to that of the retina studied as a whole.

6. THE RETINAL OXYGEN UTILIZATION OF A YOUNG MAN WITH OPEN-ANGLE GLAUCOMA WITHOUT FIELD LOSS DID NOT DIFFER SIGNIFICANTLY FROM THAT OF THE CONTROL GROUP

A 21-year-old college student was found to have an intraocular pressure of 32 mm Hg in the right eye and the left eye. He had requested examination for refraction and had no symptoms of glaucoma. Gonioscopy revealed chamber angles that were widely open. The visual fields were normal. The disks were slightly pale but not definitely cupped. The patient's father had been operated for advanced uncontrollable bilateral open-angle glaucoma some years before, and was said to have advanced glaucomatous field loss. Epinephrine alone did not control the patient's pressures. Pilocarpine was incapacitating

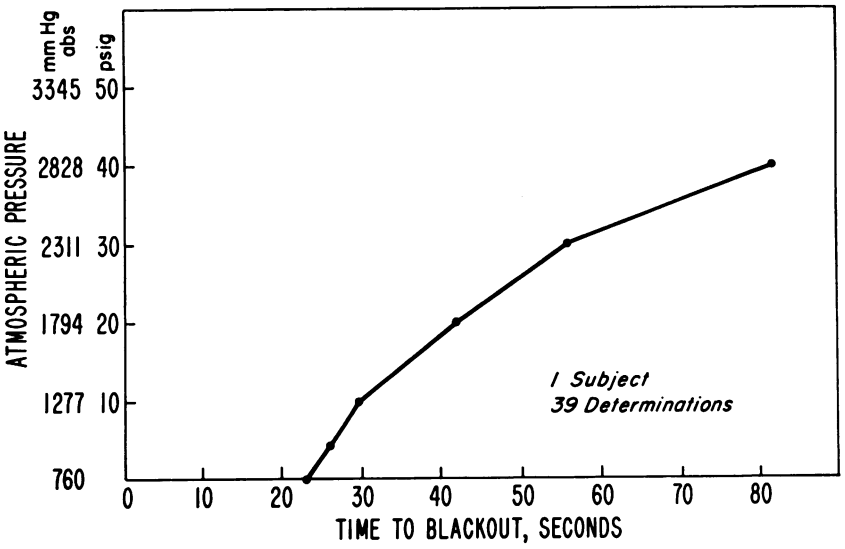

FIGURE 8
Resistance to ischemic blackout of a patient with glaucoma.

because of continuous variation in accommodative status. Ecothiophate (Phospholine) iodide 0.125 per cent and epinephrine did control intraocular pressure and were well tolerated. The patient was using these medications at the time of these studies.

Blackout was produced in the standard manner. A minimum of four minutes elapsed between blackout determinations. Blood oxygen and carbon dioxide tensions were determined during one series of blackout studies using the standard technique. (Bloods were drawn from an indwelling arterial Teflon catheter and analyzed on an Instrument Laboratories blood gas analyzer.) Four determinations at 990 mm Hg atmospheric pressure were made during decompression stops after the 2,828 mm Hg runs.

The times to blackout following circulatory occlusion are tabulated for the various atmospheric pressures in Table 9. Arterial pO_2 values are also listed in the same manner in Table 10. A complete tabulation of the data is included in the Appendix. Determination of a regression line, computation of the slope of this line, and comparison with the control group revealed no significant difference. The calculated retinal oxygen utilization for the glaucoma patient was 5.0 ml O_2/100 ml wet retina/min. (Q_{O_2} of 20) while that of the control group was 7.0 (Q_{O_2} of 29).

TABLE 9. BLACKOUT TIMES IN OPEN-ANGLE GLAUCOMA

Atmos. pressure (mm Hg)	760	990	1277	1794	2311	2828
Times to blackout (sec.)	20.9	28.8	29.4	40.2	53.0	61.2
	22.3	29.0	29.1	42.8	50.6	89.6
	28.6	31.1	32.5	41.8	52.5	93.2
	27.2	30.2	28.2	41.6	55.0	87.4
	18.1	22.2	29.3	42.5	53.2	83.2
	20.6	25.4	29.3	—	70.3	74.4
	18.1	22.3	31.0	—	—	—
	—	25.1	30.5	—	—	—
	—	22.9	30.0	—	—	—
	—	23.6	28.6	—	—	—
MEANS	22.3	26.1	29.8	41.8	55.8	81.5

TABLE 10. ARTERIAL OXYGEN TENSION IN OPEN-ANGLE GLAUCOMA

Atmos. pressure (mm Hg)	760	990	1277	1794	2311	2828
Arterial pO_2 (mm Hg)	625	1060	1140	1650	2010	2700
	—	1160	—	—	—	—
MEANS	625	1110	1140	1650	2010	2700

Although this patient's rate of oxygen utilization was within the normal range, it is quite possible that patients with advanced field changes will not have normal utilization rates by this method. Since loss of visual function in glaucoma patients may be related to chronic retinal ischemia, such patients would be particularly interesting to study. Recruiting subjects for this type of experiment is not easy since those with advanced field changes usually are of an age that cannot strictly be compared with our youthful control group. Jaeger[10] has pointed out the similarity between the progressive field loss in glaucoma and the progression of field loss in ischemic blackout. The open-angle glaucoma in this patient with a positive genetic history of the disease was not associated with a detectable metabolic respiratory abnormality in the macular region.

7. THE RETINAL OXYGEN UTILIZATION OF A PATIENT WITH PIGMENTARY RETINAL DEGENERATION DIFFERED MARKEDLY FROM THAT OF THE CONTROL GROUP

A 49-year-old man was initially seen with a chief complaint of progressive painless loss of vision for ten to twelve years and night blindness for nineteen years. There was no family history of a similar condition. Ten siblings, the parents, and eleven aunts and uncles were known not to be affected. Ocular examination revealed the typical fundus picture of retinitis pigmentosa. There were bilateral posterior

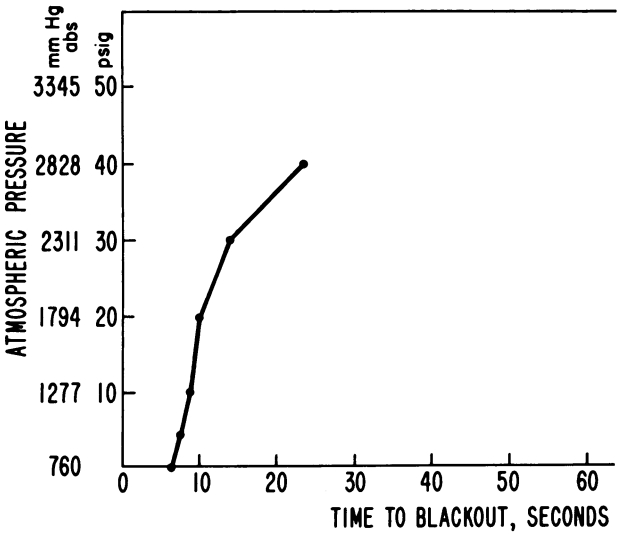

FIGURE 9
Resistance to ischemic blackout of a patient with retinal degeneration.

subcapsular polar cataracts. The pupils reacted to light and the visual fields were limited to less than five degrees bilaterally. Intraocular pressure was fifteen in each eye by applanation. Peripheral blood serologic tests for syphilis were reactive but the spinal fluid was negative. No electrical activity was found on electroretinography. This case may represent a syphilitic "pseudo-retinitis pigmentosa" or a true pigmentary dystrophy. The experimental procedure was explained and the patient consented to participate in the study. The method was similar to that previously described. The results are shown in Tables 11 and 12.*

The oxygen uptake calculated from these blackout values is 14.7 ml O_2/100 ml wet retina/min. (Q_{O_2} of 60). This is more than twice the normal uptake of 7.0 (Q_{O_2} of 29) and is significantly higher. As we have previously pointed out, the factor which determines the retinal oxygen utilization is not the absolute value of the time to blackout at any given pressure or arterial oxygen level but the slope of the line plotted through these points. In other words, although the times to blackout are short at all pressures tested, this in itself does not result

*For complete record of data, order NAPS Document 00246 from ASIS National Auxiliary Publications Service, c/o CCM Information Sciences, Inc., 22 West 34th Street, New York, New York 10001; remitting $1.00 for microfiche or $3.00 for photocopies.

TABLE 11. BLACKOUT TIMES IN PIGMENTARY DEGENERATION

Atmos. pressure (mm Hg)	760	990	1277	1794	2311	2828
Times to blackout (sec.)	6.5	8.2	8.9	12.1	15.4	35.3
	6.9	7.0	8.6	10.0	15.0	24.0
	5.8	7.1	9.2	9.2	12.3	24.9
	5.9	7.5	8.2	8.5	20.0	24.8
	5.9	7.1	—	9.8	11.3	13.9
	5.9	8.2	—	10.4	9.9	18.3
	7.0	—	—	—	—	—
	5.8	—	—	—	—	—
	6.9	—	—	—	—	—
	7.0	—	—	—	—	—
MEANS	6.4	7.5	8.7	10.0	14.0	23.5

TABLE 12. ARTERIAL OXYGEN TENSIONS IN PIGMENTARY DEGENERATION

Atmos. Pressure (mm Hg)	760	990	1794	2311	2828
pO_2 (mm Hg)	475	495	1140	1320	2840
	355	560	1080	885	1180
MEANS	415	528	1110	1102	2010

in the calculation of an abnormal retinal oxygen utilization. The absolute shortness or length of the times to blackout is a reflection of another parameter, the oxygen reservoir, metabolic reserve, or perhaps the tissue oxygen threshold necessary for function. It could also be argued that, unlike the normal subjects, equilibration of this patient's retinal tissue required more than two minutes of preoxygenation and that the higher the arterial oxygenation, the longer the time required. Strong evidence against this hypothesis is the fact that the blackout time at 2,828 mm Hg, while the subject was breathing air, was only 5.9 seconds as compared with a mean normal time to blackout under these conditions of 11.0 seconds. The equilibration time with air is essentially infinite as compared with the two-minute period employed for preoxygenation, and shortening of the time to blackout under these conditions could not be attributed to slow equilibration.

Another possible, but unlikely, explanation for these results is that a portion of the oxygen "reservoir" permitting vision under ischemic conditions is not in the form of molecular oxygen but in the form of high energy phosphate bonds. In the normal case more of these bonds might be manufactured in response to high oxygen tension than in response to low. The results could then be explained by the absence of such an oxygenation response in this patient. (If in the normal case the number of additional phosphate bonds manufactured at all hyperoxic levels were constant, loss of this capacity would alter neither the slope of the line nor the oxygen utilization value.)

It seems reasonable that the best explanation of the results is that retinal oxygen utilization is indeed abnormally high. In the study of hereditary pigmentary retinal degeneration in the mouse, rat, dog, and human, marked histologic, biochemical, and physiologic abnormalities can easily be found. The contribution of such observations to our understanding of the cause of the disease process is largely nullified by the difficulty in separating the effects secondary to cell death from those which produce cell death. This is a point of crucial importance. There is, for example, little doubt that the respiration of the retina as a whole is markedly reduced in the advanced state of dystrophy. It would be surprising if this were not so, since the disease is marked by progressive cell death eventually involving most of the neuroepithelium. Of much greater interest are the metabolic abnormalities of the functioning cells prior to death. This study is concerned with just such cells. The time necessary for loss of function is the experimental parameter, and oxygen tension in the region of these cells is the experimental variable. This study has shown that in the region of these cells, oxygen utilization is high and the metabolic reserve (oxygen reservoir) low. There is *in vitro* evidence that supports these conclusions.

In the mammalian retina, glucose may be oxidized *via* the hexose monophosphate shunt pathway.[36] In dystrophic rats between six and twenty-eight days of age, Reading[37] has shown that the activity of this shunt pathway was about double that of the normal controls. In C3H mouse retinas, Noell[38] has found that between the eighth and twelfth days of life, oxidation and aerobic glycolysis were higher than normal. He has stated (p. 62): "The increased metabolic activities prior to cell death suggest a failure of the cell to restrain oxidation and aerobic glycolysis." These studies do provide evidence of increased metabolic activity prior to cell death in dystrophic animal retinas.

If this finding can be confirmed in other patients with a definite genetic pattern of retinal dystrophy, perhaps the focus of future metabolic studies in these diseases can be sharpened. In this patient the oxygen uptake of functioning cells in the macular area was significantly higher than in the normal control group.

TABLE 13. BLACKOUT TIMES IN DIABETICS

Atmos. pressure (mm Hg)	760	990	1277	1794	2311	2828
Times to blackout (sec.)	6.2	13.9	12.1	21.9	36.9	46.6
	7.1	9.5	12.3	29.3	43.0	54.5
	6.1	10.0	10.4	35.4	40.7	56.4
		10.9				
MEANS	6.5	11.1	11.6	28.9	40.2	52.5

8. THE RETINAL OXYGEN UTILIZATION OF A PATIENT WITH DIABETES MELLITUS WITHOUT MARKED RETINOPATHY DID NOT DIFFER SIGNIFICANTLY FROM THAT OF THE CONTROL GROUP

A 46-year-old diabetic was admitted with gangrene of the left great toe and foot. He began a program of hyperbaric oxygenation to determine the effect of such treatment in delimiting the extent of the gangrene and in facilitating healing of the amputation site. During the course of these treatments, blackout studies were performed.

The patient had known of his diabetes for fifteen years. He stated that his vision in the right eye had always been somewhat poorer than that in the left, and his best corrected vision was found to be 20/40 on the right and 20/25 on the left. An exudate was noted in the left eye but no hemorrhages, microaneurysms, or areas of neovascularization were visible with the ophthalmoscope in either eye. Brachial blood pressure was 130/90 mm Hg and ophthalmodynamometry in the sitting position gave readings of 115/65 Gm in the right eye and 135/70 Gm in the left eye. No carotid bruit was heard. The experimental procedures were explained and the patient consented to participate in the study.

The method was similar to that previously described. The results are shown in Table 13.

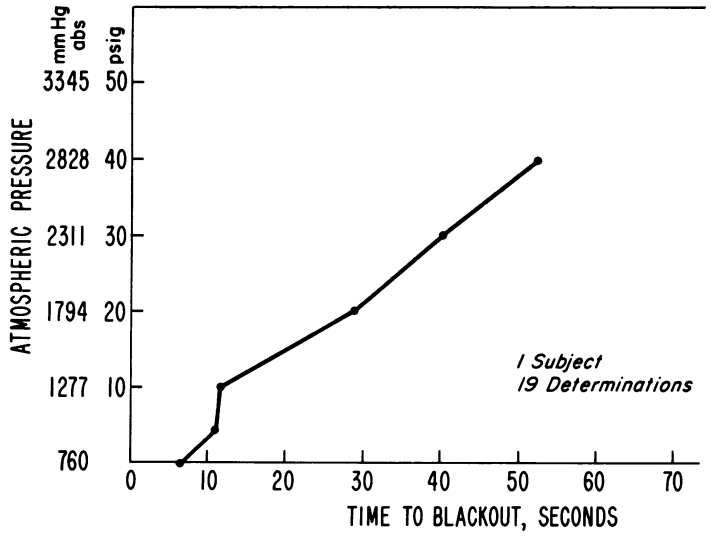

FIGURE 10

Resistance to ischemic blackout of a patient with diabetes mellitus.

Determination of a regression line, computation of the slope of this line, and comparison with the control group revealed no significant difference. The calculated oxygen utilization for the diabetes patient was 6.4 ml O_2/100 ml wet retina/min. (Q_{O_2} of 26) while that of the control group was 7.0 O_2/ 100 ml wet/min. (Q_{O_2} of 29).

Although retinopathy in this patient was not marked, a fifteen-year history of diabetes mellitus would be expected to produce changes, both vascular and metabolic in retinal tissue. Diabetic retinopathy is thought by many to develop as a response to localized and chronic retinal ischemia. It is interesting, therefore, that retinal oxygen utilization was within the normal range in this patient. The metabolic abnormality apparently had not affected oxygen utilization of retina in the macular area.

9. RECOVERY OF METABOLIC ENERGY STORES FOLLOWING ISCHEMIC BLACKOUT IS EXTREMELY RAPID AND REQUIRES LESS THAN TEN SECONDS UNDER NORMAL CONDITIONS

If the circulation to the eye is occluded by ophthalmodynamometry until blackout occurs and if pressure is immediately released, vision returns almost instantaneously. Although full visual function has returned, one might assume that the eye would be more vulnerable to loss of function if the circulation were again occluded within a short period of time. This vulnerability, or lack of complete recovery, would be revealed as a shortening of the period of ischemia necessary to produce a second blackout. Indeed, the shorter the recovery interval between the two circulatory occlusions, the more quickly one would expect the second blackout to occur. (If there were no recovery interval at all, blackout would be continuous.) On the other hand, when the second time to blackout is the same as the initial time to blackout, the recovery interval is long enough to allow complete restoration of energy reserves. In this manner one can study the dynamics of complete recovery from ischemic loss of function.

The subjects were outfitted with scuba breathing apparatus and eye patches as before. An illuminated fixation target was provided and ocular circulation was occluded with the transducer ophthalmodynamometer. In contrast to the previous studies, the kymograph was left running continuously in order that the recovery interval as well as the times to blackout could be measured directly from the tracings. The subjects continued to breathe oxygen without interruption from the start of preoxygenation through the period of the second blackout. The recovery interval and the atmospheric pressure of oxygen breathing were variables.

The factor of interest is the relationship between the recovery interval and the degree of shortening of the second time to blackout. The degree of shortening was determined by taking the mean initial time to blackout for each subject at each environmental pressure and subtracting the second time to blackout from this value. In Table 14, shortening of the time to blackout is tabulated for various atmospheric pressures according to the duration of the recovery interval.

The data in this study strikingly demonstrate the rapid recuperative powers of the retina. This rapid recovery is not merely a return of function (which is almost instantaneous when the plunger is removed), but includes the restoration of metabolic stores to their original levels as determined by normal resistance to subsequent ischemic blackout. From the family of curves plotted at various atmospheric pressures it can be seen that the interval necessary for complete recovery approximates the persistence of vision after circulatory occlusion at a given atmospheric pressure. Or, if it requires ten seconds for blackout to occur after circulatory occlusion, it will require roughly ten seconds for complete recovery to occur. At normal atmospheric pressure with the subjects breathing air, the intervals become so short that measurement errors become proportionately quite large. Nevertheless, this oversimplified relationship seems to hold. Under normal conditions complete recovery requires less than ten seconds and probably about four to six seconds in the usual case. The reader may perform his own experiment by observing the sweep second hand of his watch and pressing gently but firmly on the globe through the lid, closing the opposite eye. Note the time pressure is applied. Remove pressure when blackout occurs and note the time. Pause four seconds and repeat the procedure. The second time to blackout will be similar to the first. This recovery time closely approximates the mean retinal circulation time of 4.7 seconds as measured by fluorescence angiography.[39] During the recovery interval, oxygen is used both in cell respiration and in paying off the metabolic debt incurred during the previous circulatory occlusion. It would seem unlikely that one exchange of blood could completely meet both of these needs. There is evidence, however, that blood flow may temporarily increase in response to ischemia of this type.

Vasodilatation in response to accumulation of carbon dioxide and lactic acid may result in large increases in retinal and perhaps choroidal blood flow. An increase in retinal small vessel blood flow can be observed entopically quite easily after blackout. (Blue sky makes a good background for these observations.) Following positive G blackout with direct observation of the fundus, a "ballooning" of the

TABLE 14. DEGREE OF SHORTENING OF SECOND BLACKOUT*

Subject code	Atmos. pressure (mm Hg)	Duration of recovery interval (sec.)									Mean seconds to first blackout
		2	4	6	8	10	12	14	16	18	
002	760					3.4		(2.3)		(2.5)	16.2
003	760	2.9		0.0	1.0	(0.1)		(1.2)	(1.3)		6.4
005	760	1.8		(0.3)	0.4	0.2		(0.3)	(2.4)		8.7
				(1.3)							
006	760	7.1	4.5								15.3
		4.3									
007	760					0.1		(0.5)	0.7		14 9
Means		4.0	4.5	(0.5)	0.7	0.9		(1.1)	(1.0)	(2.5)	12.3
002	990					5.1		3.5	1.3		20.7
003	990	2.9		(0.6)	(3.0)						9.4
					(1.8)						
004	990	9.5	5.5	(1.4)							21.1
				2.8		4.3	1.3				
005	990				2.0	(0.4)		(2.1)			10.7
006	990	7.7		2.1	1.5	(2.1)					15.7
007	990	9.8		7.2	3.8	1.7					17.6
Means		7.5	5.5	2.1	0.5	1.7	1.3	0.7	1.3		15.9
002	1277		9.6		4.6	3.4					21.8
003	1277		1.6		(0.1)	(4.2)					11.5
004	1277		13.7		6.2	5.7		3.9			26.9
005	1277		3.1		1.7	0.0					12.8
006	1277		4.4	3.6		0.3					19.0
007	1277		9.5		3.3	4.1					20.4
Means			7.0	3.6	3.1	1.6		3.9			18.7

*When second time to blackout *exceeds* the first, parentheses are used to indicate the difference is of opposite sign.

TABLE 14. (Continued)

Subject code	Atmos. pressure (mm Hg)	Duration of recovery interval (sec.)													Mean seconds to first blackout
		4	6	8	10	12	14	16	18	20	22	4—30	32		
002	1794			9.4	(3.4)	7.2	(3.0)	5.4							33.0
003	1794				1.3	0.1									21.1
004	1794			12.4	9.2	12.6									43.1
005	1794			4.9	5.4		(1.2)	1.9							23.6
006	1794			6.0	3.1		(2.1)	(1.5)							28.2
007	1794			7.5	0.4		1.4								28.2
	Means			8.0	2.7	6.6	(1.2)	1.9							29.5
002	2911			10.4		11.8		(3.0)	1.5	(0.3)					39.9
003	2911		9.4	2.3	0.5	(1.3)									23.0
004	2911				27.2		8.7		4.8	(12.6)					53.0
005	2911					5.4		0.8							36.1
		18.4		12.0		10.7									
006	2911				6.7		3.4		2.8	1.3					45.8
007	2911			15.2		7.2	2.7		0.8	(4.7)					39.1
						4.1			2.5						
	Means	18.4	9.4	10.0	11.5	6.3	4.9	(1.1)	2.5	(4.1)					39.5
002	2828	41.1	15.8										0.8		67.3
003	2828	33.7	4.8	8.5								0.6	9.6		39.6
		22.3													
		19.6						(4.2)		(6.5)					
004	2828					9.1					2.2		(7.7)		66.4
005	2828		40.0	27.4	19.7					22.1			10.6		74.4
006	2828			16.2	17.4	16.9			(1.6)		2.5			(0.7)	60.3
						10.3									
007	2828				4.7		17.3			15.9	9.3				54.9
					6.1	4.9									
	Means	29.2	20.3	17.3	12.0	10.3	17.3	(4.2)	(1.6)	10.5	4.7	0.6	3.3	(0.7)	60.5

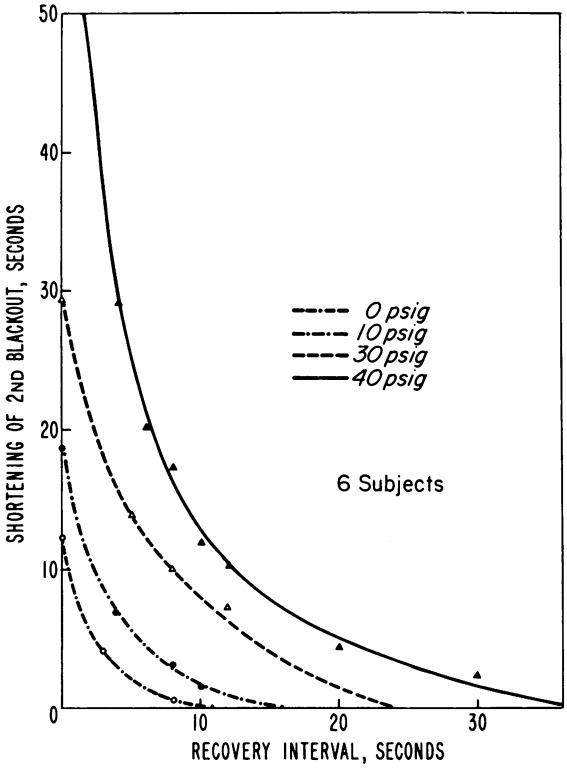

FIGURE 11

Effect of recovery interval after blackout in shortening the time to repeat blackout.

vascular tree immediately after restoration of circulation has also been described.[11] Although repeated attempts to discover autonomic innervation of small retinal vessels have been fruitless,[40] the peripheral resistance of the retinal circulation seems to drop in response to ischemia and rise in response to hyperoxia. The magnitude of this autoregulatory control mechanism seems to be quite large in our young healthy subjects.

The extent of recovery with any given interval can be assayed at high blood oxygen levels because the entire process is temporally expanded. Using short recovery intervals under these hyperbaric conditions it is possible to plot a family of recovery curves. Indeed, we can make a quantitative description of changes in retinal oxygen tension with time both after circulatory occlusion and during recovery from ischemic blackout. In Figure 12, for example, select any initial arterial

oxygen tension and its corresponding point on the single left-hand curve. The time required for ischemic blackout to occur, starting with this oxygen tension, can be read to the left from the time scale. The rate at which retinal arterial oxygen tension falls is represented by the curve. The knee in the curve at oxygen tensions below 100 mm Hg represents hemoglobin desaturation. Blackout occurs at zero time. Now select any recovery interval and the curve representing the atmospheric pressure at which oxygen is breathed during recovery. The recovery interval necessary to return retinal oxygen tension to any given level can now be determined from this curve. The dotted lines represent the fall in oxygen tension when circulation is again occluded and may be used to predict persistence of vision after any recovery interval. This plot graphically illustrates the very large circulatory reserve of the retina. Following the experimental transient ischemic attack, full metabolic recovery is possible in ten seconds with oxygen breathing at normal pressure. With air breathing at normal pressure full recovery occurs at even shorter intervals. If the retinal circulation time is about five seconds, complete recovery occurs in less time than is required for two arteriovenous transits. Oxygen transport in the retina proceeds rapidly.

10. THE ADDITION OF SMALL AMOUNTS OF CARBON DIOXIDE DURING PREOXYGENATION INCREASES RESISTANCE TO ISCHEMIC BLACKOUT

In part 4 we defended the thesis that oxygen lack was the immediate cause of ischemic blackout. Another possible, though unlikely, cause of such blackout might be the accumulation of carbon dioxide. It could be argued that although blackout under our conditions is directly

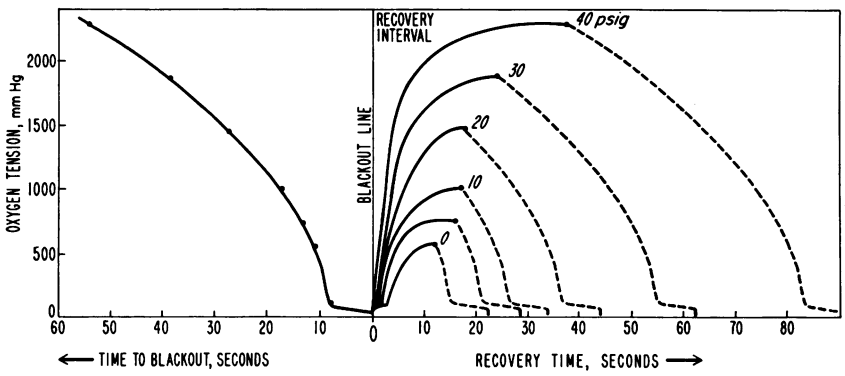

FIGURE 12

Changes in retinal pO_2 with blackout, recovery, and subsequent blackout (dotted lines).

oxygen related, the actual cause of blackout is not oxygen lack but the accumulation of the oxidation product, carbon dioxide. If such were the case, the time to blackout at any given preoxygenation level might be shortened by the addition of carbon dioxide to the breathing mixture. The time to blackout might also be shortened because the addition of carbon dioxide would require that there be less than 100 per cent oxygen in the breathing mixture. The arterial pO_2 at the end of the preoxygenation period would therefore be reduced.

In the design of an experiment to test the physiologic effect of carbon dioxide at various atmospheric pressures it seemed reasonable to attempt to maintain a relatively constant alveolar partial pressure of carbon dioxide rather than to establish a constant composition by per cent. If, for example, 1 per cent carbon dioxide were included in the inspired gas, at normal pressure (760 mm Hg) the partial pressure of the gas would be 7.6 mm Hg while at 2,828 mm Hg (40 psi) the partial pressure of the carbon dioxide would be 28.3 mm Hg.

A consequence of this decision is that a higher percentage of carbon dioxide (with less oxygen) is required in the inspiratory gas at low atmospheric pressures. Separate gas mixtures were therefore made up for the various atmospheric pressures. After mixing, the carbon dioxide content was checked on an infra-red carbon dioxide analyzer (Liston–Becker, Model 16 Gas Analyzer). The analysis technique of Scholander was employed to calibrate this analyzer. In the actual experiment, the subject was begun on 100 per cent oxygen breathing and blackout measurements were made at intervals of 120, 300, 600, and 900 seconds. The subject was then switched to an O_2–CO_2 mixture calculated to produce a partial pressure of carbon dioxide of about 30 mm Hg. Blackout determinations were made at similar intervals after

TABLE 15. EFFECT OF SMALL AMOUNTS OF CO_2 ON BLACKOUT TIME*

Condition	No. of determinations	Mean (sec.)	% Increase
4.45 psi 100% O_2	18	18.3	
$O_2 + CO_2$	18	21.4	17.0
10 psi 100% O_2	22	22.0	
$O_2 + CO_2$	21	26.3	19.6
20 psi 100% O_2	23	34.7	
$O_2 + CO_2$	24	44.5	28.2
30 psi 100% O_2	21	49.6	
$O_2 + CO_2$	21	71.5	24.3
40 psi 100% O_2	20	67.9	
$O_2 + CO_2$	17	75.2	14.1

*Alveolar pCO_2 approximately 30 mm Hg. Subjects were six normal young males.

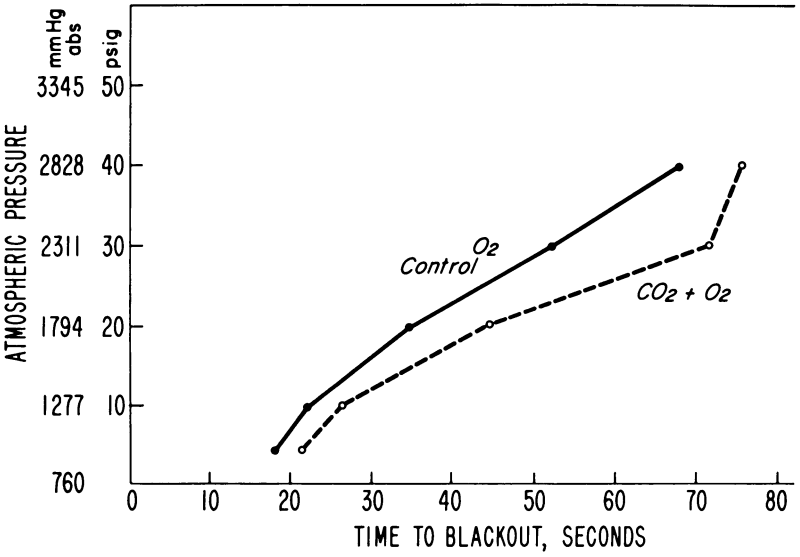

FIGURE 13

CO_2 and O_2 are more effective in prolonging vision than O_2 alone.

the start of O_2–CO_2 breathing. The results of 199 determinations upon six subjects are listed in Table 15 and plotted in Figure 13.

It is apparent that the addition of small amounts of carbon dioxide to the breathing mixture does not shorten the time to blackout at the pressures tested. If carbon dioxide had no effect or if the gas acted as a metabolic poison, shortening of the time to blackout would be expected. We have observed the opposite. The data clearly show that carbon dioxide and oxygen in the concentrations used in these experiments is more effective in protecting against ischemic blackout than is oxygen alone. The causes of such an effect are not immediately apparent. As will be discussed in part 14, oxygen is an effective vasoconstrictor of the retinal circulation. Although carbon dioxide may be ineffective or poorly effective in vasodilating retinal vessels under normal conditions, concentrations of carbon dioxide similar to those used in this experiment may prevent the vasoconstriction produced by oxygen. This effect would result in better perfusion of the retinal tissues during the preoxygenation period and might account for the observed prolongation of the time to blackout. (The slopes of the curves are similar and oxygen utilization is therefore unchanged or only slightly affected.)

High cerebral oxygen tensions are known to produce convulsions. Cerebral vasoconstriction in response to oxygen breathing may partially protect against this toxic effect. For the brain as a whole, carbon dioxide appears to have the effect of a vasodilator, since the addition of small amounts of carbon dioxide to the inspired gas enhances oxygen convulsions and raises jugular pO_2. The situation is not completely analogous to that in the retina since the retinal vessels (as opposed to the choroidal) apparently have no autonomic vasomotor control.[40,41] There is indirect evidence that carbon dioxide may lower retinal peripheral resistance.[42] It is these considerations that lead us to hypothesize that the carbon dioxide effect may be related to better retinal perfusion during the preoxygenation period.

A flaw in this hypothesis is that the oxygenation times in this experiment were deliberately made quite long (up to fifteen minutes) in order to saturate the retinal tissues before each determination. If the hypothesis is correct, the oxygen-induced retinal vasoconstriction must be severe enough to reduce tissue oxygen delivery to the point where tissue utilization produces a 20 per cent reduction in local oxygen stores. The addition of small amounts of carbon dioxide then prevents this vasoconstriction and eliminates the deficit. In view of the evidence for rapid retinal transport (part 9) and the observed oxygenation of retinal venous blood, such a mechanism seems unlikely.

It is also possible that elevated retinal-tissue carbon dioxide tensions have an oxygen-sparing effect. Craig and Beecher,[43] for example, found that carbon dioxide concentrations of 5–20 per cent depressed the oxygen uptake of whole retinas studied *in vitro*. Smaller carbon dioxide concentrations, however, doubled respiration and glycolysis when a constant *p*H was maintained. We find no evidence of a change in oxygen utilization in this study.

It would seem that at least part of the carbon dioxide effect must occur during the preoxygenation period, for, after circulatory occlusion, tissue pCO_2 must rise quite rapidly. Although carbon dioxide in the concentrations employed in this experiment does produce hyperventilation, this does not result in higher arterial oxygen tensions. Indeed, since the alveolar partial pressure of oxygen is lower, the maximum attainable arterial oxygen tension is correspondingly reduced. It is possible to elevate tissue carbon dioxide tension without elevating arterial carbon dioxide tension. This can be done with carbonic anhydrase inhibitors such as acetazolamide (Diamox). In part 11 the effect of acetazolamide on the time to blackout will be described.

The results of this study suggest that the addition of small amounts of carbon dioxide to pure oxygen results in more efficient retinal oxygenation. If oxygenation is employed in the treatment of acute retinal ischemia, the addition of small amounts of carbon dioxide may be of value.

11. INTRAVENOUS CARBONIC ANHYDRASE INHIBITOR (ACETAZOLAMIDE) GIVEN PRIOR TO PREOXYGENATION INCREASES RESISTANCE TO ISCHEMIC BLACKOUT

Acetazolamide (Diamox) is a non-competitive inhibitor of carbonic anhydrase. Carbonic anhydrase is the enzyme which catalyzes the hydration or dehydration reaction: $CO_2 + H_2O \leftrightharpoons H_2CO_3$. Central nervous system symptoms such as somnolence and paresthesias may be effects of the administration of this drug. Recent evidence indicates that the drug may also reduce the peripheral vascular resistance of the brain.[44] This circulatory effect is probably the result of increased tissue carbon dioxide tension. The increase in pCO_2 probably occurs in other tissues including the eye and is the result of impaired carbon dioxide transport and elimination. In addition to lowering the intraocular pressure, acetazolamide might also act to increase retinal pCO_2. If the prolongation of the time to blackout noted with the addition of carbon dioxide were the result of increased retinal pCO_2, acetazolamide might have a similar effect. This study was designed to test for such an effect.

The subjects were prepared for the blackout experiment in the usual manner with the exception that an intravenous infusion of normal saline was started in an arm vein and a three-way stopcock was attached to the tubing near the needle. At the selected atmospheric pressure, the subjects were preoxygenated for 120 seconds and a time to blackout determined. Blackout was repeated three times with intervals between blackouts of four minutes. Five hundred milligrams of acetazolamide (or 20 ml of normal saline as a placebo) was then injected through the stopcock. Five minutes later, preoxygenation was begun. Seven minutes after the injection, the first blackout determination was made. Four minutes elapsed between determinations and three determinations were made after each acetazolamide injection. With each subject there was a minimum of three control and three drug determinations at each atmospheric pressure. The results of 160 determinations upon five subjects are listed in Table 16 and plotted in Figure 14.

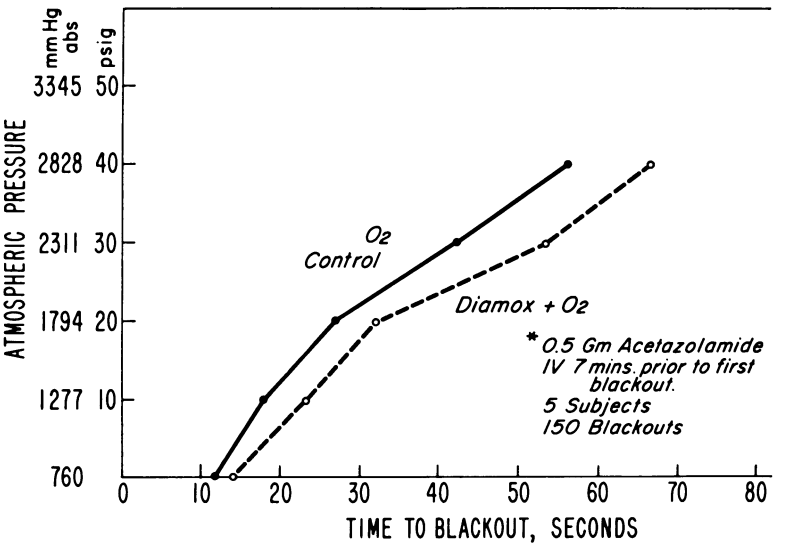

FIGURE 14

Diamox and O_2 are more effective in prolonging vision than O_2 alone.

Acetazolamide appears to protect against ischemic blackout in a manner similar to that of carbon dioxide. The mechanism, increased retinal pCO_2, may be the same in both cases. The ocular localization of ^{35}S-labeled acetazolamide is highest in the inner layers of the retina and in the iris and ciliary processes.[45] There is good evidence, therefore, that the drug does reach the retina. Pharmacologic studies have shown that the inhibition of carbonic anhydrase by the drug results in a rise in tissue and venous pCO_2 independent of change in oxygen tension.[46] Clinical studies have indicated that acetazolamide increases the oxygen available to an ischemic brain by increasing cerebral blood flow.[44,47] For this reason the drug is increasingly employed in the treatment of stroke victims.

This experiment indicates that acetazolamide may have a similar

TABLE 16. EFFECT OF ACETAZOLAMIDE ON BLACKOUT

Pressure (mm Hg)	760	1277	1794	2311	2828
No. sec. before drug	11.7	18.1	27.1	51.0	56.3
No. sec. after drug	14.1	23.2	32.1	65.9	66.6
No. sec. before placebo	(6 determinations) 55.3				
No. sec. after placebo	(6 determinations) 42.9				

effect in the eye. In patients with acute embolic retinal occlusions or partial occlusions, intravenous acetazolamide, in addition to its beneficial ocular hypotensive effect, may act to relieve vasospasm (by vasodilation), lower peripheral resistance, and increase flow. In hyperoxygenation therapy, the hyperventilation and sensation of asphyxia associated with carbon dioxide breathing are avoided and the vasoconstriction associated with oxygen breathing may be partially overcome. Intravenous administration of 0.5 Gm of acetazolamide and subsequent oral use of the drug may prove of value in the management of the acute ocular ischemic insult. Collateral retinal vascular channels do develop in time.[48] Therapy during the acute states of retinal vascular disease may limit the extent of the retinal infarct.

12. VERY HIGH ARTERIAL OXYGEN TENSIONS PRODUCED NO VISUAL FIELD ABNORMALITIES IN HEALTHY MEN AFTER FIFTEEN MINUTES OF OXYGEN BREATHING

In one of the earliest reports on the ocular effects of prolonged hyperoxia in man, Behnke *et al.*[49] described concentric constriction of the visual fields. This constriction was so severe that the diameter of the field was reduced to 20 degrees as measured with a 6/250 white isopter with about seven foot-candles of illumination. The constriction occurred after 210 minutes of 96–99 per cent oxygen breathing at three atmospheres absolute (2,280 mm Hg). The defect did not persist but gradually disappeared with air breathing at normal pressure after a period of 50 minutes. This visual field loss was associated with other toxic signs such as dilatation of the pupils, stupefaction, and a rise in blood pressure. There have been no other reports of similar visual field loss in healthy adults exposed to hyperoxic conditions but migraine scotomas have been observed following decompression.[50]

It seemed worthwhile, therefore, to investigate with more sensitive techniques the effect of very high blood-oxygen tensions on the visual fields of healthy young men. With such techniques visual field changes might be discovered before the onset of other toxic symptoms. To avoid oxygen convulsions and other serious side effects, we limited the exposure of our subjects to 20 minutes. They were, however, breathing 100 per cent oxygen at 3.04 atmospheres absolute (2,311 mm Hg), and had slightly higher arterial oxygen tensions than Behnke's subjects.

A Haag-Streit projection perimeter designed by Goldmann was set up and calibrated in the hyperbaric chamber. Using the photoelectric cell, the background brightness was set at 47.25 apostilb and the brightness of the isopter at 1,500 apostilb. The white target was 1/16

mm^2 in area. Lights in the chamber other than those of the perimeter were extinguished during calibration and during the experiments. The subjects were seated at the perimeter with the scuba mouthpiece, hoses, and nose clip positioned so as not to obstruct the upper 75 per cent of the visual field. The upper temporal quadrant was tested by moving the target from blind toward seeing field at a constant slow rate of approximately 20 degrees per second. Seven points at 15-degree intervals from horizontal to vertical were each checked twice in reverse order. Determinations on each of three subjects were made under the following conditions: (1) normal atmospheric pressure breathing air; (2) normal atmospheric pressure after oxygen breathing for 15 minutes; (3) at 2,311 mm Hg pressure after air breathing for 8 minutes; (4) at 2,311 mm Hg pressure after 100 per cent oxygen breathing for 7 minutes; and (5) at 2,311 mm Hg pressure after 100 per cent oxygen breathing for 15 minutes.

No significant change in the visual fields was noted under any of the conditions tested. The major difference between our experiment and that reported by Behnke lies in the duration of exposure. In this experiment purer oxygen was inhaled at slightly higher atmospheric pressure for a much shorter period. Measurements were made by a much more sensitive technique at high pressure with the subjects breathing oxygen and not after return to normal atmospheric pressure and air breathing as in Behnke's work. The lack of field changes under our conditions and the association of other toxic signs and symptoms in the Behnke experiment lead us to believe that central nervous system and cardiovascular toxic effects may have played a significant part in the field loss these authors reported. We find no visual field changes in healthy men breathing 100 per cent oxygen at 2,311 mm Hg for 20 minutes.

13. VERY HIGH ARTERIAL OXYGEN TENSIONS FOR DURATIONS APPROACHING THE CONVULSIVE THRESHOLD DO NOT AFFECT DARK ADAPTATION

Impairment of dark adaptation in man during hypoxia, and recovery of normal adaptation following return to more normal alveolar oxygen tensions has been demonstrated by McFarland and Evans[51] and McDonald and Adler.[52] Shard,[53] Eckel,[54] and Herlocker *et al.*[55] found no significant change in dark adaptation when subjects were breathing oxygen at or below normal pressure (760 mm Hg). The effects of oxygen breathing at higher than normal atmospheric pressure have not previously been studied.

The experiment was designed to follow the method used by McFar-

land and Evans in their study of hypoxic dark adaptation. Following an initial ten-minute period in the dark, each subject was light adapted for three minutes to a luminance of 150 millilamberts of white light. The absolute threshold to white light during a 20-minute period was then determined at 30-second intervals by slowly increasing the intensity of the test light until the subject responded to the stimulus by tapping a coin. All tests were binocular with the red fixation point 11 degrees superior to the circular white test field of the Goldmann–Weekers Dark Adaptometer. The test field subtended 11 degrees at the cornea. The maximum intensity of the test light was standardized at 5.7 lux before each adaptation experiment.

The five subjects whose control dark adaptation curves were most consistent were then tested in the hyperbaric chamber at 15 psi (1,536 mm Hg) and 30 psi (2,311 mm Hg) while breathing 100 per cent oxygen through a scuba mouthpiece with demand regulator and nose clip. The subjects breathed oxygen for two minutes before the intial ten-minute period in the dark and during the three-minute light-adaptation period for a total of 15 minutes of oxygen breathing at pressure before the first thresholds were measured. The total exposure to 100 per cent oxygen was 35 minutes. The potential hazards of this procedure were explained to each subject before entering the chamber. In addition to the experimenter, a physician was in the chamber with the subject during each test at 30 psi. Either before or after each determination at elevated pressure, a control curve was plotted in the chamber with the subject breathing air at normal atmospheric pressure through the same equipment.

One subject complained of dizziness and twitching about the mouth after breathing 100 per cent oxygen for 21 minutes at 30 psi and oxygen breathing was therefore discontinued. Another subject developed an upper respiratory tract infection and could not undergo compression easily. Each of the three remaining subjects was tested on separate occasions at 30 psi, 15 psi, and 0 psi. The results are summarized in Table 17. A typical set of points for a single subject is plotted in Figure 15. Thirty-five minutes of oxygen breathing at 15 and 30 psi did not affect dark adaptation as measured by our technique.

Exposures to very high partial pressures of oxygen have produced convulsions,[56] cytoid body retinal infarcts,[57] retinal detachment,[58] attenuation of the electroretinogram,[59] and areas of brain necrosis[60] in animals. Oxygen at pressure is known to produce convulsions in man.[61] More subtle effects on human ocular and central nervous system functions seem likely. The metabolic and neural processes involved in dark

TABLE 17. ABSOLUTE THRESHOLD TO WHITE LIGHT FOLLOWING PRE-ADAPTATION WITH 150 MILLILAMBERTS WHITE LIGHT FOR 3 MINUTES (ALL VALUES EXPRESSED IN MILLILUX (±S.D.))

Conditions	No. of determinations	Subject	Time in dark (min.) 1	2	5	10	15	20
Air	8	A	25 (±10)	11 (±5)	1.8 (±0.7)	0.28 (±0.11)	0.17 (±0.05)	0.14 (±0.04)
0 psi	7	B	8.7 (±6.9)	2.9 (±2.2)	0.47 (±0.39)	0.053 (±0.017)	0.028 (±0.008)	0.022 (±0.006)
	5	C	9.7 (±1.6)	4.0 (±0.8)	0.68 (±0.23)	0.096 (±0.017)	0.055 (±0.009)	0.056 (±0.008)
		Mean	14	6.0	0.98	0.14	0.084	0.073
100% O_2	3	A	22 (±4)	9.7 (±3.3)	1.6 (±0.7)	0.28 (±0.14)	0.17 (±0.07)	0.15 (±0.06)
15 psi	1	B	8.0	2.3	0.25	0.046	0.034	0.023
	1	C	8.0	2.9	0.43	0.080	0.051	0.046
		Mean	13	5.0	0.76	0.14	0.085	0.073
100% O_2	2	A	32 (±10)	1.4 (±0.5)	1.7 (±0.8)	0.35 (±0.02)	0.19 (±0.03)	0.16 (±0.01)
30 psi	3	B	7.4 (±4.6)	2.6 (±1.8)	0.35 (±0.19)	0.047 (±0.018)	0.021 (±0.009)	0.019 (±0.007)
	2	C	12 (±1)	4.8 (±1.2)	0.63 (±0.08)	0.11 (±0.01)	0.060 (±0.004)	0.040 (±0.002)
		Mean	17	2.9	0.89	0.17	0.090	0.073

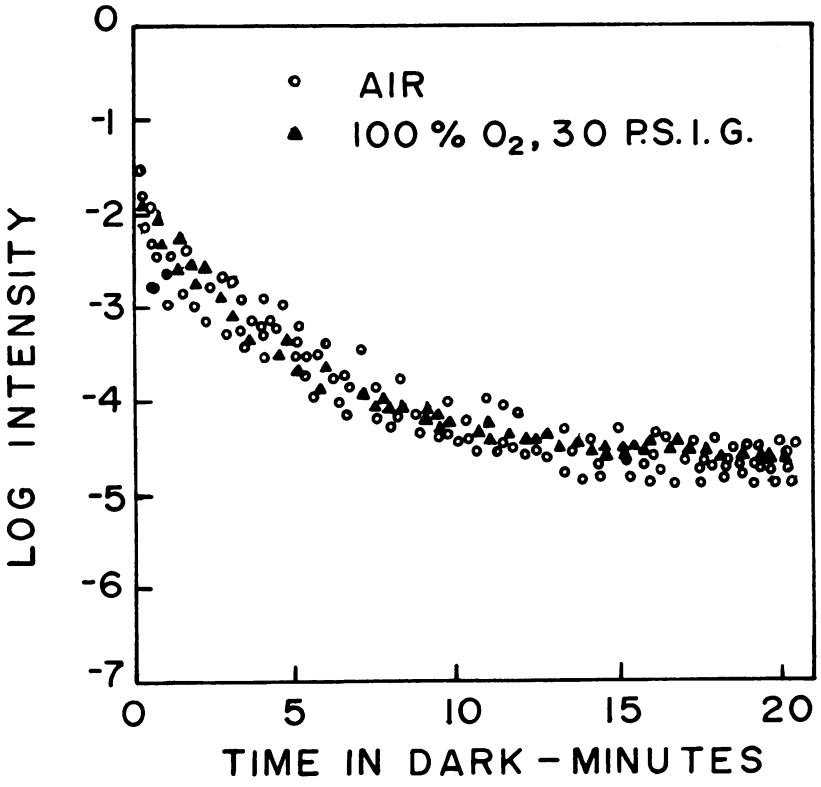

FIGURE 15

Hyperoxic dark adaptation is similar to that with air breathing at normal pressure.

adaptation are affected by low oxygen tension and might also be affected by high oxygen tension. We designed this experiment to detect such changes in dark adaptation within limits dictated by the safety of the experimental subjects. The major risk of exposure to 100 per cent oxygen at pressure is that of a generalized convulsion and this risk increases with the duration of exposure and the partial pressure of oxygen attained. Although Behnke[49] was able to breathe oxygen for more than three hours at 30 psi before he noted constriction of his visual fields, most individuals convulse after much shorter exposures. Indeed, the United States Navy Diving Manual prohibits oxygen dives at depths greater than 40 feet (17.8 psi). Although our subjects would be at rest and their carbon dioxide levels would probably be lower than during a working dive, we established 35 minutes at 30 psi as the

limit of oxygen exposure. Since the oxygen effect, if present, might require time to develop, we elected to preoxygenate our subjects for 15 minutes before beginning dark adaptation. Thresholds were therefore tested for 20 minutes. In order to reach the flatter, minimum threshold portion of the adaptation curve during this period, the preadapting light stimulus was set at 150 millilamberts after ten minutes in the dark. McFarland and Evans used similar preadapting conditions in their studies of hypoxic effects. Testing after such preadaptation with an 11-degree circular field of white light centered 11 degrees above the fovea, eliminated the inflection in the adaptation curve usually attributed to cone function.

Our subjects tolerated exposure to arterial oxygen tensions estimated at 1,860 mm Hg with no detectable effect on dark adaptation thresholds under the conditions of this experiment. The subjects also adapted no more rapidly under these conditions; nor were their final thresholds any lower. No subject convulsed. The dark adaptation curve of the subject whose test was stopped because of symptoms of impending convulsion was within the range of his control values. It appears therefore, that the metabolic and neural processes involved in human dark adaptation are not significantly affected by exposures to 100 per cent oxygen for 35 minutes at 30 psi.

14. CHOROIDAL VESSELS (IN A PATIENT WITH CENTRAL AREOLAR CHOROIDAL DYSTROPHY) DO NOT CONSTRICT AT OXYGEN TENSIONS WHICH PRODUCE MARKED CONSTRICTION OF THE RETINAL VESSELS.

Constriction of the larger retinal arterioles and venules in response to elevated oxygen tensions has been reported many times.[42,62–64] The degree of constriction seems roughly proportional to the elevation of arterial oxygen tension and is not the result of simultaneous hypocapnia.[65] There are no previous reports of the effects of changes in oxygen tension upon human choroidal vessels.

Central areolar choroidal atrophy or dystrophy is a dominant hereditary retinal and choroidal degeneration which affects the macular and paramacular area.[66,67] In this condition the retina and choriocapillaris degenerate exposing the underlying choroidal vessels, which may or may not appear sclerotic. The choroidal vessels are easily visible and may be photographed and measured. It was therefore with some interest that we examined a 19-year-old student who presented with a chief complaint of bilateral paracentral scotomas. The patient was found to have central areolar choroidal dystrophy and reported that his father had completely lost central vision in both

eyes. Correspondence confirmed that the patient's father's condition was also central areolar choroidal dystrophy. Both father and son were informed of the risks associated with the experimental procedures and agreed to the studies.

The direct visualization of these large choroidal vessels provided an opportunity to repeat many of the studies which have added to our knowledge of the retinal circulation.

The clinical appearance of the choroidal vessels was photographically recorded (Figures 16 and 17). They seemed arterial in color and serpentine pulsation could be observed. This clinical impression was confirmed by two methods. Ophthalmodynamometry revealed pressures (in instrument grams) of 90/50 right eye, largest vessel, 85/45 left eye, largest vessel, in the sitting position. Although these pressures do not represent the intravascular choroidal pressure, just as pressures measured by observing the retinal artery are not retinal artery pressures, the persistence of pulsation up to ophthalmic artery pressure levels indicated that a capillary bed did not intervene between the observed vessel and the ophthalmic artery. Fluorescein studies also demonstrated filling of these large vessels before dye was evident in the retinal arterial tree. We concluded that these large vessels were arterial, although they might have been large arteriovenous shunt channels.

To test the response of these vessels to elevated oxygen tensions, the patient's choroidal and retinal vessels were photographed with the subject breathing air at sea level pressure (760 mm Hg) and oxygen at 30 psi atmospheric pressure (Figures 16 and 17). Although marked constriction of the retinal vessels was observed, no significant change occurred in the choroidal vessels when measured directly and with the scanning densitometer (Table 18).

To generalize concerning the behavior of the human choroidal circulation from our observations of this case may be dangerous. The cause of this dystrophy is unknown and indeed may be the direct result of choroidal circulatory abnormalities. Recognizing these objectives, the difficulties of directly observing the human choroidal circulation are such that more physiologic conditions probably do not exist. Observations of the choroidal circulation in animal eyes through scleral windows are probably even less reliable since the surgical procedures, changes in intraocular pressure, and alterations in local temperature introduce many possible sources of error.

Indirect methods of assessing vasomotor reactivity may be more accurate. There is evidence that the choroidal circulation in albino

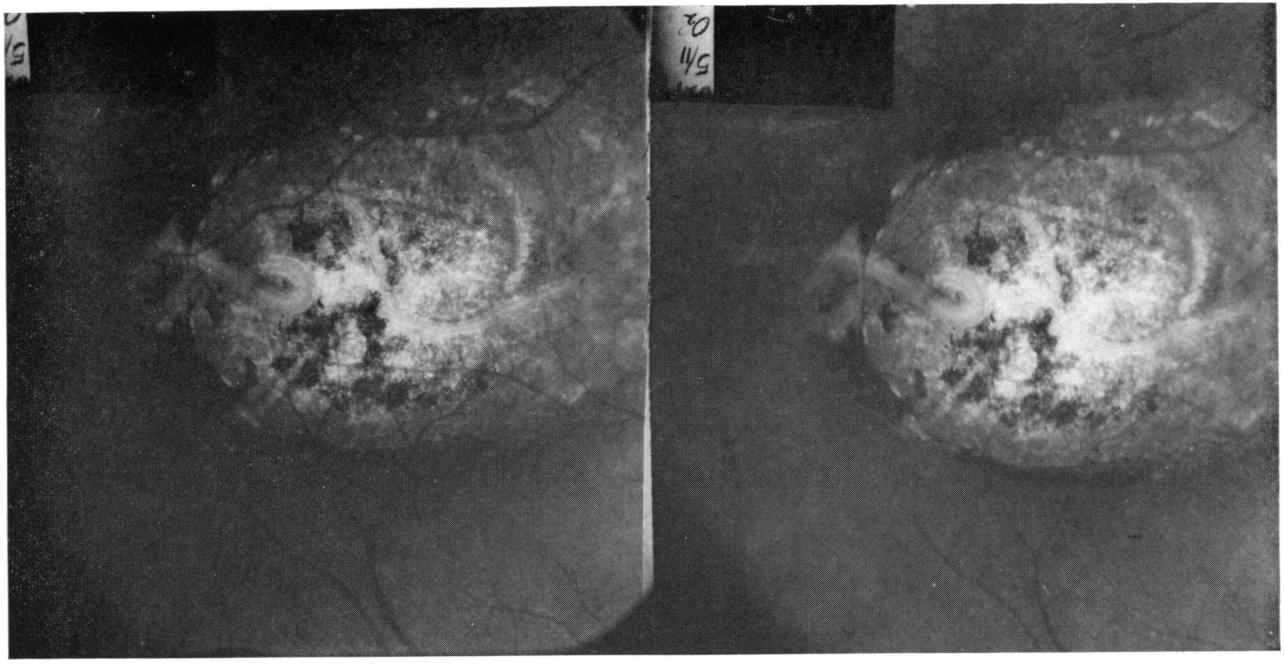

FIGURE 16

Right fundus. Breathing air (left). Breathing 100 per cent O_2 at 2,311 mm Hg (right). Note marked constriction of retinal vessels with no apparent change in choroidal vessels.

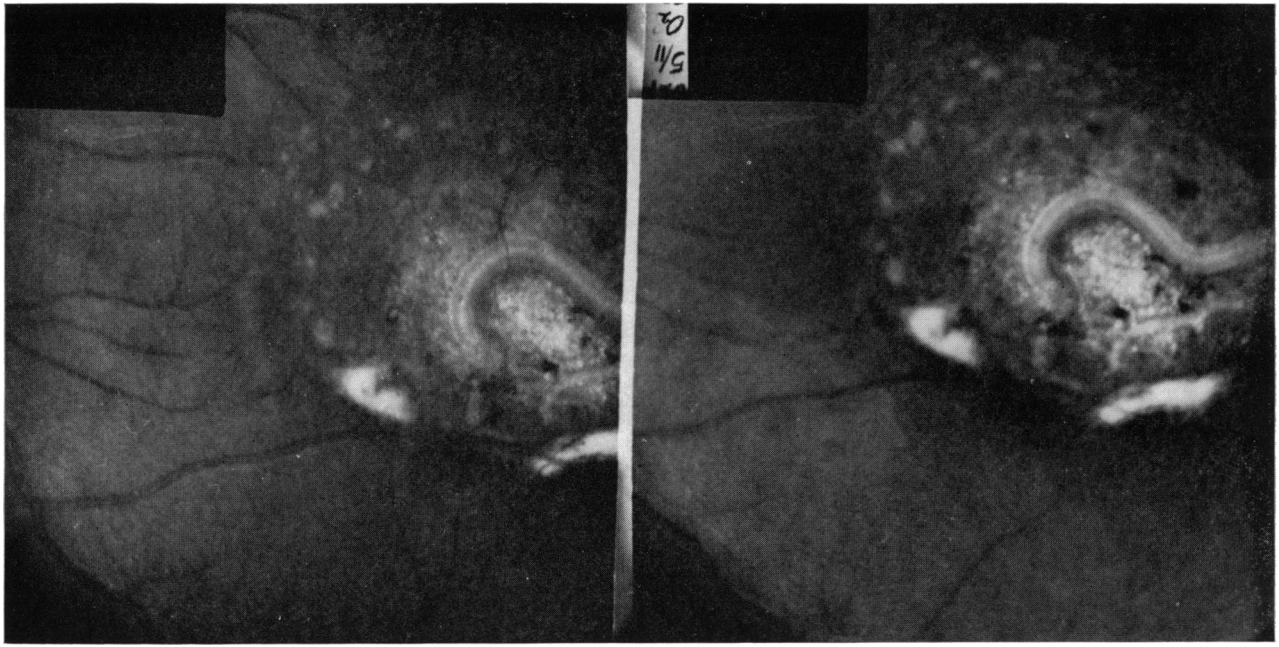

FIGURE 17

Left fundus. Breathing air (left). Breathing 100 per cent O_2 at 2,311 mm Hg (right). Note marked constriction of retinal vessels with no apparent change in choroidal vessels.

TABLE 18. CHOROIDAL VESSEL SIZE AND HYPEROXIA

Scan no., Eye	Atmos. pressure (mm Hg)	Inspired gas	Scan widths	
			Vessel A	Vessel B
16, left	760	Air	24.0	18.5
18, left	760	Air	22.5	22.0
22, left	760	Air	—	18.0
26, left	760	Air	29.0	33.5
Mean	760	Air	25.2	23.0
14, left	2311	100% O_2	24.2	27.0
15, left	2311	100% O_2	23.2	22.2
Mean	2311	100% O_2	23.7	24.6
34, right	760	Air	25.0	—
35, right	760	Air	19.5	14.5
36, right	760	Air	18.0	22.0
Mean	760	Air	20.8	18.3
37, right	2311	100% O_2	20.0	16.0

rabbits does respond to changes in respiratory gases. Trokel,[68] using reflective densitometry has calculated that 100 per cent oxygen breathing at 760 mm Hg produces a 14 per cent decrease in choroidal blood volume, a 32 per cent decrease in choroidal blood flow, and a 69 per cent increase in peripheral resistance. The addition of 10 per cent carbon dioxide to the breathing mixture reversed these changes. The decrease in choroidal blood volume suggests that much of the observed oxygen effect may be the result of changes in the caliber of the vessels of the choriocapillaris.

If we assume that the choroidal vessels measured in this case are representative of normal choroidal arteries, their lack of response to oxygen may not reflect the behavior of the choriocapillaris. On a percentage basis, the smaller retinal vessels have been noted to constrict to a greater degree than the larger vessels.[63] This may also be true of the choroid. It is also possible that the responses of the choroidal vessels to changes in blood-gas tensions differ from those of retinal vessels. Certainly, the two circulations differ in many other respects. The transition from large vessels to capillaries is much more abrupt in the choroidal circulation and the muscular wall of the arteries and arterioles is thicker. Unlike the retinal system, the choroidal circulation of cats and rabbits has been shown to respond to autonomic stimulation.[69,70] The arteriovenous oxygen difference in choroidal blood is much lower than that of the retinal circulation and the flow rate is higher.[71-75] The anatomic and physiologic differences between the two

circulatory systems are great. The vasoconstrictor response to high oxygen tension may represent one more such difference.

In this patient with inherited central areolar choroidal dystrophy, ophthalmodynamometry by observation of the choroidal vessels gave pressure readings similar to those obtained from the central retinal artery. Fluorescein was visible in these vessels in advance of its appearance in the retinal vessels. Vasoconstriction in response to high oxygen tension was not observed in these large choroidal vessels, although marked constriction of the smaller retinal vessels did occur. This dystrophy may be the result of anatomic and physiologic abnormalities in the choroidal circulation. These large vessels may be choroidal arteriovenous shunts. If so, these and future observations may establish a basis for treatment of this progressively blinding disease.

CONCLUSION

These studies of the human eye have provided information of clinical importance about the effects of local changes in oxygen and carbon dioxide tension. Oxygenation of the retina is increased by hyperoxia in spite of the concomitant vasoconstriction. The protective effect of such oxygenation against ischemic blackout is obtained in two minutes. Ophthalmodynamometry can effectively deprive the retina of all extraocular oxygen. Oxygen lack is the immediate cause of ischemic blackout. The Q_{O_2} of the intact human retina is 29 ml O_2/Gm dry wt./hr. The Q_{O_2} is unchanged in patients with diabetes and glaucoma but rises to 60 in a patient with pigmentary dystrophy. The addition of small amounts of carbon dioxide or the administration of Diamox during oxygen breathing increases hyperoxic protection against ischemic blackout. Recovery from transient ischemia requires less than ten seconds. The visual field and dark adaptation are not affected by hyperoxia with exposures below the usual convulsive threshold. The choroidal arteries of a young patient with central areolar choroidal dystrophy do not constrict with hyperoxia.

Such findings also have physiologic implications: The retina's enormous capacity for energy production is coupled with a remarkable dynamic metabolic and circulatory reserve capacity. Molecular oxygen or a metabolic energy source can be stored under conditions of plenty and utilized in time of want. Vision may persist for a minute or more after circulatory occlusion following hyperbaric preoxygenation. When circulation is restored after transient ischemic visual loss, full recovery of these metabolic stores occurs with a few exchanges of retinal blood.

This dynamic response is possible in the presence of an arteriovenous oxygen difference which is normally large as compared with that of the choroid.

As with any research endeavor, each step forward leads to a new branching into paths unknown. We would like to know if our observations on patients with ocular disease are typical of other such patients. Is hyperoxygenation with the addition of carbon dioxide or acetazolamide of any benefit in the treatment of acute retinal circulatory impairment? Can the experimental technique of ischemic blackout be used to evaluate the protective or harmful effect of such substances as nicotinic acid, nicotinyl alcohol, nylidrin hydrochloride, isoxsuprine, ethyl alcohol, and cigarette smoke? Can the technique be employed in animals by employing electroretinographic or pupillomotor changes for the ischemic end point? If this is possible, can the effects of marked hypoglycemia, vitamin A deficiency, excess lactate, and acidosis yield information of metabolic importance? The answers to these questions may lead to future discoveries of importance in understanding ocular disease.

ACKNOWLEDGMENT

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APPENDIX

CALCULATION FACTORS

To convert Q_{O_2} based upon protein weight to Q_{O_2} dry weight, multiply by 1.176.[28] (Assumption: protein is 85 per cent of dry weight of retina.)

The dry weight of cattle retina is 14.1 Gm/100 Gm wet tissue.[76]

The specific gravity (relative density) of cattle retina is 1.037.[77]

The dry weight of 100 ml of cattle retina (calculated from the above values) is 14.6 Gm.

To convert oxygen utilization in ml O_2/100 ml wet retina/min. to Q_{O_2} in ml O_2/Gm dry/hr., multiply by 4.1 (based upon cattle retina).

Specific gravity (relative density) of other retinas: pig, 1.042[77]; cat, 1.03.[75]

The weight of rabbit choroid and retina per cm^2 of fundus is 0.05 Gm.[78]

TABLE 19. REGRESSION PARAMETERS AND CALCULATIONS

Subject	N	Sum X	Sum X^2	Sum XY	Sum Y	Sum Y^2	Correlation coefficient	pO_2 fall (mm Hg/sec.)	O_2 uptake	Q_{O_2}
001	13	229.0	5,512.96	334,740	15,090	22,012,650	0.97	53.4	9.6	39
002	35	1,271.1	56,281.29	2,169,414.5	50,360	86,091,100	0.92	33.7	6.1	25
003	40	761.7	20,473.41	1,351,948.0	54,610	94,567,675	0.90	52.3	9.4	39
004	43	1,558.8	70,499.30	2,424,165.5	55,075	85,737,175	0.93	30.6	5.5	24
005	33	947.7	44,337.25	1,699,233	43,575	74,297,800	0.84	26.2	4.7	19
006	32	1,062.5	47,832.41	1,845,022.5	43,465	72,915,025	0.96	32.1	5.8	23
007	52	1,597.1	59,710.83	2,744,755	75,190	129,115,100	0.93	40.9	7.4	30
012	53	2,025.2	109,043.86	3,603,433.5	78,210	133,681,200	0.81	19.4	3.5	14
013	24	489.2	14,700.24	792,876	29,505	44,801,025	0.95	40.5	7.3	30
016	21	421.6	11,784.88	657,352.5	25,230	38,709,150	0.96	48.4	8.7	36
017	22	593.1	21,920.33	974,511.5	27,530	43,999,150	0.98	39.2	7.1	29
018	42	841.8	21,881.80	1,359,138	55,140	87,051,750	0.94	50.7	9.1	37
019	38	857.5	27,238.85	1,411,497.5	47,690	75,473,000	0.96	42.5	7.7	31
020	15	576.3	27,106.09	984,131	21,360	36,158,850	0.97	32.9	5.9	24
Mean							0.93	38.8±10.2	7.0±1.8	28.6±7.5
Retinal degeneration	38	428.7	6,484.67	669,044.5	47,390	74,872,850	0.83	81.6	14.7	60
Diabetes	19	463.3	16,816.55	787,756	24,320	38,349,250	0.98	35.3	6.4	26
Glaucoma	44	1,746.7	87,564.15	2,616,649	53,185	79,946,475	0.95	27.7	5.0	20

TABLE 20. ENVIRONMENTAL PRESSURE EQUIVALENTS

mm Hg	psi	Atm. abs.	Ft. sea water
760	0	1.00	0
990	4.45	1.30	10.0
1277	10.0	1.68	22.5
1520	14.7	2.00	33.0
1536	15.0	2.02	33.8
1794	20.0	2.36	45.0
2311	30.0	3.04	67.5
2828	40.0	3.73	90.0
3087	45.0	4.08	101.3

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