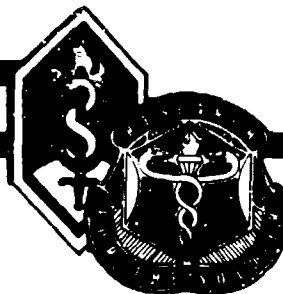


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USAARL Report No. 88-7



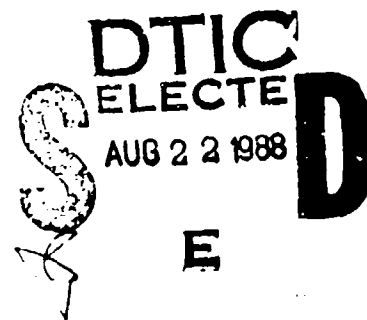
AD-A198 688

**Effects of Low and High Oxygen Tensions
and Related Respiratory Conditions
on Visual Performance:
A Literature Review**

By
Frederick N. Dyer

**Research Solutions, Inc.
2644 Habersham Avenue
Columbus, Georgia 31906**

June 1988



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Reviewed:



BRUCE C. LEIBRECHT, Ph.D.
LTC, MS
Director, Sensory Research
Division

Released for publication:



J. D. LaMOTHE, Ph.D.
COL, MS
Chairman, Scientific
Review Committee



DAVID H. KARNEY
Colonel, MC
Commanding

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SECURITY CLASSIFICATION OF THIS PAGE

ADAM98688

REPORT DOCUMENTATION PAGE

Form Approved
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1a. REPORT SECURITY CLASSIFICATION			1b. RESTRICTIVE MARKINGS		
2a. SECURITY CLASSIFICATION AUTHORITY			3. DISTRIBUTION/AVAILABILITY OF REPORT		
2b. DECLASSIFICATION/DOWNGRADING SCHEDULE					
4. PERFORMING ORGANIZATION REPORT NUMBER(S)			5. MONITORING ORGANIZATION REPORT NUMBER(S)		
6a. NAME OF PERFORMING ORGANIZATION Research Solutions, Inc.		6b. OFFICE SYMBOL (If applicable)	7a. NAME OF MONITORING ORGANIZATION U. S. Army Aeromedical Research Laboratory		
6c. ADDRESS (City, State, and ZIP Code) 2644 Habersham Ave. Columbus, Georgia 31906			7b. ADDRESS (City, State, and ZIP Code) P. O. Box 577 Fort Rucker, AL 36362-5292		
8a. NAME OF FUNDING/SPONSORING ORGANIZATION		8b. OFFICE SYMBOL (If applicable)	9. PROCUREMENT INSTRUMENT IDENTIFICATION NUMBER DAAL03-86-D-0001		
8c. ADDRESS (City, State, and ZIP Code)			10. SOURCE OF FUNDING NUMBERS		
			PROGRAM ELEMENT NO.	PROJECT NO.	TASK NO.
11. TITLE (Include Security Classification) Effects of Low and High Oxygen Tensions and Related Respiratory Conditions on Visual Performance: A Literature Review (U)					
12. PERSONAL AUTHOR(S) Frederick N. Dyer, Ph.D.					
13a. TYPE OF REPORT Final		13b. TIME COVERED FROM _____ TO _____		14. DATE OF REPORT (Year, Month, Day) 1988 July	
15. PAGE COUNT 266					
16. SUPPLEMENTARY NOTATION					
17. COSATI CODES			18. SUBJECT TERMS (Continue on reverse if necessary and identify by block number) Hypoxia, vision, eye, oxygen, hyperoxia, hyperbaric oxygen, hypocapnia, hypercapnia, carbon monoxide, retinal circulation, retinal vasodilation, retinal vasoconstriction.		
FIELD 06	GROUP 04	SUB-GROUP			
19. ABSTRACT (Continue on reverse if necessary and identify by block number) Research was reviewed on the effects of hypoxia, hyperoxia, hypocapnia, and hypercapnia on a large number of visual and ocular processes. These included absolute visual sensitivity, dark adaptation, visual acuity, contrast sensitivity, depth perception, stereopsis, fields of peripheral and central vision, critical flicker/fusion frequency, color vision, afterimages, other entoptic phenomena, persistence of vision following ischemia, the standing potential, the electroretinogram, ganglion cell and optic-tract responses, visual evoked responses, ocular vessels, blood flow, intraocular pressure, intraocular oxygen, the pupil, accommodation, myopia, the crystalline lens, convergence, heterophoria, reading, other eye movements, and the cornea. Research was also reviewed on the potential toxic effects of hyperbaric oxygenation on vision. Integration of this large body of research indicated probable dioptric changes in the eye during hypoxia that resulted from changes in blood volume associated with retinal vasodilation. One possibility is that anterior chamber "shallowing" occurs during hypoxia because of increased pressure behind the lens					
20. DISTRIBUTION/AVAILABILITY OF ABSTRACT ☐ UNCLASSIFIED/UNLIMITED ☐ SAME AS RPT. ☐ DTIC USERS			21. ABSTRACT SECURITY CLASSIFICATION Unclassified		
22a. NAME OF RESPONSIBLE INDIVIDUAL Chief, Scientific Information Center			22b. TELEPHONE (Include Area Code) (205) 255-6907		22c. OFFICE SYMBOL SGRD-UAX-S-I

18. (Continued)

intraocular pressure, intraocular oxygen, pupil, crystalline lens, cornea, contact lens, accommodation, convergence, reading, dark adaptation, absolute sensitivity, contrast sensitivity, acuity, depth perception, stereopsis, peripheral vision, visual fields, critical flicker frequency, color vision, afterimages, entoptic phenomena, retinal ischemia, Craik blindness, standing potential, corneoretinal potential, electroretinogram, ganglion cells, optic tract, EEG, visual evoked responses, myopia, refractive errors, heterophoria, oxygen toxicity, eye movements, nystagmus, aqueous humor, night myopia.

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and/or reduced anterior chamber pressure. This may cause increases of myopia in some hypoxic conditions. Since retinal oxygen requirements increase in darkness, a "night hypoxia" probably exists that may lead to "night myopia" as a result of this vascular oxygen regulation which leads to dioptric "deregulation." Research needs related to these and other hypotheses were identified along with gaps in research on the effects of hypoxia and hyperoxia on vision.

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DTIC TAB	☐
Unannounced	☐
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Availability Codes	
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Introduction

The major impetus for research on the effects of hypoxia on vision was the advent of aviation. Balloonists were among the first to discover the perils of hypoxia and some did not live to describe them. The reports of those who did survive extreme hypoxia provide some of the earliest data on the visual effects associated with hypoxia and these are mentioned in this review. These incidents have been described more extensively by McFarland (1932) in his review of behavioral and physiological effects of hypoxia.

Many aviators flying at high altitudes without oxygen observed a general darkening of vision and this stimulated the extensive research that has been conducted on the effects of hypoxia on absolute and differential visual sensitivity (McFarland and Evans, 1939). Loss of ability of balloonists and pilots to focus on close instruments led to research on the effect of hypoxia on the near points of accommodation and convergence and to research on visual acuity during hypoxia (McFarland, 1932). Prolonged and intense visual afterimages were experienced by some pilots flying at high altitudes and this led to research on the effects of hypoxia on afterimages and other entoptic phenomena (McFarland, 1937b).

As Bean (1945) pointed out, aviation also was a large factor in "restimulating" research on the effects of hyperoxia, i.e., higher-than-normal oxygen pressures. Breathing of pure oxygen (or at least high concentrations of oxygen) solved many of the problems pilots experienced while flying at high altitudes. However, even when pure oxygen is breathed, the greatly reduced atmospheric pressure at altitudes above 32,000 feet still results in oxygen tensions lower than the tension of oxygen in air at sea level. The pressurization of oxygen breathed through masks and, later, the pressurization of aircraft cabins prevented hypoxia during flight at these higher altitudes.

This provision of oxygen to aviators routinely led to breathing of higher-than-normal tensions of oxygen at lower elevations. This raised many questions about possible problems of this hyperoxia for visual performance. It also raised the logical question of whether or not there would be benefits to vision (and to other types of human performance) as a result of breathing higher than normal levels of oxygen. If less oxygen than normal was detrimental to performance, didn't it follow that more oxygen than normal would lead to better performance? These questions raised by the aviation-stimulated practice of breathing pure oxygen led to

another body of research on the effects of hyperoxia on vision and on other aspects of human performance.

Hyperoxia includes the breathing of oxygen in hyperbaric chambers at pressures above one atmosphere (including pressures of two, three, and even more atmospheres). At these higher pressures, so much oxygen is dissolved in blood plasma, that many of the metabolic requirements for oxygen in the body are met with this dissolved oxygen instead of the normal hemoglobin-attached oxygen (e.g., Anderson, 1968) and this overabundance of oxygen has many implications for clinical treatment of circulation-related disorders and other diseases as was described by Gabb and Robin (1987). Gabb and Robin also stressed that medical use of hyperbaric oxygenation has not been and is not being adequately evaluated. As will be described throughout this review but particularly in Chapter 20: "Oxygen toxicity," there are health problems as well as health benefits associated with exposure to hyperbaric oxygen.

Changes in vision may be experienced with oxygen tensions that are only slightly below normal and some of these may be relevant to aviator performance, especially in low luminance environments. As mentioned, humans readily can tolerate oxygen pressures that are much higher than those encountered at sea level. However, vision (including absolute and contrast sensitivity) is remarkably unchanged for a range of oxygen tensions from about half the normal oxygen tension, through the five-times-normal tension that occurs when pure oxygen is breathed at sea level, to the 20-times-normal oxygen tension that occurs in a hyperbaric chamber where pure oxygen is breathed at greater than three atmospheres. This shows that the eye and body are remarkably adept at extracting and regulating the oxygen in a huge range of oxygen mixtures. Research on these regulatory mechanisms is discussed extensively in this review, particularly in Chapter 12: "Ocular vessel and blood flow changes."

Organization of this literature review

This review of literature is organized into five sections. The first section deals with studies of the effects of hypoxia and hyperoxia on vision and includes chapters on absolute sensitivity and dark adaptation, acuity and contrast sensitivity, depth perception and stereopsis, critical flicker-fusion frequency, visual field size, color vision, afterimages and other entoptic phenomena, and persistence of vision following retinal ischemia.

The second section deals with studies of the effects of hypoxia on electrophysiological and neurophysiological processes associated with and underlying vision. It includes chapters on the

electroretinogram and standing potential, ganglion-cell activity, and the visual evoked potential and EEG.

The third section deals with studies of the striking effects of hypoxia and hyperoxia on the ocular vasculature and blood circulation. The section also includes a chapter that reviews studies of intraocular pressure changes during hypoxia which often mirror general shifts in blood pressure of the eye and body, but which also reflect changes in production of aqueous humor which may be influenced by hypoxia. This section also includes a chapter dealing with a relatively new class of studies which have used electrodes sensitive to oxygen to determine the actual tensions of oxygen in different parts of the eye.

The fourth section deals with studies of the effects of hypoxia and hyperoxia on other ocular structures and behaviors and includes chapters dealing with the pupil, accommodation and refraction, convergence and heterophoria, reading and other coordinated eye movements, the cornea, and oxygen toxicity.

The fifth section attempts to integrate the major research results reviewed in the other chapters. It also summarizes research needed to resolve contradictory results or research needed to test hypotheses that arose during the integration of existing research. One major unresolved paradox is that reduced oxygen saturation appears to differ in its effect on vision and other performances if the drop in blood oxygen results from breathing of carbon monoxide or if it results from breathing oxygen at low tensions (Christensen et al., 1977). Research is needed to identify the bases for these differences. The striking interdependence between hypoxia effects on vision, ocular structures, ocular muscles, visual electrophysiology/neurophysiology, and actual oxygen levels in the eye, indicate that research on the effects of hypoxia or hyperoxia should include dependent variables from several of these different classes.

Existing reviews of literature in these areas

As might be expected, there have already been a number of reviews of literature in this important area of oxygen and vision. These have been concentrated on the effects of hypoxia as opposed to hyperoxia, even as the bulk of research has dealt with hypoxia effects. Sauer (1924) provided a review of data on hypoxia and vision with the bulk of the article dealing with results of Wilmer and Berens (1918) plus other research that largely replicated the research of Wilmer and Berens. McFarland, Evans, and Halperin (1941) provided a superb review of early research, although one suspects from brief treatment of some foreign research, such as the work of the Japanese researcher Furuya, that some of the information was gleaned from brief abstracts in German journals.

Gellhorn and Hailman (1943) covered much of the same ground as McFarland, Evans, and Halperin (1941) and discussed other senses in addition to vision.

Mercier and Duguet provided an extensive review in 1947 entitled Physiopathologie Oculaire de l'aviateur which covered early European and other research that was not included in earlier reviews. The U.S. Air Force provided an English translation of this important 1947 report (Mercier and Duguet, 1950).

Nicholls (1950b) provided an extensive review of the effects of hypoxia (also fatigue) on convergence and heterophoria in the second of a series of three papers on the relationship of heterophoria to depth perception in aviation (Nicholls, 1950a; 1950b; 1950c). Bietti (1953) provided a brief review that appeared to be comprehensive for a large body of Italian research on the effects of hypoxia on vision and ocular functions. Van Liere and Stickney (1963) brought the McFarland, Evans, and Halperin (1941) review up to date, but depended strongly on McFarland, Evans, and Halperin for the earlier research. A general review of psychological effects of hypoxia by Tune (1964) covered research from 1950 to 1963 and included a dozen studies dealing with vision and more than half of these dealt with effects of hypoxia on the critical flicker-fusion threshold. Michael (1973) provided a general review of neurophysiological effects of hypoxia, but only a few key studies in the area of vision were discussed in a brief section. Almost without exception, studies discussed in these earlier reviews are also covered in the current review and, wherever possible, the original articles were obtained and read.

Limitations of the present review

Unfortunately, resources were not available to obtain and/or translate a number of key foreign articles and secondary sources and English-language abstracts were relied on to provide the findings of these studies. In some secondary sources there was almost no discussion of methodology in the original studies and even these sources often seemed to be "tertiary" sources depending on abstracts and other secondary sources. The extensive work of Furuya (1936a; 1936b; 1937a; 1937b; 1937c; 1937d; 1937e) is in Japanese and covered a wide range of vision and ocular functions as they were affected by hypoxia. The current review provides all of the information about the findings of Furuya that was available in secondary sources, but often these provided few details. His studies of the pupil (Furuya, 1936b) and muscle balance (Furuya, 1937d) received almost no mention by previous reviewers. Researchers with a knowledge of Japanese might obtain additional insights about hypoxia effects by obtaining these articles and providing their own integration of his results with other research results reviewed in this report. The same can be said for the

extensive research of Carapancea and his associates conducted in the 1960s and 1970s which dealt with effects of hypoxia on a range of visual and ocular functions including intraocular pressure, accommodation, and changes in the chemical and ionic content of the aqueous humor. This Carapancea research is largely in French and Rumanian although a few English articles and English summaries have allowed some discussion of these results in the present review.

Normal oxygenation of the eye

Considering its weight, neural tissue uses a disproportionate amount of the oxygen consumed by the body (Van Liere and Stickney, 1963). The retina, in turn, uses a disproportionate share of the oxygen consumed by neural tissue (Anderson, 1968). It is thus not surprising that a shortage of oxygen (hypoxia) would have deleterious effects on visual function. Even low levels of hypoxia have been shown to reduce absolute sensitivity to light (e.g., McFarland and Evans, 1939) and sensitivity to small differences in brightness contrast (e.g., McFarland, Halperin, and Niven, 1944). However, as will be seen throughout this review of literature, rather substantial reductions of oxygen are required to have any major impact on most visual performances or their ocular and neural underpinnings. A total loss of vision as a result of hypoxia usually precedes unconsciousness, but typically not by much (Ernsting, 1965).

The blood's hemoglobin transports an enormous quantity of oxygen that is used by tissues for their metabolism (Anderson, 1968). Oxygen also is dissolved in blood plasma, but at normal atmospheric pressure such dissolved oxygen occurs only in small quantities and contributes little to the oxygen requirements of body tissues. However, blood plasma can carry much more dissolved oxygen if the gas being breathed contains a high percentage of oxygen and it is breathed under pressure (Anderson, 1968). For example, at 2,000 mm Hg pressure, pure oxygen goes into solution with blood plasma in sufficient quantities to meet the body's metabolic needs without any contribution of oxygen from hemoglobin (Anderson, 1968). Such hyperbaric oxygenation has much potential for providing oxygen to oxygen-starved tissues due to circulatory and other disorders. It also contributes to the healing of ulcers of the skin that resist other treatment. Hyperbaric oxygenation also has potential for damage to ocular tissues, however, and much evidence of this toxic potential for the eye will be included in this review of literature (see Chapter 20: "Oxygen toxicity").

The retina receives oxygen for its metabolic needs from the retinal vascular system which supplies the inner retina (adjacent to the vitreous) and the choroidal vascular system which supplies the rods and cones and the pigment epithelium of the outer retina

(Wolbarsht, Stefansson, and Landers, 1987). The ciliary vascular system supplies the rest of the eye's blood needs (Kronfeld, 1969).

Oxygen levels within the eye show wide variation from aqueous to vitreous and within the vitreous there are large gradients in oxygen tension as the retina closely is approached (with oxygen-sensitive electrodes) which reflect the large consumption of oxygen by retinal elements. Even within the retina there are oxygen gradients and Alder, Cringle, and Constable (1983) reported that the lowest oxygen tension was at the inner nuclear layer which reflects both the high oxygen requirement of this layer and the limit of oxygenation via choroidal circulation (See Chapter 14: "Intraocular oxygen").

This oxygen is used in the eye to prevent depolarization of neurons (operate the Na/K pump) and to maintain synaptic integrity (Michael, 1973). It also aerobically powers the ciliary and iris muscles. The extraocular muscles also require oxygen and decrements in convergence amplitude and rapid fatigue of convergence during hypoxia (e.g., Wilmer and Berens, 1918) and fatigue-like slowing of reading movements during hypoxia (Bietti and Scano, 1946) indicate the high susceptibility of these extraocular muscles to hypoxia. On the other hand, oxygen appears less critical for the photochemical processes of the receptors (Chase and Hagan, 1943; Craik, 1940).

Sources of hypoxia in natural and laboratory settings

A given level of hypoxic hypoxia¹ can be produced by actually ascending to a specific altitude, by lowering the atmospheric pressure in a decompression chamber to the equivalent atmospheric pressure for that altitude, or by increasing the nitrogen content of oxygen-nitrogen mixtures breathed at sea (ground) level until the oxygen percentage of the mixture is lowered to the equivalent tension provided at the altitude. For example, breathing an oxygen mixture with 10 percent oxygen and 90 percent nitrogen is equivalent to breathing air at approximately 20,000 feet. In their extensive series of studies of hypoxia and vision, Wilmer and Berens (1918) used both a decompression chamber and low-oxygen mixtures to examine hypoxia effects and they typically found equivalent results on vision and ocular performance. The extensive series of studies of hypoxia by McFarland and his associates used

¹ Hypoxic hypoxia refers to reduction of oxygen in the blood because of lack of oxygen in the respiratory mixture. Hypoxia can also be produced when oxygen is displaced in the blood stream by carbon monoxide which forms carboxyhemoglobin (COHb) instead of the normal oxyhemoglobin. This latter hypoxia has been referred to as hemic hypoxia.

low-oxygen high-nitrogen mixtures, decompression chambers, and some actual ascents to high altitudes. Where comparable tasks were presented in these different "equivalent" hypoxic settings, the results typically were similar.

On the other hand, sources of hypoxia may not be as equivalent as McFarland and others have claimed. For example, Newberry, Johnson, and Smiley (1965) studied the effects of hypoxic hypoxia on nystagmus induced by angular acceleration. In one trial, hypoxia was produced by decompressing the subject to an altitude of 20,000 feet. In another trial, hypoxia was produced by having the subject breathe a 10 percent oxygen/90 percent nitrogen mixture. Although nearly equivalent oxygen tensions existed, only the decompression treatment produced marked changes in nystagmus. As will be discussed further in Chapter 18: "Reading and other eye movements," hyperventilation associated with anxiety during decompression apparently was the reason for the large changes in nystagmus found in the study of Newberry, Johnson, and Smiley and hypoxia by itself had little or no effect. When contradictions are found among different research findings, attention should be given to differences between research studies in the mode for producing hypoxia. An initial attempt at this has occurred in some portions of this review.

Hypoxic changes in alveolar and blood CO₂

This review includes much research that looked at effects on vision and the eye of low levels of CO₂ (hypocapnia or acapnia) and high levels of CO₂ (hypercapnia), as well as research on hypoxia and hyperoxia. Many researchers found that hypoxia caused hyperventilation in their subjects (e.g., Frayser et al., 1971; Livingston, 1944a; Ernest and Krill, 1971). Hyperventilation produces a rapid drop in the level of CO₂ in the blood. This hypocapnia has large effects on many of the same visual processes (e.g., Alpern and Hendley, 1952) and ocular processes (e.g., Kielar et al., 1977) that have been of major interest to researchers looking at effects of hypoxia. As will be seen throughout almost every chapter of this report, these concomitant drops in arterial oxygen and arterial CO₂ often complicate the results of much research on hypoxia.²

² Hyperventilation also boosts arterial oxygen because of the increased oxygen entering the lungs. This typically does not totally counter the drop in oxygen associated with the low oxygen tension of the gas being breathed, but it does account for large individual differences that have been found in blood saturation for a given oxygen tension (Ernest and Krill 1971), and this can make a major difference in performance when critical low levels of oxygen are breathed (Lassen et al., 1987).

Chapter 1

Absolute sensitivity and dark adaptation

More research on the effects of hypoxia and hyperoxia on vision has dealt with these topics of absolute sensitivity and dark adaptation than any other visual processes and it is no coincidence that this first chapter is the longest in the review. This focus of research interest probably reflects the fact that there is a larger effect of hypoxia on absolute sensitivity and on the time course of the changes in sensitivity of the eye as it adapts to darkness than on most other visual performances. As will be seen in the next few chapters, when other visual processes such as visual acuity are affected by low oxygen levels, these hypoxia effects typically are found to be large only when the limits of visual sensitivity are approached. Later chapters will describe research indicating the eye actually uses more oxygen at low levels of retinal illumination than when illumination is high (e.g., Stefansson, Wolbarsht, and Landers, 1983b; Linsenmeier, 1986) and this would appear to explain why hypoxic decrements are most apparent in visual tasks with low retinal illumination.

Hypoxia and sensitivity

Numerous observers and investigators have reported a substantial reduction in the brightness of lights and objects during the onset of hypoxia and a corresponding noticeable brightening of these lights and objects when air or higher oxygen tensions are breathed following hypoxia. These observations undoubtedly were a key factor in the initiation of scientific investigations of visual sensitivity changes during hypoxia. An example of these was provided by Schroeder (1918) who discussed changes in brightness and loudness of stimuli when he set an altitude record of 28,900 feet. McFarland (1932) quoted Schroeder:

"When I reached 25,000 I noticed the sun growing dim. I could hardly hear my motor run and I got very hungry. The trend of my thought was that it must be getting late for the sun was getting so dim and I went on talking to myself. I then turned on the oxygen and the sun grew bright again, the motor became so loud that I thought something must be wrong with it. I was no longer hungry and I felt like singing from sheer joy."

McFarland and Evans (1939) reported that such darkening of the visual field was a frequent observation of pilots flying without oxygen at 18,000 feet and above. They also described their own experiences of a dimming of the visual field when introduced suddenly to low oxygen mixtures simulating 12,000 to 14,000 feet and the "marked increase in the brightness of lights on being quickly changed back to room air." According to McFarland and Halperin (1940), Goldmann and Schubert (1933) also reported brightening of the visual field following exposure to oxygen after having been in a hypoxic state. Scano, Bietti, and Schupfer (1947) reported that nearly all of their subjects had a "feeling of darkening of the room" during hypoxia. More recently, Smith, Ernest, and Pokorny (1976) studied the effect of hypoxia on color vision and they found all subjects who performed in the experimental 10 percent oxygen condition first and control condition (normal air) later, reported the color chips appeared lighter in the control condition.

Whiteside (1957) stressed that some observers do not experience this phenomenon of a darkening of the visual environment during hypoxia and, even for this nonscientific observation of dimming, the large individual differences in the effects of hypoxia on vision are encountered. These individual differences in hypoxia effects will recur throughout this review. Several studies have found the pupil to constrict with hypoxia (e.g., Züst, 1940), and rapid hypoxic constrictions of the pupil might explain part or all of the noticeable drops in perceived brightness during hypoxia and rapid pupil dilation might explain the sudden brightening upon return to breathing of higher oxygen tensions. Research also has shown large individual differences in hypoxic response of the pupil, including constrictions for some subjects and dilations for others (e.g., Duguet and Mercier, 1951). These individual differences in pupillary response to hypoxia might account for the fact that not all persons experiencing hypoxia "feel the darkening of the room." However, this is not to imply that pupil changes are the basis of the perceived illumination phenomena (and retinal sensitivity changes are not), especially given that no area of research on hypoxia has shown more contradictory results than the hypoxia-pupil research (see Chapter 15: "The pupil").

In perhaps the earliest experiments investigating the effects of hypoxia on visual sensitivity, Wilmer and Berens (1918) required subjects to adjust a neutral density wedge held before their eye until a tiny 3-mm diameter spot of white light 20 feet away became too dim to see. The procedure was repeated for monochromatic red and green lights. These measures were made at sea level and again with reduced oxygen tensions using the Henderson rebreathing device which reduced oxygen tensions from the 21 percent at sea level to 10 percent or less in around 20 minutes (McFarland, 1932). Carbon dioxide in this "rebreathed" air was removed by having the air pass over a CO₂-absorber such as sodium hydroxide.

Wilmer and Berens found the threshold for seeing the distant light was not changed reliably by hypoxia when the target was a white light. One-fourth of the subjects were as apt to see it with more filtering, 30 percent saw it with less filtering, and nearly half saw it at the same intensity as while breathing air. For some unexplained reason, hypoxia did decrease the visibility of monochromatic red and green lights. For both red and green, 71.4 percent of subjects showed a decrement in sensitivity with the remainder showing no change or a gain in sensitivity. Wilmer and Berens also discussed "former tests with a blue light, which was not absolutely monochromatic" which showed an improvement of sensitivity under hypoxia in 66.6 percent of subjects tested and a falling off in 33.4 percent. Unfortunately, the numbers of subjects for these particular tests were not provided and the statistical significance of these differences in percentages cannot be determined.

According to McFarland, Evans, and Halperin (1941), Tanaka and Sekiguchi (1935) exposed 12 normal subjects to low pressure and tested their visual sensitivity with a Nagel adaptometer. They reported a decrease in "dark adaptability" (presumably, absolute sensitivity) with decompression which was proportional to altitude. This decrease was counteracted by administration of oxygen. They also found prolonged exposure to a pressure corresponding to that at 3,000 meters caused the sensitivity to return toward normal. However, increased exposure to an oxygen tension corresponding to 4,000 meters produced further deterioration of sensitivity rather than adaptation.

Fischer and Jongbloed (1935), according to McFarland, Evans, and Halperin (1941), studied dark adaptation of two subjects in a low-pressure chamber. They measured the time in darkness following exposure to a bright adapting light before a dim light could be seen. This was done repeatedly as a series of increasing intensity filters were placed before the eye. They did not measure the final threshold. On the basis of their criteria, they reported a slight delay in time before the dim light was visible compared to sea level at 3,000 meters and a marked delay at 6,000 meters. According to McFarland, Evans, and Halperin, they erroneously interpreted the change as "... the physiological expression of interference with the regeneration of the photosensitive substance of the retina." Studies from other laboratories have shown hypoxia does not interfere strongly with photochemistry (e.g., Chase and Hagan, 1943) and that the effect of hypoxia on dark adaptation observed by Fischer and Jongbloed (1935) lies elsewhere, presumably, in neural processes.

One of these studies that countered Fischer and Jongbloed (1935) was carried out by Bunge (1936). According to McFarland, Evans, and Halperin (1941), Bunge administered oxygen mixtures of 8 to 11 percent oxygen to 7 subjects with "an artificial respiration apparatus." Dark adaptation was measured "with the Engelking-

Hartung instrument." Bunge made the critical finding that after complete dark adaptation in normal air, exposure to a low-oxygen mixture made the retina less sensitive. As McFarland, Evans, and Halperin (1941) described: "Since this change took place in a dark-adapted subject, destruction of visual pigments, or a delay in their regeneration could hardly have been involved. Moreover, administration of oxygen resulted in a return of retinal sensitivity at a rate which was more rapid than could be accounted for by regeneration of the visual purple."

Other evidence against a photochemical basis of hypoxic reductions in sensitivity came from Wischnewsky and Zirlin (1935).¹ According to McFarland, Evans, and Halperin (1941), Wischnewsky and Zirlin found that a lowered atmospheric pressure produced a decrease in both the light sensitivity and the electrical excitability of the eye, although no details of oxygen tensions or testing procedures were provided in the secondary source. Wischnewsky and Zirlin concluded that since electrical stimulation does not involve the photochemical system, hypoxia had its primary effect on the neural tissue of the visual mechanism.

McFarland and Edwards (1937) measured visual sensitivity during a round-trip airplane journey from California to the Philippines. They used a neutral density wedge and had subjects alter the density of the filter as they viewed a "test object" which probably was a small distant light like that used in a similar procedure by Wilmer and Berens (1918). On alternate trials, the wedge density was increased until the object disappeared and decreased until it appeared. It was not clear whether these adjustments were made by the subject himself, as occurred in the research of Wilmer and Berens, or whether the experimenter made the adjustments. McFarland and Edwards (1937) found a significant loss of retinal sensitivity at 10,000 and 12,000 feet compared to later readings made at sea level. Unfortunately, no sea level readings were reported that preceded the readings at altitude and it is possible that some or all of this improvement reflected practice effects and not the change from low oxygen to normal oxygen.

According to McFarland, Evans, and Halperin (1941), Clamann (1938) concluded an extraretinal process was involved in dark adaptation, since his studies on three subjects indicated monocular thresholds were affected differently by hypoxia than binocular thresholds. According to Rose (1950b), the effect was a change with hypoxia in the difference between the binocular and monocular thresholds. As Rose stated, "To determine whether oxygen deficiency has a retinal or extraretinal effect, the sensitivity was deter-

¹ McFarland, Evans, and Halperin (1941) provided a different spelling of Wischnewsky and Zirlin, namely, Vishnevskiy and Tsyrlin.

mined for one eye and for two by the Engelking-Hartung adaptometer. Clamann found the sensitivity at an altitude of 4,000 meters (13,100 feet) to be diminished by a factor of 10. At that altitude there was still a difference between the monocular and binocular thresholds which became greater when oxygen was given. The extra-retinal system apparently recovered more quickly than did the retinal when oxygen was given after the low-pressure test."

Although the Clamann article was not translated, the article was obtained and examination of the figures indicated that, during hypoxia, late stages of monocular dark adaptation proceeded more slowly than late stages of binocular dark adaptation. Oxygen also produced a faster recovery of sensitivity for binocular viewing than it produced for monocular viewing. One of three subjects actually showed a slight drop in monocular sensitivity following several minutes of oxygen breathing after hypoxia, while his monocular sensitivity continued to increase.

Although central factors were implicated by Clamann as the basis for the monocular-binocular difference during hypoxia, and although no challenge to this was provided by McFarland, Halperin, and Evans (1941) or Rose (1950b), it appears to the current reviewer that this difference could have been caused by accurate convergence in the binocular condition with this accurate convergence causing more accurate accommodation and sharper focus of the image of the target light. If, as some evidence indicates, hypoxia alters accommodation or by some other means changes the refractive state of the eye (see Chapter 16: "Accommodation, myopia, and the crystalline lens"), the improved focus associated with convergence during binocular vision might make the binocular visual system appear even more sensitive than the monocular visual system during hypoxia than during "normoxia."

Other early evidence for hypoxic effects on oculomotor function that might have influenced measurements of sensitivity during hypoxia came from research on absolute sensitivity by Schmidt (1939). According to Schmidt (1950), Schmidt (1939) studied red and green thresholds under low oxygen tension. Normal trichromats showed an increase in the red threshold above 13,000 feet but no change in the green threshold. This differential sensitivity for widely separated wavelengths suggests chromatic aberration of the eye may have been a factor in this result, in combination with a hypoxic reduction in the distance of the far point, such as that reported by Ohlbaum (1969). This explanation (of the current reviewer) would hold if Schmidt's targets were fairly distant (no target distance was mentioned in the 1950 Schmidt article) and a myopic shift made the red targets blurry without substantially altering focus for the optically closer green targets.

It is interesting that Kobrick et al. (1984) also found a differential effect of hypoxia on sensitivity for red and green

targets presented at threshold durations. However, unlike Schmidt (1939), Kobrick found green light sensitivity was affected by hypoxia, but red light sensitivity was not. Kobrick et al. used relatively close targets (57.6 cm). The frequently reported loss of accommodative power with hypoxia (e.g., Ohlbaum, 1969)² may have prevented accurate focus for the optically close green without causing problems for the more "distant" red.

In a landmark English-language study of hypoxia and absolute sensitivity, McFarland and Evans (1939) studied alterations in dark adaptation under reduced oxygen tensions. They measured both the rate of dark adaptation and final levels of sensitivity. The subjects were 20 graduate students (18 males and 2 females). One was 42 years old and the others ranged in age from 20 to 30. All were free of organic disease and of ocular defects other than correctable refractive errors. After a period of dark adaptation, subjects were light adapted by viewing a 100-mil white screen for 3 minutes. Immediately following this, two 70-minute diameter circles were brightened until visible and the subjects reported this and fixated the upper of the two. A somewhat dimmer 70-minute diameter circle to the lower right of the fixation circle also was brightened and the subjects reported when it first became visible and this threshold intensity was recorded. Following this, the illumination of fixation and target circles was dropped to zero and the process repeated. The time to increase of the illumination of the sensitivity target was varied from 3 to 10 seconds to prevent temporal cues from influencing reports of stimulus visibility.

The tests were carried out in an oxygen chamber and oxygen levels were lowered by admitting nitrogen. Two hours of practice on the task was given prior to the series of control and experimental tests and this led to highly consistent results for each subject. Two 20-minute control series of adaptation measurements were given in air followed by 20-minute tests at 15.7 percent oxygen (7,400 feet), 13.7 percent oxygen (11,000 feet), and 11.7 percent oxygen (15,075 feet). Total time at each altitude was approximately 35 minutes. The total time for the series of adaptation trials was about 3 hours. After the final 15,075-foot series, 100 percent oxygen was administered and thresholds were measured every 30 seconds thereafter until a constant threshold was reached. The chamber then was returned to normal air and, after a 15-minute rest, another adaptation series occurred for each subject.

McFarland and Evans (1939) found thresholds were elevated by an average of 0.103 log units at 7,400 feet, 0.224 log units at 11,000 feet, and 0.397 log units at 15,075 feet. Although a larger

² Ohlbaum (1969) found an increase in myopia and a recession of the near point during hypoxia in the same subjects.

elevation of threshold occurred for rods, the effect also appeared for the cone segment of the adaptation curve. The typical cone-rod break in this curve occurred at the same point in time following the start of dark adaptation, regardless of the oxygen tension. Pure oxygen administered at the end of the test at the 15,075-ft "altitude" restored adaptation to levels measured in air. Recovery occurred within 5 minutes and typically within 2 or 3 minutes. The final adaptation series in air provided sensitivity levels that corresponded closely to the initial two series in air that preceded testing at altitudes. Individual differences were large, but consistent over the three elevations, with correlations of 0.76 between sea level/altitude differences for altitudes I and II, 0.71 between sea level/altitude differences for altitudes I and III, and 0.88 between sea level/altitude differences for altitudes II and III.

One cannot find much fault with this methodology which provided some of the most reliable data on the effects of hypoxia on absolute sensitivity that have ever been gathered. However, a few problems did exist. No artificial pupil was used and at least some researchers have found reliable pupil changes with hypoxia (See Chapter 15: "The pupil"). Another problem that existed was that (contrary to claims by the authors) changing the rate of increase in target illumination must have influenced rheostat settings since response times of subjects would have averaged a relative constant and faster movement of the rheostat would have led to higher levels of illumination, simply because the rheostat was turned farther during faster changes. Any increase with hypoxia on time for subjects to report when the target reached threshold also would have added a constant illumination increase to the recorded threshold and this would have exaggerated hypoxia effects since only ascending luminance levels were included.

Finally, no attempt was made to account for the large individual differences in threshold elevations as a result of hypoxia. These varied from 0.126 log units to 0.618 log units for the 15,075-foot "altitude" (above thresholds measured at sea level). Correlations between sea level data and altitude data were not reported, but these might have provided insight into the bases of these individual differences, since subjects with poor sea level performance might be predicted to have poorer performance at altitude. These large individual differences in visual sensitivity during hypoxia remain an important research question (see Chapter 21: "Summary and integration of needed research").

McDonald and Adler (1939) studied the effects of hypoxia on the dark adaptation of a normal subject and of the same subject after a diet that made him deficient in Vitamin A. They used only one healthy well-trained observer. Measurements of adaptation were made with the adaptometer of Hacht and Schlaer (1938) and their recommended procedures. The subject breathed a mixture of air and

nitrogen with approximately 10.4 percent oxygen for from 15 to 20 minutes after which there was a return to air breathing. Both rods and cones showed a decrease in sensitivity of 0.4 log units as a result of hypoxia. Full dark adaptation preceded hypoxia on many trials. Despite this, observations made immediately following the onset of reduced oxygen tension often showed an unexplained increase in sensitivity prior to the eventual 0.4 log unit reduction in sensitivity.³ Vitamin-A deficiency produced a reduction in sensitivity with rods showing a decrement of about 0.8 log units and with cones showing a decrement in sensitivity of about 0.3 log units.

McFarland and Forbes (1940) extended the research of McFarland and Evans (1939) on hypoxia effects on absolute sensitivity and also determined the effects of hypoglycemia. The subjects were 15 normal fasting subjects varying in age from 25 to 37. The visual stimulus consisted of a circle three degrees in diameter located seven degrees to the left of a fixation point. The stimulus was viewed with the right eye. Light adaptation was produced by a 1,500 ml field which was viewed for 3 minutes. After this, the dark field with its fixation point was viewed and the test stimulus was raised in intensity until reported visible.

Intensity thresholds were determined approximately every 2 minutes. Chamber characteristics and oxygen conditions were similar to those for McFarland and Evans (1939). Oxygen levels were 13.4, 11.5, and 10.1 percent corresponding to altitudes of 11,500, 15,400, and 18,500 feet, respectively. One subject was tested with 7.3 percent oxygen. Some adaptation series were followed by ingestion of 70 to 80 gm of glucose. Some adaptation series were preceded by 5 to 8 units of insulin and followed by inhalation of 100 percent oxygen and ingestion of 70 to 80 gm of glucose. An artificial pupil was used for some series of adaptation trials.

Thresholds were elevated by an average of 0.26 log units at 11,500 feet, 0.42 log units at 15,400 feet, and 0.63 log units at 18,500 feet. Although larger for rods, the effect also appeared for cones and the typical cone-rod break in the adaptation curve occurred at the same point following the beginning of dark adaptation, indicating no change in the time course of adaptation under hypoxia. When pure oxygen was administered at the end of the

³ Use of an artificial pupil was not always recommended by Hecht and Schlaer (1938) and it was not stated whether an artificial pupil was used by McDonald and Adler (1939). If not, an initial pupil dilation may have produced this heightened sensitivity. Another possibility is hypoxia-induced hyperventilation and the resultant hypocapnia which increases absolute sensitivity (e.g., Alpern and Hendley, 1952).

altitude trial, visual sensitivity was quickly restored to levels in air and sometimes to slightly more sensitive levels than those measured in air.

Visual sensitivity was shown to gradually decrease as totally adapted subjects were subjected to gradual reductions of oxygen concentration from 13 to 10 percent. Sensitivity changes averaged 0.41 log units for 5 subjects who went to 10.2 percent from 12.6 percent oxygen and was 0.54 log units for 1 subject who went to 7.3 percent from 12.3 percent oxygen. This was claimed by McFarland and Forbes (1940) to correspond to a five-fold and eight-fold increase, respectively, when intensity was measured in absolute rather than log units. However, my calculations indicate this corresponds to factors of 2.6 and 3.5, respectively. McFarland and Forbes (1940) may have been describing increases from sea level thresholds, but even these (0.56 log units and 0.79 log units) did not reach the five-fold and eight-fold levels they indicated.

Administration of glucose in these low-oxygen conditions typically restored sensitivity almost to levels in air in these subjects who had fasted prior to testing. Sensitivity was found to decrease when hypoglycemia was induced by administration of insulin. Administration of oxygen then would increase sensitivity as long as the administration of oxygen continued. When alveolar oxygen levels were below normal and blood sugar was not elevated, sensitivity was directly related to the product of alveolar oxygen tension and the concentration of blood sugar with the correlation being -0.96. The effect of eating breakfast was to increase final sensitivity by 0.3 log units when testing occurred in normal air.

McFarland and Forbes (1940) claim the combination of insulin-induced hypoglycemia and low oxygen produced a greater decrement in visual sensitivity than hypoglycemia or low oxygen separately. This may have been true, but none of the experiments reported in their study provided truly comparable separate and combined conditions of hypoxia and hypoglycemia.

Wald et al. (1942) assessed the effects of hypoxia on visual sensitivity and also looked at the effects of hypocapnia induced by hyperventilation and hypercapnia induced by breathing CO₂ mixtures. Their study included an enormous range of conditions and provided a wealth of data. Subjects were six or more individuals who were highly trained on the adaptometer used to measure sensitivity and who also were "comfortable" with the hypoxic conditions. These subjects were first dark adapted and then exposed to sudden changes in oxygen tension (low oxygen mixed with nitrogen). Sensitivity was determined for a 1-degree or 2-degree diameter circular test field presented 13 or 10 degrees, respectively, below a red fixation star. This test field was exposed to the subject for 0.02 second with the shutter controlled by the subject. Test field intensity was controlled with a pair of circular neutral-density

wedges, with adjustments (probably) made by the experimenter. Monocular observation was used and either a 1.6- or 2-mm artificial pupil usually was presented in the spectacle plane. Oxygen and other gas mixtures were breathed through a mouthpiece and all expired gases escaped into the room. Oxygen mixtures from 20.9 percent to 8.0 percent were used. In some experiments, the normal respiration rate was doubled. CO₂ was added to various gas mixtures in other experiments to test the effects of hypercapnia on visual sensitivity.

Sudden extreme reductions of oxygen tension produced rises in the threshold of these dark-adapted subjects that ranged from 0.2 to 0.5 log unit within 1 to 10 minutes of exposure to the low-oxygen mixture. The average decrease in sensitivity for 6 subjects exposed to air-nitrogen mixtures containing 8 to 10 percent oxygen was 0.35 log unit. The threshold typically returned to normal within a few minutes of return to room air. Some of these experiments showed brief wide fluctuations in this threshold after introduction of the low-oxygen mixture with thresholds increasing (sensitivity decreasing) as much as 0.7 to 1.0 log unit above thresholds in normal air.

One subject in these experiments involving rapid shifts in oxygen tension showed a remarkable increase in sensitivity upon return to room air in four of seven experiments. This was a 0.6-log-unit improvement over the subject's level of sensitivity in room air prior to hypoxia. This "hypersensitivity" lasted for about 5 minutes and then returned to normal in the one experiment for which data were presented graphically. This subject typically also experienced "vivid visual hallucinations" during this period of hypersensitivity. It may be no coincidence that no artificial pupil was used in the single experiment of the four showing this hypersensitivity in which results were presented graphically. The report does not discuss whether this hypersensitivity ever was displayed with an artificial pupil, nor was there discussion of whether any of this series of seven experiments used an artificial pupil.

One subject showed a paradoxical increase in sensitivity after a shift from breathing air to breathing reduced oxygen (11 percent). This was followed by a decrease in sensitivity well below his normal air sensitivity upon return to normal air. This paradoxical increase in sensitivity with hypoxia and decrease upon return to normal oxygen appeared in two of three experiments conducted with this subject. No artificial pupil was used in the graphically displayed results of one of these experiments and it was not stated whether the same natural-pupil condition held for the other two.

Despite providing cues in the study that some of the anomalous responses may have been related to pupil size changes, this was not

the explanation given by Wald et al. (1942). Instead, individual differences in rate of respiration were seen as the basis for these individual differences, since they disappeared in later experiments where subjects breathed at a constant rate set by a metronome. However, even if respiration differences were the basis of these changes they could have been mediated by pupil changes.

Wald et al. (1942) also carried out experiments where there was a gradual reduction of oxygen over long periods (5 to 6 hours). They found that thresholds first rose slowly until an oxygen percentage of 14 percent was reached, then rose more sharply as the oxygen percentage dropped to 11 percent. Subjects often became ill or were unable to perform for other reasons at lower oxygen percentages in these long-duration exposures. Thresholds returned to normal within 5 to 6 minutes when subjects were reexposed to air. Wald et al. (1942) also found that hypoxia of several hours did not change thresholds from thresholds determined with much shorter periods of hypoxia.

When the respiration rate was controlled with a metronome and a twice than normal rate was used, thresholds were reduced sharply (sensitivity increased), even when breathing room air. Thresholds returned to normal within 2 to 3 minutes when breathing rates returned to normal. When higher-than-normal oxygen concentrations (32 to 36 percent) were first breathed at a normal rate, then at a double-normal rate, this improvement in thresholds with hyperventilation still was noted. This showed the result was not the result of the increased oxygenation of the blood that results from hyperventilation. What is more, this breathing rate improvement in sensitivity could be completely abolished by adding 2 percent CO_2 to the 32 to 36 percent mixture. This indicated the improvement with increased respiration was a result of reduced CO_2 levels (hypocapnia) produced by hyperventilation. This was confirmed when raising the CO_2 level to five percent in gas mixtures actually increased thresholds by 0.2 to 0.5 log units at both normal and doubled rates of respiration.

Hyperventilation while breathing a 10 percent oxygen mixture delayed the drop in visual sensitivity and also prevented some of the typical reactions to 10 percent oxygen such as "subjective light," difficulty in concentrating, lassitude, etc. Somewhat surprisingly, adding 5 percent CO_2 to 10 percent oxygen did not alter thresholds from those obtained when breathing this oxygen mixture with almost no CO_2 included in the mixture. Five percent CO_2 had reduced sharply sensitivity for normal and above normal oxygen tensions. Five percent CO_2 did make it difficult for subjects to alter their respiration rate, however. They typically could not keep their breathing rate as slow as the metronome pace for the slow breathing condition (actually the normal respiration rate in air). They also were unable to complete the experiments

when this gas mixture was breathed rapidly, although no description of the specific problem(s) which caused them to quit was mentioned.

In summary, the series of experiments by Wald et al. (1942) provided more data for different respiratory conditions than probably all of the previous research on absolute sensitivity combined. Unfortunately, many of the observations reflect small numbers of subjects and some of the most interesting changes were for single subjects. The rather remarkable hypersensitivities, plus the paradoxical increases and decreases in sensitivity following decreases and increases, respectively, in the oxygen content of respiratory gases, all indicated absolute sensitivity is highly variable for single subjects as well as between subjects. Additional research might disclose that pupil changes or refractive changes (perhaps mediated by hypocapnia instead of hypoxia) account for some of these surprising effects.

At least two authors (Whiteside, 1957; Ernsting, 1965) provided data that apparently were collected by Goldie in 1942, although no original Goldie reference was provided and details were sketchy. Apparently airborne observers were flown by Goldie to various altitudes while breathing air or while breathing oxygen and the ranges at which they could detect targets in conditions of darkness were determined as a function of altitude and the resultant hypoxia. It was not clear whether these were ground or air targets. According to Whiteside, "the absolute threshold deteriorated even at the low altitude of 4,000 feet." Whiteside presented Goldie's results which were "expressed in terms of reduction in pick-up ranges."

Table I (from Whiteside, 1957)

Altitude in feet	Average % decrease in range of night vision if oxygen is not used.
4,000	5
6,000	10
8,000	15
10,000	20
12,000	25
<u>14,000</u>	<u>35</u>
16,000	40

This percentage reduction in "pick-up ranges" was relative to performance while breathing oxygen at these altitudes. The shift from linearity in these results at 14,000 feet was not discussed in either of the sources presenting these same results.

The form of these results and the 10 percent jump from 12,000 to 14,000 feet make one somewhat skeptical about their validity. On the other hand, the data apparently show effects of hypoxia on an operational task of aviators that could produce large performance differences in combat settings. This field research on hypoxia was unique and perhaps deserving of replication and emulation.

Chase and Hagan (1943) showed the photochemical bleaching of visual purple and the thermal reactions that follow such bleaching occurred with little or no modification in the absence of oxygen. They do not discount the possibility that hypoxia effects on sensitivity might reflect hypoxic effects on the regeneration of visual purple, however, contrary to what McFarland, Halperin, and Evans (1941) reported when they discussed this research.

Hecht et al. (1946) assessed the effects of hypoxia on brightness discrimination and also dark adaptation. Subjects for the contrast discrimination experiment were seven men and one woman. One man (S.H.) was 51 and the others ranged between 17 and 25 years. These brightness discrimination results are described in the next chapter on contrast sensitivity. Subjects for the dark adaptation thresholds were one man and one woman from the earlier younger group of subjects. To measure absolute thresholds, a circular 3-degree field was observed seven degrees nasally with one eye. Seven oxygen levels in addition to normal air were used: 16.4, 14.9, 13.2, 12.2, 11.1, 10.6, and 9.4 percent.

Absolute thresholds were increased significantly as a result of low-oxygen levels. For both rods and cones, a 0.5 log unit increase in the test spot luminance was required for detection when the oxygen percentage was 9.4 compared to test spot luminance with 21 percent oxygen (normal air). These absolute threshold elevations while breathing low oxygen corresponded closely to similar data obtained by McFarland and Evans (1939) and Wald et al. (1942). On the other hand, for both subjects, rod sensitivity actually improved when oxygen levels dropped to 11.1 from 12.2 percent with a subsequent resumption of the drop in sensitivity as oxygen was further decreased to 10.6 percent and (for one of the two subjects) to 9.4 percent. A similar improvement for contrast discrimination was found at low background intensities for this 11.1 to 12.2 percent change in oxygen tension. This improvement in sensitivity going to 11.1 from 12.2 percent oxygen may reflect a hypoxic change in some ocular process such as accommodation which improved focus of the sensitivity targets. No mention of an artificial pupil was made by the authors and it also is possible that pupil dilation occurred at this severe hypoxic level boosting effective retinal illumination. A pupil dilation was observed in cats when hypoxia reached severe levels by Sohmer, Freeman, and Malachi (1986), and this probably was the basis for a heightened visual evoked response compared to that occurring with less severe hypoxia.

Sheard (1946) assessed the effects of air and oxygen breathing on cone and rod thresholds at various altitudes, with and without increased intrapulmonary pressure. He first tested the absolute sensitivity of several subjects at altitude without increased intrapulmonary pressure. Four of these same subjects later participated in tests with increased intrapulmonary pressure. Dark adaptation was measured in a decompression chamber with the fixation stimulus and test stimulus presented in the chamber window one meter from the subject. One-half degree diameter light stimuli were presented either 1 degree (cone tests) or 10 or 15 degrees (rod tests) from the fixation light. Cone and rod adaptation thresholds were measured at altitudes of sea level, 5,000, 10,000, and 15,000 feet while subjects breathed air and while breathing oxygen. Other data collection occurred after dark adaptation. These were measures of the effects of different altitudes and different intrapulmonary pressures while breathing oxygen. Altitudes of sea level, 15,000, 37,500, 40,000, 42,000, and 43,000 feet were tested in these investigations.

At 15,000 feet, oxygen breathing improved cone sensitivity over an air-breathing condition by 0.31 log units and improved rod sensitivity by 0.62 log units. Breathing of pure oxygen at 37,500 feet and above, without increased intrapulmonary pressure, produced lower sensitivity for cones (1-degree stimulus) relative to conditions where the intrapulmonary pressure was increased. Thresholds were 0.5 or more log units lower when intrapulmonary pressures of 7.5 to 15 mm Hg were exerted. At 15,000 feet and below, pure oxygen produced maximum sensitivity and there was no increase in sensitivity as a result of increasing intrapulmonary pressure.

At the higher altitudes, an intrapulmonary pressure of 7.5 mm Hg typically produced the same maximum sensitivity as a pressure of 15 mm Hg. The greatest changes with increased intrapulmonary pressures occurred for rod thresholds and this paralleled the larger hypoxic effects on rod thresholds Sheard (1946) found with air breathing at 15,000 feet. The study gave insufficient discussion of the large individual differences observed. For example, Sheard predicted a correlation between differences in thresholds between air and oxygen breathing at 15,000 feet and differences in thresholds between nonpressurized and pressurized oxygen breathing at higher elevations. However, there was no subsequent discussion in the report of whether or not this predicted correlation actually was found.

Giardini (1948) used the Engelking-Hartung adaptometer and compared visual sensitivity for oxygen tensions corresponding to altitudes of 3,900, 4,900, and 5,900 meters with sea level sensitivity. These comparisons were made both with and without alcohol consumption. According to their English summary, alcohol caused fluctuations in final sensitivity. Hypoxia reduced sen-

sitivity with the effect directly related to altitude, but there apparently was no further reduction when alcohol was administered. The figures in their Italian-language report indicated the effect on sensitivity of 13 percent oxygen appeared to be minimal. However, an oxygen percentage of 11.4 produced a drop in sensitivity of about 0.25 log unit. Surprisingly, 10 percent oxygen appeared to have a slightly smaller effect on final sensitivity producing decrements of about 0.21 log units. However, there may have been only a single subject tested at each of these different oxygen tensions.

Posternak (1948a) reported that visual thresholds were lowered, i.e., sensitivity increased, as a result of a 10-day stay at an altitude of 3,450 meters on the mountain Jungfrauoch. Initial testing of absolute sensitivity at altitude did not differ from testing at 550 meters. However, absolute sensitivity increased almost linearly on successive tests at altitude and the average absolute threshold on the tenth day (sixth test) was approximately 0.3 log units lower than on the initial test at altitude or the prealtitude testing at 550 meters. Subsequent testing at 550 meters 2 days after returning from altitude showed a slight decrease in sensitivity. Although the altitude of 3,450 meters is certainly well below the 6,000 meters that typically produces large reductions in visual sensitivity, it is not clear why sensitivity increased as a result of stay at this moderate altitude over prealtitude testing and postaltitude testing.

Rose (1949) found results that were opposite to those reported by Posternak (1948a). He studied the effects of decompression in a chamber to 10,000 feet on night vision and the effect of a 2-week stay at an actual altitude of 10,000 feet on night vision. He used about 10 subjects for various sensitivity and muscle-balance measures. No discussion of subject characteristics was given. Measures were made of dark adaptation, "twilight acuity," phoria, abduction, and adduction at near sea level and then repeatedly during a nearly 2-week stay at 10,000 feet. Following the stay at elevation, additional measures were made in a decompression chamber and in normal air at near sea level.

A significant reduction in sensitivity from ground-level sensitivity was found by Rose (1949) in decompression chamber tests carried out at an "altitude" equivalent to 10,000 feet. However, on the first testing at an actual 10,000-foot elevation, visual thresholds measured during and following dark adaptation were not different from baseline measures at ground level. Testing at altitude occurred 1 day after arrival and it is possible that several hours of adaptation to this altitude prior to testing accounted for the failure to find reductions in sensitivity at an actual 10,000-foot altitude.

Rose (1949) did find some reduction in sensitivity over the extended stay at altitude suggesting a cumulative effect of hypoxia. The contrast with Posternak's (1948a) improvement in sensitivity over a stay at a similar altitude was striking. It is tempting to speculate that the distance of sensitivity targets for the two studies differed and that some change in refraction of the eye produced by extended stay at altitude improved focus and sensitivity for Posternak and decreased focus and sensitivity for Rose.

Alpern and Hendley (1952) studied the effects of metabolically-induced blood pH changes and respiration-induced blood pH and blood CO₂ changes on visual sensitivity and critical flicker frequency.⁴ Subjects were up to 28 normal young adults for various conditions of the study. Visual thresholds after 30 minutes of dark adaptation were measured with a Hecht-Shlaer adaptometer. Metabolic acidosis was produced by oral administration of ammonium chloride and the resultant pH change was -0.10. Metabolic alkalosis was produced by oral administration of sodium bicarbonate and the resultant pH change was +0.10. Hypercapnia (respiratory acidosis) was produced by having the subject breathe a mixture of 7 percent CO₂ and 93 percent O₂ and the resultant pH change was -0.12. Hypocapnia (respiratory alkalosis) was produced by having the subject hyperventilate voluntarily and the resultant pH change was +0.18.

Hypercapnia significantly impaired sensitivity. Rod thresholds were raised by an average of 0.23 log units and this corresponded to the results of Wald et al. (1942) for a similar condition. It is significant that this sensitivity reduction occurred despite the high oxygen content of the CO₂-oxygen mixture. Hypocapnia significantly improved sensitivity, lowering rod thresholds by an average of 0.16 log units and this too was consistent with Wald et al. (1942). Metabolic acidosis and alkalosis did not significantly change thresholds, although for alkalosis the effect was to increase the threshold (+0.01 log units for metabolic acidosis, and +0.10 log units for metabolic alkalosis). The implication was that it was CO₂ levels and not pH levels of the blood that altered vision. A substantially higher blood pH was produced by hyperventilation than by sodium bicarbonate, however, and this may be part of the reason that hypocapnia had a greater effect than metabolic alkalosis.

McFarland and Fisher (1955) noted some similarities between changes in dark adaptation as a function of hypoxia and changes in dark adaptation as a function of age. Both reduced final absolute sensitivity and sensitivity levels during dark adaptation. Despite

⁴ Critical flicker frequency results generally paralleled sensitivity results and are discussed in a later chapter.

these changes in sensitivity, the cone-rod "break" in the adaptation curve was not displaced earlier or later in time for different age groups. The same absence of change in timing of this cone-rod break occurred during sensitivity changes with hypoxia (e.g., McFarland and Evans, 1939).

Miller (1956) studied the effect of acetazolamide on the dark adaptation function in 6 patients with glaucoma who ranged from 42 to 80 years old. A Goldmann-Weekers adaptometer was used and testing occurred prior to the start of acetazolamide treatment and on a weekly or biweekly basis following this treatment. The changes noted were reductions in thresholds (increases in sensitivity). However, these were discussed as being practice effects occurring on the first few tests after pretreatment testing. On the other hand, this could have reflected improved performance as a result of acetazolamide.

Given the potent effects of acetazolamide on the standing potential of the eye (Yonemura and Kawasake, 1979) and the intraocular pressure (e.g., Bietti, 1972), and given the possible parallel effects of acetazolamide and hypoxia on visual field size (Kobrick, 1970),⁵ it would appear that research is needed on the effects of acetazolamide on dark adaptation and final sensitivity of normal eyes with subjects who are highly practiced on the dark adaptometer and with placebo treatments counterbalanced with acetazolamide over trials to separate drug and practice effects. The parallels between many acetazolamide effects and hypoxia effects could make such research highly relevant for our understanding of the mechanisms underlying hypoxic decrements in visual sensitivity.

Pierson (1967) examined mild hypoxia effects (8,000 and 9,300 feet) and effects of pure oxygen on absolute visual sensitivity and on reading performance measured by the "USAF Hypoxia Demonstration Chart." Subjects were 10 males with 20/20 uncorrected acuity whose average age was 28.3. The "adaptometer" in the study was a light source viewed by a group of subjects and "not all subjects were equidistant from the target in the brightness threshold tests." Ground-level testing preceded "altitude" testing which again was followed by another ground-level test in a repeated-measures design. Chamber air and pure oxygen were counterbalanced across the first two sessions. Thirty minutes of dark adaptation occurred prior to visual sensitivity testing.

According to Pierson, there were no effects of altitude or 100 percent oxygen on either the reading test or on the test of visual sensitivity and no effects of wearing an Oro-Nasal mask in the ambient air condition compared to not wearing the mask. However,

⁵ These studies are described in detail in following chapters.

there were substantial differences in the reported averages for these different conditions with altitude reducing sensitivity and with the mask reducing sensitivity. The standard deviations presented in the table would indicate these differences to be highly significant. However, standard deviations described in the report were smaller by a factor of 100 and probably the Table I standard deviations were reported incorrectly. The questions about statistical significance and the rather crude test of visual sensitivity make the results of this study somewhat in doubt.

Pretorius (1970) measured dark adaptation and final sensitivity levels at an actual altitude of 5,000 feet while breathing air and while breathing 100 percent oxygen. Subjects were "100 healthy young men with an average age of 19.5 years." A Goldmann-Weekers adaptometer was used with all subjects first tested in air and then the test was repeated at least 24 hours later while the subject breathed oxygen through an Oro-Nasal mask. A 25.9 percent improvement in sensitivity occurred in the second session with oxygen compared to the first session with air. The largest improvement occurred at scotopic levels late in the session. About 6.5 percent of this improvement may have been a practice effect, given the results for two identical air-breathing sessions of another 10 subjects. For these "control" subjects the improvement early in the session (after about 6 minutes of adaptation) was greater than for the subjects tested with pure oxygen at their second session.

There were a number of problems with the research. There was no discussion of how long subjects were at 5,000 feet above sea level before they were tested. There was the failure to counter-balance air and oxygen sessions. It was not clear from the report, but apparently the mask was only used for breathing of 100 percent oxygen and not for air breathing. Hyperventilation has been reported during mask breathing by Ernest and Krill (1971) and a possible resultant hypocapnia may have accounted for the improvement during oxygen breathing and not the oxygen itself. Alpern and Hendley (1952) found a 0.16 log increase in sensitivity following hyperventilation and this was considerably larger than the 25.9 percent improvement (in actual rather than log units) found by Pretorius (1970).

Ernest and Krill (1971) measured visual sensitivity changes under hypoxia while providing the important control of maintaining constant hemoglobin oxygen saturations. Three subjects were used who ranged in age from 24 to 34. They were tested in four different experiments over a period of 9 months. A modified Goldmann-Weekers adaptometer was used with a 20-minute diameter red fixation light and five test targets subtending arcs of 12 minutes, 30 minutes, 1 degree, 3 degrees, and 5 degrees. Targets were presented in the nasal field at a horizontal distance of 5 and 45 degrees from fixation. Test lights were either white, yellow, red, or blue. Subjects breathed a mixture of 90 percent nitrogen and 10

percent oxygen through a nasal mask during hypoxic conditions. Pupil size was observed or photographed using infrared light and it was concluded hypoxia did not alter pupil size. Ten percent oxygen led to a stable hemoglobin oxygen saturation of 75 ± 2 percent unless subjects hyperventilated which increased the oxygen saturation level. When subjects hyperventilated, it was judged to be primarily because of anxiety associated with the testing situation and not because of the hypoxia itself. All subjects initially showed hyperventilation, but all were trained to overcome this tendency and oxygen saturation of hemoglobin remained at the constant 75 percent level for all testing.

In all experiments, the authors used an ascending-descending threshold technique (both appearance and disappearance of the test target were reported) with the arithmetic average of these two readings taken as the threshold. This led to "scallop" of data for successive measurements (ascending thresholds were higher than descending thresholds). It is of major interest that this scalloping was much larger during hypoxic conditions than air breathing conditions. This indicated delays in decision making and/or responding during hypoxia. Such delays were well controlled with the technique used by Ernest and Krill (1971) of averaging of appearance and disappearance thresholds. However, these decision or response delays with hypoxia would be expected to bias results in the direction of a larger hypoxia effect in much more typical absolute and differential sensitivity measurements that include only ascending test target luminances and reports of the appearance of the target.

The first experiment of Ernest and Krill (1971) compared effects of hypoxia on the central retina with effects of hypoxia on the peripheral retina. They found the increase in absolute visual threshold with 10 percent oxygen over normal air was significantly greater for the 45-degree-eccentric targets than for the 5-degree-eccentric targets. This was particularly true for the smallest 12-minute target which required 3.77 log units more luminance to be seen under hypoxia when it was located 45 degrees from fixation but only 0.25 log units more luminance to be seen under hypoxia when it was located 5 degrees from fixation.

The second experiment concentrated on relative hypoxia effects for different-sized peripheral targets at an eccentricity of 45 degrees. Increases in threshold during hypoxia were not found to differ at the 45-degree location for two different target sizes of 0.5 and 5 degrees.

The third experiment examined relative effects of hypoxia on rod and cone vision. Under hypoxia (compared to air), red targets 5 degrees in diameter presented at an eccentricity of 5 degrees required a significantly larger increase in luminance for detection (0.42 log units) than luminance required for similar size/ec-

centricity blue targets (0.15 log units). The authors viewed this as a greater effect of hypoxia on cones than rods in this area of the retina, but were unsure why this was the case. As will be discussed later, Kobrick et al. (1984) found no effect of hypoxia on peripheral (and central) red targets, but did find a decrease in sensitivity for green targets.

The fourth experiment examined effects of hypoxia on the time course of dark adaptation. Hypoxia effects did not appear during the first 4 minutes of dark adaptation. Later stages of dark adaptation did show hypoxia decrements. These were larger for the yellow light than for the blue light used in this experiment. Both stimuli were 1 degree in diameter and presented at an eccentricity of 5 degrees. Data for the yellow light showed a pronounced rod-cone break since preceding light adaptation was for a blue light which, presumably, largely light-adapted the rods. Data for the blue light showed no such break since preceding light adaptation was for a red light which, presumably, left the rods in a condition of dark adaptation. The time of the rod-cone break for the yellow light occurred at about 12 minutes both during hypoxia and during air breathing, suggesting that hypoxia did not alter the adaptation process for either rods or cones, but instead affected the neural processes underlying or communicating sensitivity.

Problems with the research of Ernest and Krill (1971) included the large targets that confounded target eccentricity with target size. This confounding may account for nonmonotonic effects of hypoxia on target size at the 5-degree peripheral location since the peripheral location probably was less than 5 degrees for larger targets. Where provided, actual threshold luminances helped explain hypoxic results and such data might help explain the puzzling lack of difference found for 0.5-degree and 5-degree targets at 45-degrees eccentricity. Unfortunately, actual threshold luminances were not given for that experiment, but only the differences between air and low oxygen conditions. Actual threshold luminances were only presented for the series of tests providing the dark adaptation curve and for a figure showing the dramatic increase in "scalloping" of ascending and descending thresholds that was described earlier.

Kobrick and Appleton (1971) studied the effects of extended hypoxia on visual performance and retinal vascular state. They assessed a variety of visual functions with eight healthy soldier volunteers ranging in age between 18 and 25. Dark adaptation was measured at sea level and after 1, 18, 24, and 48 hours of exposure to an altitude of 15,000 feet in a decompression chamber. The adaptometer presented a 0.25-second flash of violet light subtending 1 degree of visual angle. This was displaced 10 degrees to the right of a fixation point. Viewing was monocular with the right eye. Flashes occurred every 4 seconds. Subjects used a control knob to raise the luminance of the flash to the level allowing

detection. Luminance levels were plotted automatically on a strip chart recorder.

Changes occurred in dark adaptation and some other visual performances as a function of hypoxia. The maximum drop in absolute sensitivity was found at the initial test 1 hour after reaching altitude. Recovery then occurred to near sea level performance for the test at 24 hours. Some increase in thresholds (decrease in sensitivity) then was observed at the 48-hour test compared to the 24-hour test. As will be discussed in Chapter 5: "Critical flicker/fusion frequency," CFF decrements also were maximal at the 1-hour test and also showed some recovery at later testings.

Wiedman (1973) measured a number of visual functions at different altitudes on Mount Everest. He found an average drop in absolute sensitivity of 0.4 log unit when measurements were made at 4,000 meters compared to 1,200 meters for 15 subjects ranging in age from 9 to 68. Three subjects tested at 5,000 meters each showed a further drop in visual sensitivity. Distance of the sensitivity target was a close 33 cm and it may be no coincidence that lowest sensitivities and the largest changes in sensitivity with altitude typically occurred for the subjects of presbyopic age.

Jones and Wilcott (1977) reported sharply increased thresholds while running on a treadmill compared to a control condition of standing on the treadmill. The phenomenon apparently was most noticeable at early stages of cardiovascular exercise. Thresholds in the inferior visual fields were particularly elevated compared to superior visual fields when both were measured during exercise. These thresholds were both higher than temporal fields measured during rest. Unfortunately, key control conditions of inferior and superior fields at rest were not included in the research. Jones and Wilcott pointed out the parallels between their apparent finding of an inferior field loss of sensitivity with running and research by White (1961) on the effect of "G" forces on retinal circulation. White found "gray-out" occurs earlier in the inferior field when the subject is upright and "gray-out" occurs earlier in the superior field when the subject is upside down.

Schull et al. (1981) investigated the effects of extended exposure to altitude on 2,3-diphosphoglycerate levels and on night vision. The glycolytic intermediate 2,3-diphosphoglycerate decreases the affinity of a hemoglobin solution for oxygen (making oxygen more available to tissues) and changes in the amount of 2,3-diphosphoglycerate may account for part of the adaptation that occurs to extended hypoxia. Four males and four females were used as subjects. All were free of ocular defects or organic disease other than correctable refractory errors. There was no description of their age. Subjects were tested at sea level and again 5 weeks

later at 4,250 meters after 5 weeks of residence in the Andes with most of the time spent at elevations above 4,080 meters. Light-tight goggles presented a light-emitting diode of increasing brightness and subjects responded when it became visible. Prior to dark adaptation, bleaching occurred for 1 minute while a sheet of bond paper one foot from the eyes was illuminated by a 150-watt white incandescent bulb located about one foot away from the paper.

Hemoglobin levels, 2,3-diphosphoglycerate levels, and hematocrit levels were measured at sea level and again at elevation after 5 weeks and these then were correlated with changes in dark adaptation. Higher luminances were required at 4,250 meters for detection of the light throughout the dark adaptation period. This held for both men and women. There was an increase of 2,3-diphosphoglycerate from sea level levels, and the subjects showing largest increases tended to see the dim stimulus light sooner during dark adaptation. However, these changes did not strongly predict the visual sensitivity changes that occurred for hypoxia compared to sea level testing. Hemoglobin and hematocrit also increased over the adaptation period, but there was no discussion of the correlation between these changes and sensitivity changes.

With the adaptometer used by Schull et al. (1981), subjects had 1.5 seconds to respond to the stimulus before it doubled in luminance. This may not always have been enough time to respond to the luminance level, especially if it became visible relatively late in the 1.5 second "on" period. If so, a substantially higher target luminance level would have been recorded than was actually required to see the target. The slowing of decision and/or reaction times with hypoxia indicated by direct reaction time measures (e.g., McFarland, 1937b) and by the increased scalloping of ascending and descending thresholds found with hypoxia by Ernest and Krill (1971) would increase the chances of a higher (doubled) luminance being recorded than the actual luminance that was required for target detection. Thus, there is another possible explanation of the results of Schull et al. (1981) based on hypoxic reaction time increases.

Kobrick et al. (1984) studied the effects of extended hypoxia on night vision using a microprocessor-controlled, light-emitting diode dark adaptometer developed by O'Mara et al. (1982). Subjects were 12 healthy male soldiers volunteers, aged 18 to 30 with normal acuity (corrected if necessary), normal stereopsis, normal phoria, and normal color sense. Measurements were made at sea level, then on days 2, 4, 8, 9, 11, 13, and 16 following travel to an elevation of 4,300 meters. Followup testing occurred after their return to sea level. Prior to these tests, subjects received extensive training on the task of making measurements with the adaptometer.

The adaptometer presented five lights simultaneously with one at the center and four at the corners of a 20-degree square

surrounding the center. The lights were 57.6 cm from the subject. Red or green stimuli were flashed at increasing brightness (actually increased duration) until the subject indicated he saw them. No fixation point was used. Subjects were light-adapted for 5 minutes prior to adaptation and thresholds were measured for 20 minutes. Red and green stimuli were alternated on successive threshold measurements.

Substantial elevations of threshold occurred for the green display at altitude on days 4, 6, 9, and 16, particularly for the trials occurring between 1.5 and 9 minutes during dark adaptation. These altitude-associated reductions in sensitivity occurred only for the green display and not for the red display. A "rest and relaxation" trip to 3,200 meters for 8 hours on day 11 appeared to overcome much of the hypoxic effect on sensitivity. Measures made in the evening after their trip on day 11 and at the following test on day 13 did not show decrements. No discussion of the followup testing at sea level occurred and there also was no discussion of whether central or peripheral lights of the 5-light display were first detected.

The wide disparity between the wave lengths of the red stimuli (610-660 nm) and the green stimuli (555-575 nm) used by Kobrick et al. (1984) suggests chromatic aberration of the eye may have been a factor in these results. If hypoxia were to alter the refraction of the eye so that an increase in blur of the optically close green stimulus occurred and/or a reduction in blur of the optically distant red stimulus occurred, this could account for the differential effects of hypoxia on red and green stimuli. Since 4 of the stimulus lights were located 14 degrees peripherally in the upper left, upper right, lower left, and lower right quadrants and only 1 was presented in the center, accurate focus for the peripheral stimuli may have been more critical than central focus.

Abraham et al. (1984) measured scotopic thresholds of the human retina during a period of treadmill running at 60 to 75 percent of maximum effort. Running increased thresholds, but this appeared to be only because of head movements and associated eye instability, since thresholds did not differ between measurements made in the first minute and measurements made after 10 minutes of running. Another study by some of the same authors showed no change in threshold as a result of pedaling a bicycle ergometer at 60 to 75 percent of maximal effort. The implication was that physical tasks demanding of oxygen do not lead to any significant reduction of blood flow to the retina or other visual centers. Earlier, Jones and Wilcott (1977) had reported sharply increased thresholds in the lower visual field while running compared to rest (standing on the treadmill) and Abraham et al. speculated that head movements may have been the reason for higher thresholds, not reduced circulation of blood oxygen to the retina.

Luria and Knight (1987) measured scotopic sensitivity while subjects breathed 10 percent oxygen or 21 percent oxygen. Subjects were dark adapted for 30 minutes before scotopic thresholds were measured. Blood-oxygen saturations were measured during the experiment. All 6 subjects showed a decrease in scotopic sensitivity and these drops averaged 0.38 log units. Blood oxygen saturation changed from an average of 97 percent while breathing air to an average of 77 percent after 7 minutes of breathing the 10 percent oxygen mixture. Luria and Knight also measured blood levels of CO₂ and found no change for the two oxygen tensions and concluded hypocapnia was not a factor in the sensitivity change. In earlier research, these authors had not found any significant decrease in sensitivity for subjects breathing 13 percent oxygen and this indicated that decrements in sensitivity as a result of hypoxia are minor prior to the breathing of some critical oxygen tension between 13 percent oxygen and 10 percent oxygen.

Carbon monoxide hypoxia and sensitivity

Abramson and Heyman (1944) studied the effects of inhalation of carbon monoxide on dark adaptation. They assessed effects of CO-breathing levels on visual sensitivity after 30 minutes of dark adaptation. Their subjects were 14 people "aged about 20 years." A Hecht-Shlaer-type adaptometer was used for data collection with nine subjects and a "biophotometer" was used for the other five. Dark adaptation was measured, after which different air-CO mixtures were breathed for 20 minutes and COHb levels ranging from 5 to 30 percent resulted. Absolute sensitivity then was measured again. No diminution of dark adaptation was found when adaptation was measured with the biophotometer. The Hecht-Shlaer-type adaptometer data indicated some subjects showed reductions in sensitivity of up to 0.65 log units. However, 5 of the 9 showed decrements of 0.1 log unit or less and the loss was not correlated with COHb levels. Subjects with the two highest COHb levels (26.5 and 30 percent COHb) showed no change before and after CO inhalation. A problem with the study was that dark adaptation may have continued beyond 20 minutes, producing increased sensitivity during the second testing following elevation of COHb and this may have countered the COHb effects. On the other hand, since COHb levels apparently reduce blood oxygen saturation without causing the subjective discomfort that low-oxygen hypoxia produces for comparable reductions of blood oxygen saturation, the question is raised whether or not the greater discomfort in hypoxic hypoxia is a factor in reduction in visual sensitivity, perhaps via stress-induced lens or pupil adjustments that increase the retinal blur of sensitivity targets.

Scobee and Chinn (1944) used the Hecht-Shlaer adaptometer to measure light and form thresholds in an unspecified number of

subjects breathing CO mixtures. They did not find any reduction in night vision even with COHb levels greater than 20 percent.

McFarland et al. (1944), studied the effects of carbon monoxide and altitude on visual thresholds both separately and in combination using "young men aged 16-25" as subjects. They found the effects of a given level of COHb on sensitivity were roughly the same as an equal loss of O₂Hb due to breathing of reduced oxygen mixtures. This result contrasts with that of Abramson and Heyman (1944) and Scobee and Chinn (1944). This study will be discussed in more detail in the next chapter on contrast sensitivity.

Luria and McKay (1979) studied the effects of low levels of carbon monoxide on a "night vision" test requiring detection of peripheral targets presented at different locations. No effect of a 10 percent increase in COHb levels was found on the number of targets detected.

Hyperoxia and sensitivity

According to Beehler (1964), Becker-Freysing (1950) found no decrease in dark adaptation of subjects who spent 60 hours living in a 90 percent oxygen environment. Eckel (1951) studied the effects of breathing oxygen under high tensions up to pure oxygen and also found no change in the course of dark adaptation or final levels of sensitivity.

Herlocher et al. (1964) studied dark adaptation under conditions of increased oxygen partial pressure, including long exposures to oxygen at increased pressure with and without associated nitrogen. Subjects were 8 healthy airmen ranging in age from 18 to 24. Four subjects were exposed for 30 days to an oxygen partial pressure of 233.1 mm Hg along with a nitrogen partial pressure of 436.1 mm Hg. and a CO₂ partial pressure of 4.1 mm Hg (total pressure 700 mm Hg). Four other subjects were exposed for 30 days to an oxygen partial pressure of 254.1, CO₂ partial pressure of 1.3 and nitrogen partial pressure of 0.5 (total pressure 258 mm Hg). Dark adaptation was measured with a Goldmann-Weekers dark adapter. Dark adaptation curves were made 3 times before the experiment, 15 times during the experiment, and 3 times after the experiment. No changes in adaptation were noted in either of the increased oxygen atmospheres or following return to ambient air.

Paulson and Ryan (1981) reported that Gallagher et al. (1965) investigated the effects of breathing 100 percent oxygen at sea level for 24 hours and found no significant changes in a wide variety of visual functions including acuity, stereopsis, perimetry, color vision, and dark adaptation.

Kent (1966) studied the effects of breathing pure oxygen at one atmosphere and at 2.82 atmospheres on dark adaptation measured with the Hecht-Shlaer adaptometer. Subjects were qualified diving instructors, aged 25 to 35, plus one 57-year-old who was not an instructor. A stable absolute threshold was obtained after from 30 to 45 minutes of adaptation and then the mask-breathed air was changed to oxygen. Five subjects were tested at a pressure of one atmosphere and four of the five showed no significant change. The fifth demonstrated a 0.20 log unit decrease in sensitivity. This subject demonstrated this increase in thresholds on a number of subsequent testings.

Four subjects were tested at 2.82 atmospheres. Two showed small rises in rod thresholds, one showed no change, and one showed an uneven lowering of the threshold (increased sensitivity) which reached a final level of 0.25 log units below that for air breathing at one atmosphere. Kent called for further research on what appeared to be a reduction of sensitivity under hyperoxia. However, the most substantial change was the 0.25 log unit improvement and it may be that some other factor such as oculomotor adjustments in the situation improved stimulus visibility for some subjects and decreased stimulus visibility for others.

Pierson (1967) looked at the effects of breathing pure oxygen as well as the effects of hypoxia on sensitivity. No effect of breathing pure oxygen was noted. This study was described in more detail earlier in this chapter.

Elsas, Anderson, and Lefler (1968) determined the effects of hyperbaric oxygen (pressures of two and three atmospheres) on visual sensitivity. Subjects were five persons who provided full data and another three who provided partial data. No discussion of subject characteristics was given. A Goldmann-Weekers adaptometer was used with a red fixation point 11 degrees above the circular white test field which subtended 11 degrees. Dark adaptation curves were obtained in normal air and pressure while breathing 100 percent oxygen at 15 psi (1,536 mm Hg) and while breathing 100 percent oxygen at 30 psi (2,311 mm Hg). Fifteen minutes of oxygen breathing preceded the initial threshold testing.

Dark adaptation under hyperoxia was similar to that with air breathing at normal pressure. Data in one table appeared to indicate faster adaptation at 30 psi during the first 2 minutes. However, according to the authors, no effects were found on the rate of adaptation or on final sensitivity as a result of oxygen breathing under increased pressure compared to breathing of air at normal atmospheric pressure. These same data were reported in Anderson (1968).

Large individual differences were found by Elsas, Anderson, and Lefler (1968). Subjects varied in final thresholds from 0.15

millilux to 0.019 millilux and this extreme variation of data among the 5 subjects suggests that a replication of hyperoxia effects on dark adaptation may be in order. It also suggests that the Goldmann-Weekers adaptometer magnifies individual differences in refraction or individual differences in some other visual process which may be influenced by hypoxia.

Conclusions and research needs

Hypoxia produces definite reductions in absolute visual sensitivity, but most studies have found little effect on visual sensitivity until oxygen tensions are only half that with oxygen at sea level. These low oxygen tensions that produce reliable decrements in visual sensitivity already are approaching the oxygen tensions that lead to unconsciousness.

Subjective changes in world brightness associated with hypoxia and recovery from hypoxia may reflect the same changes in retinal sensitivity that underlay the decrements found in laboratory research on the effects of hypoxia on dark adaptation and absolute sensitivity. On the other hand, these subjective brightness shifts could be the result of pupillary changes since pupillary changes have regularly, though inconsistently, been reported to occur with hypoxia.

The studies reviewed in this chapter showed that a reduction in the oxygen in the blood hemoglobin as a result of carbon monoxide usually does not have the same deleterious effect on visual sensitivity as a comparable reduction of blood hemoglobin due to low oxygen tension. This has also been noted for other types of human performance (Christensen et al., 1977). Severe hemic hypoxia (carbon monoxide poisoning) is much less unpleasant than severe hypoxic hypoxia. It may be that the stress associated with hypoxic hypoxia produces changes in the system or behavior that influence visual performance to a greater extent than the low oxygen content of the blood. Hyperventilation is stimulated by anxiety, but hyperventilation probably is not the explanation of the greater hypoxic hypoxia decrements than hemic hypoxia decrements, since hyperventilation typically improves visual sensitivity. Reduced breathing rates may magnify hypoxic problems or even lead to CO₂ buildups that reduce sensitivity, but this has received no investigation as the explanation of the difference between hemic hypoxia and hypoxic hypoxia. These differences between the two types of hypoxia and their effects on vision would appear to provide an important area for future research.

The key role of hyperventilation in visual changes during hypoxia was recognized early (Wald et al., 1942). Without control of hyperventilation or measurement of CO₂ levels in the lungs and blood, hypoxic effects on sensitivity are apt to be masked by the

large changes in vision produced by low (and high) levels of CO₂. Hyperventilation has been associated with hypoxia in many studies and the resultant increased oxygen and reduced CO₂ would tend to maintain visual sensitivity in the face of reduced oxygen tensions. The not unusual finding of an improvement in sensitivity, despite a reduction in oxygen tension, may reflect hypoxic initiation of hyperventilation and hypocapnia. Studies like that of McFarland and Evans (1939) which found decrements in sensitivity with only moderate hypoxia may have been very successful in preventing hyperventilation. Hopefully, their results did not reflect lower-than-normal ventilation which would both magnify hypoxia and lead to hypercapnia. It is critical that future research on hypoxia and vision include measures of arterial oxygen tensions and CO₂ tensions.

Acetazolamide produces effects on the acid-base balance of the blood and tissues, and, as mentioned earlier, produces large effects on the standing potential of the eye (Yonemura and Kawasake, 1979) and the intraocular pressure (e.g., Bietti, 1972). There also are possible parallel effects of acetazolamide and hypoxia on visual field size (Kobrick, 1970). These ties of the drug acetazolamide to hypoxia indicate a need for research on the effects of acetazolamide on dark adaptation and final sensitivity. This should be conducted with normal eyes of subjects who have had extensive practice on the adaptometer and with placebo treatments counterbalanced with acetazolamide over trials to unconfound the confounded drug and practice effects in Miller's (1956) research.

Response slowing may account for some of the sensitivity changes with hypoxia obtained by McFarland and most other researchers who only used ascending levels of target luminance to measure sensitivity. When Ernest and Krill (1971) used descending as well as ascending target luminances, they still found decrements in sensitivity with hypoxia, but the large scalloping of successive thresholds they found also illustrated the hypoxia-enlarged response (or decision) component that would have falsely enlarged their hypoxia effect had they used the typical procedure of only raising luminance levels until targets were seen.

Almost every study has reported large individual differences in visual sensitivity decrements as a result of hypoxia. Even Ernest and Krill (1971), who monitored blood saturation and maintained it at a constant level, provided data in their tables that indicated large threshold differences among their three subjects. Research specifically aimed at identifying the bases of individual differences in decrements in sensitivity associated with hypoxia would appear to have much value for selection of aviators and other personnel who might be faced with hypoxic challenges in military situations. Such research might also lead to cardiovascular training or other training that might improve visual performance in hypoxic conditions.

The research reviewed in this chapter included a number of studies which examined factors in addition to hypoxia to determine whether and how they would influence the decrements in absolute sensitivity produced by hypoxia. These included binocular vs monocular stimulation, Vitamin A, insulin, glycogen, 2,3-diphosphoglycerate levels, and hematocrit levels. Researchers interested in replicating or extending research on these variables mediating the effects of hypoxia on vision would probably be better off using measures of differential visual sensitivity rather than measures of dark adaptation and absolute sensitivity. As McFarland, Halperin, and Niven (1944) pointed out, the absolute sensitivity research paradigm lacks sensitivity and has other disadvantages compared to the differential sensitivity paradigm (see Chapter 2: "Visual acuity and contrast sensitivity"). The research recommended above on individual differences in hypoxic decrements on visual sensitivity and the recommended research on differences between hemic hypoxia and hypoxic hypoxia also would be better carried out on differential sensitivity instead of absolute sensitivity.

There are at least two sets of contradictory results in the area of absolute sensitivity that probably could be resolved through additional research. One was the changes in hypoxic decrement in absolute sensitivity as a function of long-term exposure to moderate hypoxia. Some studies showed adaptation (Kobrick and Appleton, 1971; Posternak, 1948a) over several days and another showed increasing hypoxia decrements in sensitivity over a similar time period (Rose, 1949). The other was the opposite effects of hypoxia on absolute sensitivity found for colors widely separated on the spectrum (Kobrick et al., 1984; Schmidt, 1939). In both sets of contradictions, an interaction of target distance and hypoxia-caused refractive changes may have been the basis for the different results.

Chapter 2

Visual acuity and contrast sensitivity

Contrast sensitivity sometimes has been measured by having subjects simply report when they first can see a target against a background and this methodology is highly similar to research paradigms for absolute sensitivity. Subjects in other studies have been required to identify the orientation of gratings or other contrast targets. All of these studies can be considered studies of visual acuity, although measurement of visual acuity typically has involved small high contrast targets. As will be discussed in this chapter, studies of contrast sensitivity with low background luminance actually have provided more reliable measures of the effects of hypoxia on visual sensitivity than studies of absolute sensitivity.

Although the literature on the effects of hypoxia on contrast sensitivity and acuity was large, only a small amount of research was found on the effects of hyperoxia, carbon monoxide, hypocapnia, and hypercapnia. As a result, the few studies that were not confined to hypoxia are included chronologically with the hypoxia research, rather than in separate sections as was the case with absolute sensitivity and dark adaptation research.

Wilmer and Berens (1918) looked at retinal sensitivity in their study of hypoxia and ocular functions and one of their targets was a dark gray square on a lighter background which was viewed through a neutral-density wedge. However, despite discussion of the methodology for testing sensitivity to this contrast difference and despite presentation of sea level settings of the wedge which just rendered the square invisible, no discussion of hypoxic changes in sensitivity to the dark square on its slightly lighter background was provided in the report. This probably indicated that hypoxia did not influence sensitivity for this stimulus.

Wilmer and Berens (1918) also measured visual acuity using the Ives visual acuity test object. They indicated that their attempt to use Snellen's type was "unsatisfactory." Their Figure 1 illustrated a small decrease in acuity for subjects who experienced hypoxia through use of the Henderson rebreathing apparatus which over a period of about 20 minutes reduces normal oxygen tension to a tension equivalent to about 20,000 feet or higher. In the 25 subjects tested, visual acuity was unchanged for 15, improved for 3, and deteriorated for 7. These proportions provide little basis for concluding that a decrement in acuity occurred with hypoxia in their study.

Bagby (1921) used a series of tests to measure aptitude for dealing with hypoxia in pilots. The Henderson rebreathing apparatus was used and they measured visual acuity, but found the Ives test "not well adapted to research, the scale of adjustment being too coarse." They did find that acuity performance was reduced markedly, but this only occurred just before the subject collapsed. This period of low performance not only reflected deterioration of acuity, but of attention and cooperation, as well.

According to McFarland, Evans, and Halperin (1941), Schubert (1932) used Masson disks and found that hypoxia induced by breathing an oxygen concentration between 8 and 10 percent produced "a considerable decrease in visual intensity discrimination." The exact level of oxygen tension probably is reported in the original article. McFarland, Evans, and Halperin combined their comments about the Schubert study with a discussion of Gellhorn (1936a) and Gellhorn did use a range of oxygen levels from 8 to 10 percent. Masson disks and the Gellhorn results are described in considerable detail below.

The effects of hyperoxia on visual acuity also received early emphasis. Behnke, Forbes, and Motley (1935) included measurements of visual acuity in their study of circulatory and visual effects of oxygen at a pressure of three atmospheres. During the first 3 hours visual acuity decreased by up to 25 percent and it may be no coincidence that there also was dilation of the pupils which would have increased spherical and chromatic aberration of the eyes (Bachman and Behar, 1987). In the fourth hour when the subjects were near collapse, visual acuity was reduced as much as 60 percent or even temporarily lost. Color acuity also was typically lost at impending collapse.

Although it is not clear what photopic visual performance was tested, Strughold (1936), according to Cooke (1970), reported that exposure of man to altitudes just under 10,000 feet affected photopic vision when air was breathed.

Gellhorn (1936a) assessed the effects of hypoxia, elevated CO_2 , and hyperventilation on visual intensity discrimination. He used a limited number of highly-trained subjects. Two Masson disks were presented at a distance of one meter. They were rotated rapidly and this caused white marks on the disks to appear as a series of rings of differing brightness and the subject reported how many rings could be distinguished against their darker background. Subjects then breathed oxygen at low levels (8 to 10 percent) for approximately 10 minutes with the same intensity discriminations taking place at 1 or 2 minute intervals during breathing of the low-oxygen mixture. Similar experiments occurred in another condition where the air that was breathed contained six percent CO_2 and in another condition where testing occurred during and following 2 minutes of hyperventilation.

Gellhorn found all three treatments produced reliable decrements in intensity discrimination. The one subject who received 8, 9, and 10 percent oxygen showed decrements in contrast sensitivity inversely proportional to these three levels. Ten percent oxygen produced only a small decrement in the number of rings that were visible, whereas nine and eight percent oxygen caused a sharp drop in their number.

Recovery from hypoxia was typically swift following a return to breathing normal air. The same was true of recovery from hyperventilation. Recovery from CO₂ was slower for some subjects. A return to air breathing frequently led to intensity discriminations that were better than prior to hypoxia or hyperventilation. Apparently no such "hypersensitivity" followed CO₂ breathing. Artificial pupils were used during some of these trials and it was reported that this led to similar results as when they were not used.

Many experimenters have found hyperventilation to improve visual performance (e.g., Alpern and Hendley, 1952) and Gellhorn's claim of a reduction of contrast sensitivity with hyperventilation may be misleading. His measurements of low sensitivity during hyperventilation are suspect given the interference between the simultaneous activities of breathing maximally 35 times per minute and making intensity discriminations. Gellhorn reported measurements made following hyperventilation "not infrequently" showed increases in sensitivity over prehyperventilation levels. This may correspond to the later Alpern and Hendley findings of increased sensitivity with hyperventilation.

Gellhorn (1936b) partially replicated his earlier study of hypoxia effects and added a condition where three percent CO₂ was combined with low oxygen mixtures of eight or nine percent. The CO₂ almost totally eliminated decrements in contrast sensitivity as a result of hypoxia. Improvement in cerebral circulation was seen as one probable basis for the change. Other factors mentioned were a shift to the right of the oxygen dissociation curve of the blood and improved muscular tonus which increases the venous return to the heart. No discussion was given of the probable increase in breathing rate associated with CO₂ breathing which presumably would increase blood oxygen saturation and, given the fairly low percentage of CO₂ in the breathing mixture, may have actually reduced arterial CO₂.

According to McFarland, Evans, and Halperin (1941), Berger and Bøje (1937) found that hypoxia had little effect on subjects' ability to resolve the separation between luminous squares, but had a strong effect on resolution of the gap between black squares. They had two ametropic subjects breathe an 8.7 percent oxygen mixture. Squares were moved apart until separation was noted and moved together until they were "fused." The separation-fusion

thresholds for black squares rose 30 percent with hypoxia for one subject and 100 percent for the other. On the other hand, for white squares, these separation and fusion thresholds were largely unchanged. Although no actual improvement in resolution was reported, this absence of any deterioration in square resolution may have reflected an effective decrease in stimulus brightness as a result of hypoxic sensitivity changes. Decreasing the brightness of close together bright targets on a dark background reduced the distance required for their perception as separate (Berger et al., 1943).

Evans and McFarland (1938) measured visual acuity in their research on the effects of hypoxia on the size of the angioscptomata. They used four healthy subjects who were highly trained in experiments on oxygen deprivation. Acuity was measured with a Snellen chart illuminated by 5 footcandles and acuity remained unaffected when breathing low oxygen mixtures equivalent to 8,000, 17,000, and even 20,500 feet. However, spherical correction changed substantially during exposure to these different oxygen tensions for two of the subjects, as is described in the chapter on hypoxic changes in accommodation.

A more thorough investigation of hypoxia effects on acuity was carried out by McFarland and Halperin (1940). They studied the relationship between foveal visual acuity and illumination in one series of experiments where the subjects breathed oxygen-nitrogen mixtures of normal air, 10.34 percent oxygen (18,000 feet), and 100 percent oxygen. In another series of experiments, subjects breathed air, 14.31 percent oxygen (10,000 feet), 10.34 percent oxygen, and 100 percent oxygen. Two subjects were used for the first series at numerous luminance levels and two gas mixtures. Nine subjects were used for the second series and were tested at low and high luminance levels and with three gas mixtures. Illumination of the backgrounds for the acuity targets ranged from -2.7 log photons to 3.12 log photons in the first series and ranged from 1.159 log photons to 3.12 log photons in the second series.

The acuity target was a black Landolt C which was adjustable in size. This was presented at a distance of one meter against a red background. The gap could be presented in one of eight different meridians, 45 degrees apart. The Landolt C first was presented at a size too small to resolve the gap location and was increased in size continuously until the subject responded. An incorrect response led to a change in gap location and a resumption of the increase in size. Following a correct response, the acuity was recorded and the stimulus reduced in size and reoriented for the next presentation.

For low luminance backgrounds, hypoxia caused highly significant drops in acuity compared to acuity while breathing air. The decrement in visual acuity at 18,000 feet was about twice that

at 10,000 feet. Much smaller decrements with hypoxia occurred at higher background luminance levels, although these decrements also were statistically significant. Following breathing of oxygen, acuity returned to normal and even to higher-than-normal levels. McFarland and Halperin (1940) pointed out that these hypoxia effects on sensitivity corresponded to the effect of a simple reduction in target luminance.

As with research on absolute sensitivity where the stimulus intensity always is increased until the target is seen, these acuity measurements would be influenced by hypoxic slowing of reactions to the continuously increasing stimulus, and the faster the increase in stimulus size the greater this probable effect. At the highest background luminance, there was only a six percent drop in acuity with hypoxia and this could be considered the upper limit of any hypoxia-slowed-reaction-time effect in the McFarland and Halperin (1940) study.

According to Rose (1950b), Raber (1941) assessed the effects of decompression to various altitudes (sea level, 2,000, 3,000, and 5,000 meters) using the "nyktometer" which, according to Rose (1950b), measured changes in visual acuity for a series of dim targets during a 2-minute period following adaptation to a bright adapting field. Impairments (delays to letter recognition) were found which were directly related to altitude, although performance at 2,000 meters differed little from performance at sea level. Performance at 3,000 meters was more similar to performance at 5,000 meters than to performance at 2,000 meters. One test at 5,000 meters occurred while the subjects breathed pure oxygen. Visual acuity appeared to be somewhat higher during the second minute of testing in this hyperoxic condition than for other conditions, including the testing at sea level. Apparently, this was because the sea-level air in the small decompression chamber was "stale" and not because of any real improvement of acuity for higher-than-normal oxygen tensions.

Raber (1941), according to Rose, also measured acuity with the Novak-Wetthauer apparatus (Rose, 1950b) which requires 45 minutes of dark adaptation prior to testing of acuity with very dim targets (this also can be considered a test of absolute sensitivity). Hypoxia (decompression to 3,000 and 5,000 meters) decreased performance. Subjects with highest acuity at ground level experienced the largest decrements. This sounds to this reviewer like regression to the mean. Rose (1950b) also was not certain it was a real effect, but he hypothesized that it might be a function of probable higher intelligence of the high performers at sea level and that "extraretinal" intelligence functions were more susceptible than retinal functions to hypoxia. Another interesting possibility is that refractive shifts may have occurred with hypoxia (Evans and McFarland, 1938; Ohlbaum, 1969) and these

improved performance for some subjects and/or reduced it for others at the four-meter distance of acuity targets.

Rose (1950b) reported that Lehmann (1943) found sharp reductions in "rate of adaptation" when oxygen tensions were below normal (oxygen pressures equal to 41, 47, 53, and 62 mm Hg). At 41 mm Hg, the rate was one-half that at 100 mm Hg. The rate was about 15 percent higher than normal for a hyperoxic condition with an oxygen tension of 500 mm Hg. They used Graf's Fahrbahn testing procedure with low illumination. This procedure was not described by Rose (1950b).

Berger et al. (1943) studied the effects of hypoxia on ability to see the gap between a pair of bright dots presented against a less bright background. It was expected resolution of the gap between dots would actually be improved by hypoxia as it is by a reduction in dot luminance. Such a result would add support to data from acuity experiments that indicated effects of hypoxia were directly comparable to simple reductions in target luminance.

Subjects in this critical experiment were four emmetropes. Two bright dots against a darker background were moved apart until they were seen as separate. They then were moved together until they were seen as one. These fusion and separation distances were recorded. Different dot brightnesses of 10, 64, 753, 4,085, and 7,200 lux were used. Viewing distance was four meters and a three-mm artificial pupil was used in front of the right eye. The left eye was occluded with an opaque disk. Observations were made with each dot brightness while breathing air and while breathing 10 percent oxygen. Observations also were made while breathing 100 percent oxygen at 4,085 lux. Gas mixtures were counterbalanced across subjects, as were ascending and descending levels of dot luminance. Gas mixtures, including air, were administered with a nasal mask.

On the average, increased luminance of dots required larger separation of the dots for their resolution. This finding was independent of the gas mixture breathed. Since the dim 10 lux dots were not visible in the hypoxic condition, the minimum luminance during hypoxia was raised from the 10 lux used in air to 18 lux. Under hypoxia, three subjects showed a decrease in resolving power, although a fourth showed the expected increase in resolving power. These results for three of four subjects are paradoxical. The additional luminance required for visibility of the dimmest dots during hypoxia indicated hypoxia had the effect of decreasing effective luminance. On the other hand, the requirement for increased separation of the bright dots to allow resolution under hypoxia compared to breathing air, suggested that hypoxia had the effect of increasing luminance of these dots.

The fact that one subject did show the expected improvement of resolving power with hypoxia is highly significant and suggests that some artifact explains the results for the three who did not show it.¹ Some factor such as a hypoxic change in the pupil, accommodation, or eyeball length probably was increasing the blur of the dots on the retina to a greater extent than the hypoxia was simultaneously decreasing the sensitivity of the retina to this blur. It appears to this reviewer that a refraction increase with hypoxia was the probable culprit (e.g., Ohlbaum, 1969; Evans and McFarland, 1938). A three-mm artificial pupil probably would not increase the depth of field sufficiently to overcome any nontrivial refraction increase. If the experimenters had checked and corrected the refraction of their subjects during the hypoxic treatment, as was done by Evans and McFarland (1938) for two subjects who became myopic, possible hypoxia-caused myopic reductions in resolving power might have been eliminated in the three of four subjects who did not demonstrate the predicted result. Replication of this critical experiment with this additional control is needed.

Livingston (1944b) measured acuity with targets that were the letters "C" and "E," with the task being to indicate the orientation of the letter. No effect on acuity of depressurization to 15,000 or 17,000 feet occurred. A decrement in acuity did occur at 19,000 feet, but this was still relatively small and other signs of severe hypoxia were apparent, including an unwillingness to report responses verbally.

In perhaps the best known experiment on contrast sensitivity, McFarland, Halperin, and Niven (1944) studied foveal intensity discriminations as a function of light intensity and degree of hypoxia produced by lowering the partial pressure of oxygen. Subjects were nine trained males ranging in age from 18 to 26 years. Subjects had "no physical or ocular abnormalities other than mild refractive errors." The Crozier-Holway apparatus was used. Subjects viewed an illuminated background and reported when they first saw a brighter test square against the background. Exposure duration of the square was 1/10 second and its luminance was increased by about 0.03 log units with each succeeding exposure. Data were collected over a large range of background intensities (2.26 log milliphotons to 7.23 log milliphotons). Subjects first were light-adapted and differences in luminance between the square and its background required for detection of the

¹ If it seems inappropriate to call a result demonstrated by only one of three subjects as "correct," consider the evidence that children can survive long periods submerged in icy water that is provided by one out of four survivors of such tragic accidents.

square were determined repeatedly over a 16-minute period of dark adaptation.

The low oxygen condition typically was 10.81 percent oxygen corresponding to an elevation of about 17,500 feet. Some testing of subjects occurred with oxygen levels ranging from 8.9 percent oxygen (22,000 feet) to 15.7 percent (7,500 feet). Following exposure to low oxygen, subjects typically were exposed to 100 percent oxygen for several minutes and then additional thresholds were determined. These experiments were conducted with a breathing mask that allowed rapid shifts in oxygen tension that were undetected by subjects.

Oxygen deprivation caused a decrease in differential brightness sensitivity which was greatest at the lowest field intensities and became progressively smaller as the field intensity became brighter. At the highest field intensity, the effect of hypoxia almost was nonexistent. Oxygen tension was related inversely to sensitivity for tensions corresponding to sea level, 7,500, 10,000, 13,000, 15,800, and 22,000 feet. Differential brightness sensitivity that had been reduced by hypoxia returned to normal within 20 minutes after breathing 100 percent oxygen.

Large individual differences were found in the hypoxic changes in contrast sensitivity. The effects on blood oxygen saturation of exposure to a particular tension of oxygen also showed wide individual changes and this suggested individual differences in respiration rate (or volume) occurred during hypoxia.

The remarkable sensitivity of these experimental procedures for detecting performance changes with small changes in oxygen tension led McFarland, Halperin, and Niven (1944) to discuss several advantages associated with use of measures of differential sensitivity with low luminance backgrounds over measures of absolute sensitivity for determining the effects on visual sensitivity of hypoxia or other environmental conditions. These advantages were:

- a. The absolute threshold tends to keep diminishing even after comparatively long periods in the dark. This interferes with the interpretation of changes caused by the experimental conditions. On the other hand, a dimly illuminated field maintains the eye at a constant state of adaptation after the first few minutes of exposure. Control experiments showed no appreciable change during periods of over 2 hours.
- b. Less time is necessary to reach a stable state at the beginning of the experiment than in the case of absolute thresholds.

- c. The subject has less difficulty in fixating, when he sees a circular field as compared with total darkness.
- d. Entoptic phenomena are less disturbing.
- e. The results have more direct practical application to aviation since even night vision generally involves a background with very dim illumination rather than total darkness.

As was mentioned earlier, there has been only a small amount of research on effects of hyperoxia, carbon monoxide, hypocapnia, and hypercapnia on visual acuity and contrast sensitivity. The above arguments indicate that measures of contrast sensitivity at low background luminance levels would be an important way to fill this research gap.

Halperin et al. (1959) reported further results of the extensive study conducted in 1944 and 1945 by McFarland and his associates. These results dealt with the time course of the effects of carbon monoxide on visual thresholds. Subjects for this phase of the research were four young men, aged 16 to 25 with no physical or ocular problems, who were highly trained on the Crozier-Holway discriminometer. Changes in visual sensitivity were measured after dark adaptation. Air and various gas mixtures with below normal oxygen tension were breathed. CO was administered for brief periods and levels of COHb monitored.

COHb hypoxia reduced sensitivity with the effect of a certain percentage of COHb being similar to the percentage reduction of oxygen saturation during hypoxic hypoxia. On the other hand, COHb hypoxia required much more time for clearance during subsequent air or pure oxygen breathing than hypoxic hypoxia. There was a lingering effect of CO breathing that reduced thresholds even after COHb levels had dropped as a result of breathing air, 100 percent oxygen, or oxygen-CO₂ mixtures. The suggested explanation was that neural or retinal processes were disrupted by some chemical other than hemoglobin that showed an affinity for CO such as hemoglobin does.

The study provided data indicating significant decrements on contrast sensitivity of COHb levels as low as five percent. This further indicated the remarkable sensitivity of contrast discrimination measures at low background luminance with highly trained observers as was pointed out earlier by McFarland, Halperin, and Niven (1944).

The study also indicated that when COHb levels were elevated, breathing pure oxygen produced higher contrast sensitivity than occurred when breathing normal air (21 percent oxygen) in this circumstance of elevated COHb. This pure oxygen benefit contrasted

with the typical failure of pure oxygen to increase sensitivity over normal air when COHb levels are not elevated. This suggests that smokers with their higher COHb levels might show a benefit for visual sensitivity from oxygen breathing whereas nonsmokers would not. Hyperventilation also might be expected to improve visual sensitivity for smokers because of the increased oxygen produced.

McFarland (1970) reported still further results from the same series of 1944-1945 experiments that showed the great sensitivity of the Crozier-Holway discriminometer with low luminance backgrounds to changes in respiratory conditions. Single cigarettes which produced only a little more than a percentage point change in COHb were found to produce significant increases in target luminance required to detect targets against dim backgrounds.

On the other hand, Ramsey (1972; 1973) did not find effects of low COHb levels on vision, but he did find a significant slowing of responses. Another possible explanation of the COHb changes in differential sensitivity found by McFarland and his associates would be the increased levels of luminance that would occur during their exclusive ascending luminance trials simply as a result of COHb delays in subjects' reports of when they could see the targets.

Hecht et al. (1946) assessed the effects of hypoxia on brightness discrimination and dark adaptation. The dark adaptation results were discussed in the previous chapter. Subjects for the contrast discrimination experiment were seven men and one woman. One man (S.H.) was 51 and the others ranged between 17 and 25 years. Contrast discrimination was measured by projecting Landolt Cs on a light background with openings of the Cs in one of eight different positions. Subjects increased the brightness of each projected target until they could report the orientation and this intensity was recorded. Landolt Cs were exposed for 1/5 second. Three background field intensities were used: .00085, 0.0102, and 0.12 ml. Six oxygen levels in addition to normal air were used: 16.6, 14.8, 13.2, 12.1, 11.2, and 10.3 percent.

Reduced oxygen pressures reliably increased the contrast required to detect Landolt C openings compared to their detection in air. These effects were much more pronounced when the background luminance on which the brighter Cs were projected was low than when it was "high." For the 11.2 percent oxygen tension and the .00085-ml background, the increase in "C" luminance above the background required for detection was nearly 100 percent greater than the increase above the background required for detection when breathing air. For the 0.12-ml background the comparable increase for lowest oxygen over air was slightly less than 40 percent.

The increase in brightness required to detect "C" openings going from 12,000 to 15,000 feet was twice as great as the increase required for "C" opening detection going from 6,000 to 9,000 feet. However, above 15,000 feet the authors claim that there was less rapid deterioration of brightness discrimination. The authors suggested that "this may be due to compensation by the body for the anoxia" at these higher levels. On the other hand, review of the averages indicated that this only occurred for the series of measures made at the lowest background intensity. The authors do not discuss hypoxia changes in some other visual process, but this improvement above 15,000 feet may reflect hypoxia produced changes at these low oxygen levels in some other ocular process such as accommodation which leads to improved focus of targets.

Otis et al. (1946) used the Hecht et al. (1946) acuity task where a Landolt "C" was projected on a light background with openings of the "C" in one of 8 different positions and where the 11 subjects increased the brightness of each projected "C" until they could report the orientation. They manipulated oxygen tension and CO₂ levels both singly and in combination. A decompression chamber was used to simulate altitudes of 12,000, 15,000, 18,000, 20,000, and 22,000 feet. Hyperventilation produced lower-than-normal CO₂ levels. Adding dead space between the mask and control valve increased CO₂ levels.

Reduced oxygen tensions increased the amount of luminance necessary to identify "C" orientations. The required luminance increase was small at 12,000 feet. The luminance required for acuity increased linearly from 12,000 to 18,000 feet. Luminance required for acuity then increased sharply for the 20,000- and 22,000-foot altitudes indicating a major decrement in contrast sensitivity at these highest altitudes.

According to the authors, decreasing alveolar CO₂ by hyperventilation also increased the luminance required to maintain acuity and when low oxygen and reduced alveolar CO₂ were combined, the effects were reported to be approximately additive. On the other hand, they also reported that hyperventilation improved contrast discrimination at altitude and the figures of the report indicate that it was only when CO₂ tension was lower than 25 mm Hg that contrast discrimination suffered. Like many other researchers (e.g., Livingston, 1944a), Otis et al. (1946) mentioned that hyperventilation normally accompanied hypoxia and this further illustrates the importance of CO₂ monitoring and control of respiration in research on hypoxia effects.

Other studies frequently have shown hyperventilation and associated hypocapnia to produce improved visual sensitivity (e.g., Alpern and Hendley, 1952) and thus the hyperventilation decrements reported by Otis et al. (1946) are puzzling. A hand steadiness test also was included in the research and hyperventilation and

associated hypocapnia had a stronger negative effect on this than on contrast discrimination. This reliable decrement in motor performance with hypocapnia makes the Otis et al. procedure of having the subject himself adjust Landolt "C" luminance in the contrast-discrimination task questionable. Decrements in motor performance or increased attention required for the manual luminance adjustment task may have contributed to the surprising low contrast sensitivity scores with hypocapnia.

Scano, Bietti, and Schupfer (1947) reported hypoxic reductions in resolving power of the eye in their English summary. Hypoxia was produced with a rebreathing apparatus with the hypoxia lasting at least 10 minutes. Retinal resolving power was measured with the interferometer of Schupfer. A significant decrement in resolving power was found at 5,000 meters. Resolving power continued to decrease as elevation increased and this decrement accelerated at about 7,250 meters. Bietti (1953) noted that these decrements were comparable to the reductions in resolving power of the retina found by Mercier and Duguet (1950), Giardini (1949), and McFarland and Halperin (1940).

Giardini (1949), according to Bietti (1953), found hypoxia produced a reduction of the central visual acuity. Details about hypoxic conditions or the acuity task were not given by Bietti.

Rose (1949) included visual acuity in his study of acclimatization during a 2-week exposure to 10,000 feet and acuity was measured with the nyktometer (Rose, 1950b). There were about 10 subjects for various acuity, sensitivity, and muscle-balance measures. No discussion was provided of subject characteristics. "Twilight acuity," as Rose refers to nyktometer-measured acuity in this paper, was a combined dark adaptation and acuity measure where the acuity task was presented following light adaptation and time to various acuity performances was measured as well as the level of visual acuity following adaptation for 2 minutes. The measures of "twilight acuity" were made at slightly above sea level and then repeatedly during nearly 2 weeks at 10,000 feet. Subsequent to the stay at elevation, additional measures were made in normal air at slightly above sea level and in a decompression chamber at an "altitude" of 10,000 feet.

Rose (1949) did not find decrements in acuity at altitude compared to sea level. On the other hand, measures of acuity in the low pressure chamber and even ground-level measures made after the stay at 10,000 feet showed a significant drop in acuity. In fact, chamber measures showed the largest effects found in the study on these nyktometer measures of the time following light adaptation to reach criterion acuity levels. The puzzling absence of sensitivity and acuity decrements at first exposure to the 10,000 foot altitude (Leadville, Colorado) which the decompression chamber data would predict, may reflect the 24 hours or more of

adaptation that preceded testing at altitude in contrast to the immediate testing upon decompression in the chamber. The puzzling decrements in acuity at ground level 2 to 8 weeks following the 2 weeks at 10,000 feet suggest some environmental influence subsequent to the altitude experience (such as a night on the town).

Miller (1958) was concerned that the finding by Behnke, Forbes, and Motley (1935) of a 60 percent reduction in acuity following several hours of hyperbaric oxygen might indicate that a reduction in acuity would occur for pilots who breathed pure oxygen for extended periods. He measured acuity of six male Navy enlisted personnel while they breathed 100 percent oxygen at normal ground level pressure for 4 hours and in a control condition where air was breathed (the order of air and pure oxygen was counterbalanced over subjects). A Clason acuity meter projected Snellen letters on a screen. Both central and peripheral acuity were measured with two peripheral locations of 5 and 10 degrees from fixation. The results indicated central acuity nearly was identical for air breathing and oxygen breathing and this result held for tests at 1, 2, 3, and 4 hours of oxygen exposure. Although peripheral acuity did not differ between air and oxygen breathing, a substantial improvement in acuity over the hourly tests occurred with both respiratory gas conditions. This undoubtedly was a training effect. It is interesting to speculate that this may reflect learning to adjust accommodation for maximum sharpness of peripheral images, even though blurring of the fixation target results.

Gallagher et al. (1965), according to Paulson and Ryan (1981), found no significant changes in a wide variety of visual functions including acuity, stereopsis, perimetry, color vision, and dark adaptation as a result of breathing 100 percent oxygen at sea level for 24 hours.

Kobrick (1968) studied the effects of exposure to 12,800 feet and acetazolamide on visual performance. A variety of visual functions were tested at sea level and at altitude with half of the subjects using the drug acetazolamide which may reduce altitude sickness and the other half taking a placebo. Subjects were 36 male soldier volunteers ranging in age from 19 to 36. Vision of subjects was normal and they had no physical defects which might be aggravated by hypoxia. CFF, visual acuity, stereopsis, lateral phoria, and vertical phoria were measured at sea level and again after 24 hours of exposure to an altitude of 12,800 feet. Acuity was measured at near and far with an orthoptic-type vision tester at a dim test-field luminance of 0.1 fl and at a conventional test-field luminance of 10 fl. Hypoxia did not produce any changes in visual acuity or in any of the other variables for either the placebo group or the acetazolamide group. This was true even though previous research had shown changes in acuity when subjects

breathed low-oxygen mixtures equivalent to the tension at 10,000 feet (McFarland and Halperin, 1940).

Kobrick and Appleton (1971) included standard Orthorater measures of acuity in their study of extended hypoxia (decompression to 15,000 feet) which found marked changes in CFF and absolute sensitivity after 1 hour of exposure and considerable recovery at 24 hours of exposure. However, the acuity measures did not show changes from sea level performance for any duration of exposure. Unlike the low luminance acuity measures included by Kobrick (1968) in an earlier study, only the standard Orthorater luminance was used.

Weltman, Smith, and Egstrom (1971) studied central visual acuity and peripheral detection during simulated pressure-chamber exposure. As is described in the chapter on visual fields, substantial decrement in detection of the peripheral stimulus occurred when subjects thought they were making a 60-foot dive in the chamber. Central acuity did not differ for these subjects from central acuity for the control group. However, the subjects who believed they were making a real dive responded significantly more slowly during the acuity task than the control group. Whatever the basis of this delay, it would augur for changes in measures of sensitivity, acuity, CFF, etc., if all trials were ascending or all trials were descending for the manipulated variable. In fact, delay of reporting an increasing intensity peripheral stimulus may account for the decrement found by Weltman, Smith, and Egstrom (see Chapter 4: "Fields of peripheral and central vision").

In a vigilance study that looked at sensitivity to differences in the contrast levels of successive stimuli over a prolonged period, O'Hanlon and Horvath (1973) measured neuroendocrine reactions, cardiorespiratory reactions, and performance of hypoxic men. Subjects were 8 unacclimatized male volunteers aged from 21 to 30. All had at least 20/20 acuity, with correction if necessary. The three smokers among the subjects refrained from smoking on days of the experiment. Subjects breathed oxygen with a mouthpiece at pressures of either 159 mm Hg (sea level) or 90 mm Hg. (4,570 meters) and the order of these conditions was counterbalanced between halves of the group. Subjects judged whether a small circle of light that flashed for 1 second every 3 seconds was a dimmer "nonsignal" or a brighter "signal." Each subject viewed a nonsignal brightness selected to produce correct detections on 90 percent of trials with no more than 5 percent incorrect nonsignal identifications in a condition of maximal alertness.

The vigilance task had two parts. In the first "alert" segment 10 signals were randomly (though never successively) interspersed among 50 nonsignals. In the second segment, 10 signals were interspersed randomly among 290 nonsignals in every 15-minute

period of a 90-minute test. Subjects responded to signals with one push button and to nonsignals with another.

The percentage of signals detected while breathing standard oxygen was 73 and this was significantly greater than the 62 percent for the low-oxygen condition. The decrement in signal detection over time was considerably sharper for the low-oxygen condition. Substantial individual differences existed and respiration rate increases during hypoxia were correlated strongly with signals detected ($r=.87$). Hemoglobin oxygen saturation was not measured, but increased respiration probably increased blood oxygen and maintained performance. Cortisol levels increased most strongly in subjects showing larger decrements ($r=-.80$).

Kobrick (1976) assessed the effects of hypoxia and preliminary adaptation to lower levels of hypoxia on visual search time. Subjects were 60 young male soldiers with normal vision (corrected, if necessary). Slides depicting a crouching soldier were presented with the soldier located at the center and three different peripheral locations right and left of center. Different size "soldiers" also were included simulating viewing distances of 75 to 275 feet. Actual viewing distance of the large screen on which these slides were projected was six feet. Subjects reported when they first saw the figure and the response time was recorded. Subjects then reported the location and apparent distance of the figure. Subjects were tested first at sea level (actually 200 meters) then retested 3 to 5 weeks later at 4,300 meters. Three of the four groups spent 2 to 4 days at intermediate altitudes of 1,600 or 3,000 meters before going to 4,300 meters.

The group that went directly to 4,300 meters showed a decrement in performance from their performance at 200 meters. The other three groups actually performed better at the higher altitude than at 200 meters. Apparently, this difference between the groups was related closely to a higher level of mountain sickness for the group going directly from sea level to altitude than for the groups with intermediate altitude experience.

Hess and Garner (1977) found that anoxia-induced edema of the cornea produced a reduction in visual acuity that was substantial for high-frequency gratings. However, they exposed goggled eyes to pure nitrogen, and their results probably would not generalize to hypoxic conditions where oxygen is present at tensions that allow subjects to remain conscious. Oxygen at these levels totally would prevent corneal swelling of eyes without contact lenses (See Chapter 19: "The cornea").

Kobrick (1983) studied the effects of hypoxia on the luminance thresholds for target detection using a realistic target object. Data were obtained at the top of Pike's Peak (4,420 meter elevation) from nine healthy male soldier volunteers ranging in age

from 18 to 35 whose vision was normal (20/20 Snellen), with correction, if necessary. Acuity for projected photographic slides of five tactical targets (soldier, tank, etc.) was measured by increasing slide brightness until the specific target could be identified. Targets were presented at three different sizes simulating distances of 60, 90, and 120 yards. Subjects were dark adapted prior to the 15-stimulus series and a 30-second readaptation period separated each of the slides. Testing first occurred at sea level then subjects were transported to the laboratory at the summit of Pike's Peak and tested on the second, fourth, sixth, eighth, and tenth day after arrival.

Significant increases in target brightness over sea level target brightness levels were required to allow target identification on the initial two tests at altitude. Test results on the final three occasions did not differ significantly from results at sea level. The increment in luminance required for target identification for the first altitude test was about 0.2 log units over luminance required at sea level. Huge individual differences appeared in subjects' responses to hypoxic stress.

A problem with the research was the failure to describe target viewing distance, although one suspects it was 6 feet as was the case for another study with projected targets (Kobrick, 1976). Hypoxia-induced increases in myopia (Ohlbaum, 1969) may have accounted for the decrements observed on the first two tests. Individual differences in sea level refraction and/or individual differences in hypoxic changes in refraction may have accounted for the large individual differences in target identification.

Leber, Roscoe, and Southward (1986) assessed contrast sensitivity with low levels of hypoxia at low light levels with and without night vision goggles. They also observed the effect on sensitivity of breathing pure oxygen. Subjects were four male Air Force pilots with normal uncorrected vision and substantial experience wearing the AN/PVS-5 night vision goggles. Sensitivity was assessed by determining the lowest illumination level that allowed the subject to identify the orientation of the grating. This was measured after dark adaptation and after physiological adaptation to oxygen tensions corresponding to sea level, 7,000, 10,000, and 13,000 feet above sea level. Square wave gratings of four frequencies were used: 14, 7, 3.5, and 1.75 cycles per degree (cpd). These gratings subtended 20 degrees of visual angle and were presented at optical infinity. Subjects first were tested without night vision goggles followed by testing with night vision goggles. Adaptation checks indicated that visual sensitivity was not altered substantially by looking through goggles. On the other hand, the pure oxygen condition always followed all other conditions and always was preceded immediately by viewing through the goggles.

Small decrements in sensitivity occurred at the reduced oxygen tensions. Hypoxia effects appeared largest for the coarsest gratings which were resolved at lowest luminance levels. Subsequent breathing of pure oxygen improved sensitivity to sensitivity values found with sea level oxygen tensions. Even the sea level condition appeared to benefit slightly following breathing of pure oxygen.

Vision with the night vision goggles generally was unaffected by oxygen conditions and this undoubtedly reflected the relatively bright cathode ray tube ($1 \text{ cd} \cdot \text{m}^{-2}$) that is viewed with each eye and the minimal effects of hypoxia on contrast sensitivity at higher levels of target luminance (e.g., McFarland, Halperin, and Niven, 1944). The light amplification allowed resolution of the coarse 1.75-cpd and 3.0-cpd gratings at much lower grating luminance levels than with the naked eye. The 7-cpd gratings were viewed nearly as well without as with the goggles. The 14-cpd gratings were not visible at all through the goggles due to the goggle's comparatively poor frequency response.

Conclusions and research needs

Hypoxia produced definite reductions in differential visual sensitivity as it did for absolute visual sensitivity. However, as with absolute sensitivity, most studies have found only minor effects on visual sensitivity until oxygen tensions are reduced to half the tension at sea level. Perhaps the most consistent finding in the research reported in this chapter was that decrements in acuity or contrast sensitivity were greatest when the retinal illumination was lowest. At photopic levels, changes in acuity and contrast sensitivity typically did not occur until the subject was near collapse. The higher requirement of the retina for oxygen with low illumination than with high illumination probably accounts for the increase of hypoxia effects at low illumination (e.g., Stefansson, Wolbarsht, and Landers, 1983b; Linsenmeier, 1986).

The mechanism of hypoxic reduction of contrast sensitivity and acuity typically operated in near identical fashion to placing a filter over the eye and reducing target brightness. When measured acuity or contrast sensitivity are plotted as a function of target luminance, the curves for hypoxia correspond to the curves for normoxia except shifted to the right on the luminance axis indicating the higher luminance level required for equivalent performance under hypoxia.

This straightforward prediction about the comparability of hypoxia effects to the effects of lowered target luminance led Berger et al. (1943) to a "critical experiment" that predicted better visual resolution under hypoxia than in normoxia. One subject showed the predicted improvement with hypoxia, but the

other three did not. The Berger et al. research needs replication, since if one subject showed the effect, all almost certainly would show it, if some confounding variable (perhaps a hypoxic shift in refraction) were controlled in the research. Not only would this elegantly show that hypoxia and reduced target luminance produce a similar retinal response, the research also would identify the important oculomotor, pupil, or other changes with hypoxia which caused decrements in visual resolution for three of four subjects in the original study and which may frequently detract from visual performance during hypoxia.

The few studies reviewed in this chapter that looked at carbon monoxide poisoning (hemic hypoxia) showed that the reduction was comparable to the reduction for comparable reductions in oxyhemoglobin by hypoxic hypoxia. These results came from McFarland's highly sensitive differential sensitivity procedure and the changes were not large, although they were statistically significant. It may be significant for understanding of normal and carbon monoxide-inhibited visual sensitivity that hemic hypoxia was slow to recover following the replacement of the CO mixture with air or pure oxygen. The beneficial effect on differential sensitivity of higher-than-normal oxygen tensions when COHb was elevated probably is related to the slow recovery. However, even low levels of CO slow response time (Ramsey, 1972; 1973) and this could be a factor in the "sensitivity" result, since McFarland and his associates always used only ascending luminance trials.

Hyperventilation produced ambiguous results in this research on contrast sensitivity and acuity. No clear cut benefits of hypocapnia were found as were found for absolute sensitivity and critical flicker-fusion frequency (CFF) as were found by Alpern and Hendley (1952) and Granger and Ikeda (1961) and often hyperventilation led to decrements in acuity and contrast sensitivity. However, these early studies may not have produced comparable hypocapnic changes to the research of Alpern and Hendley or Granger and Ikeda. Another possibility is that hypocapnia causes pupil dilation or lens changes that detract from acuity tasks, but do not detract from (or even improve) performance on CFF and sensitivity tasks where large stimuli do not need accurate focus for their viewing. Additional research looking at hypocapnia on contrast sensitivity with large low-contrast gratings would probably show improvements, even if there were a decrement in target focus. Additional research looking at hypocapnia on acuity with control of possible changes in refraction also would be expected to lead to improvements like those found for absolute sensitivity and sensitivity to flicker.

The discussion about large individual differences in absolute sensitivity in the previous chapter applies totally to results on contrast sensitivity and acuity. Research specifically aimed at identifying the bases of individual differences in decrements in

sensitivity and acuity associated with hypoxia would appear to have much value for selection of aviators and other personnel who might be faced with hypoxic challenges in combat situations. Such research also might lead to cardiovascular training or other training that might improve visual performance in hypoxic conditions.

No one appears to have followed up the Behnke, Forbes, and Motley (1935) finding of an immediate decrement in visual acuity with hyperbaric oxygenation. Several studies have found that oxygen at one atmosphere does not produce decrements in acuity and the poorly-documented decrement with hyperbaric oxygenation found by Behnke, Forbes, and Motley may have been a spurious result. Study of visual acuity and/or contrast sensitivity under hyperbaric oxygenation would appear to be worthwhile, especially if subjects would be subjected to the potentially toxic environment for other medical reasons and the acuity study would not increase or modify this exposure. If decrements in performance were found, investigation of their bases should follow.

Chapter 3

Depth perception and stereopsis

The small decrements produced by hypoxia on visual acuity would be expected to lead to similar small decrements in depth perception and stereopsis. Any unusual sensitivity of depth perception and stereopsis to hypoxia might indicate some hypoxia-sensitive brain site critical for binocular function.

Wilmer and Berens (1918) investigated the ability to maintain stereoscopic vision with an ordinary stereoscope at different levels of hypoxia. Hypoxia was produced with a rebreathing apparatus or in a low pressure chamber. At high altitudes (typically 20,000 feet or more), "confusion" appeared in three of nine normals and in two of six subjects considered visually unfit for aviation duty. Administration of oxygen restored stereoscopic function rapidly in one confused subject who received it. It is not clear if oxygen was administered to any other subject experiencing stereopsis problems.

According to Nicholls (1950b), a study of the U. S. War Department (1919) investigated stereoscopic vision under hypoxic conditions in candidates acceptable for pilot duty. Three of 19 normal subjects showed loss of stereopsis at 20,000 feet and 1 of 7 subnormals (men disqualified for visual reasons) showed a similar loss. No changes in stereopsis were found at altitudes lower than 20,000 feet. Another series of tests on seven normals and nine subnormals showed similar results with only one subnormal showing stereopsis problems (which appeared at 15,000 feet). This subject rapidly recovered stereoscopic function upon administration of oxygen.

According to a review of research on depth perception during oxygen deficiency provided by Rose (1950a), Heinke (1942) used Koch's depth perception testing apparatus on 11 subjects who were familiar with its use. Subjects were tested following decompression to altitudes of 5,000, 6,000, and 7,000 meters. Disparities were presented to subjects which at ground level they were just able to combine into one three-dimensional image. Seven subjects showed a decrease in the value of this fusible disparity and two showed an increase. Two other subjects "had a wider scatter." According to Rose, Heinke attributed his results "to a decreasing adjustment precision which, in turn, is due to a lack of concentration, to a decrease of the extent, and to a change in the efficiency limit of depth perception." Heinke also reported that it took longer for subjects to adjust the depth perception

apparatus at higher altitudes. Rose (1950a) also mentioned a dissertation by Stolze (1943) which looked at binocular depth perception during acute anoxia, but no results of that research were provided.

Livingston (1944b) required subjects to adjust a center post of a depth perception apparatus (three pin test) to the same distance as the two fixed posts on either side of the movable center post. He found performance under hypoxia (decompression to 17,000 feet or more) differed from sea level in that the center post was positioned closer to the subject than the surrounding posts ("to the near or exophoric side of the instrument."). This was seen as a loss of power to "maintain binocular concentration," due apparently to difficulty in converging at the distance of the posts, despite that this required only a 'small degree of convergence."

According to Nicholls (1950b) and Mercier and Duguet (1950), Duguet (1947) found stereoscopic vision to be "particularly resistant to anoxia." Four subjects demonstrated no change in stereoscopic acuity when tested at elevations ranging from zero to 6,000 meters. Three subjects showed a transient decrease in stereoscopic acuity at intermediate altitudes but regained sea level stereoscopic acuity at 6,000 meters. Nicholls indicated this finding was in agreement with the results of Heinke (1942).

Paulson and Ryan (1981) reported that Gallagher et al. (1965) found no effect of breathing 100 percent oxygen at sea level for 24 hours on stereopsis. No studies were found which examined depth perception as a function of breathing pure oxygen at pressures greater than atmospheric pressure.

Kobrick (1968) studied the effects of exposure to 12,800 feet on a variety of visual functions at altitude with and without the drug acetazolamide which may prevent altitude sickness. Subjects were 36 volunteer male soldiers ranging in age from 19-36. Vision was normal and there were no physical defects which might be aggravated by hypoxia. Stereopsis was measured using a Titmus Model T/O vision tester at sea level and again at an altitude of 12,800 feet after 24 hours of exposure to the altitude. Stereopsis was measured at the conventional test field luminance (10 fl) and also at a dim field luminance of 0.1 fl. Hypoxia did not produce any changes in stereopsis (or in any of the other visual performances). The day at altitude prior to testing may have acclimatized subjects and prevented changes that were seen during immediate exposure to altitude in previous research.

In his study of the effects of hypoxia on a number of visual functions, Ohlbaum (1969) assessed effects of hypoxia on stereopsis. His subjects were 19 men ranging in age from 20 to 39. A decompression chamber was used to investigate stereopsis at

altitudes of 0, 7,000, 15,000, and 18,000 feet. Stereopsis was measured with the U.S. Air Force Verhoff Stereopter, but with an increase of testing distance to 1.6 meters to degrade performance that was perfect for these subjects when tested at the usual 1-meter distance. At the 1.6-meter distance, subjects were correct on 12 of 15 trials when tested at sea level. Subjects entered the chamber in groups of three or four and testing of each took about 10 minutes. Oxygen masks provided oxygen until 10 minutes prior to testing.

Ohlbaum found stereopsis showed a highly significant decrease as a function of hypoxia that was related linearly to altitude. Average performance at 7,000 feet was 91 percent of sea level performance. The comparable figures for 15,000 and 18,000 feet were 84 and 75 percent, respectively.

Kobrick and Appleton (1971) included stereopsis in their study of the effects of extended hypoxia on visual performance and retinal vascular state. Eight healthy soldier volunteers, aged between 18 and 25 with normal near and far acuity, normal stereopsis, and normal peripheral vision were used as subjects. Dark adaptation, CFF, near and far acuity (Orthorater), depth perception (Howard-Dolman test), and stereopsis (Orthorater) were measured at sea level and after 1, 18, 24, and 48 hours of exposure to an altitude of 15,000 feet in a decompression chamber.

Retinal vessel enlargement occurred following 48 hours of hypoxia with some changes greater than 100 percent. Changes also occurred in CFF, dark adaptation, and peripheral visual response as a result of hypoxia with maximal changes at the initial 1-hour test followed by recovery to sea level performance or to near sea level performance over 24 or 48 hours. On the other hand, neither stereopsis nor depth perception were changed as a result of hypoxia of any tested duration. It is surely no coincidence that the same negative results were found for visual acuity.

Ramsey (1972) studied the effects of small quantities of carbon monoxide (CO) on depth perception. Twenty normal subjects, 20 subjects with anemia, and 20 subjects with emphysema breathed 0.03 percent CO for 45 minutes with a resultant increased COHb of about 5 percent. There was no effect of this COHb level on depth perception for any subject group and the same was true for "visual discrimination of brightness." On the other hand, reaction time showed a small but significant elevation following CO breathing.

Even larger percentages of COHb (7.6 and 11.2 percent) were found in another study by Ramsey (1973) to have no effect on depth perception. These levels also did not affect visual discrimination for brightness. These levels of COHb did significantly elevate reaction times to a visual stimulus, however. This was an increase

of about 7 and 8 percent, respectively, for the 7.6- and 11.2 percent COHb levels.

Wright, Randell, and Shephard (1973) also investigated the effects of small increases of COHb (averaging 3.4 percent) on depth perception in a double-blind study. No deterioration in judgments of depth was found as a result of this slightly increased COHb.

Conclusions and research needs

Stereopsis and depth perception appear to require severe hypoxia before there is any deterioration in performance. This also is true for visual acuity, and it probably can be assumed that deterioration in visual acuity produces the deterioration in stereopsis and depth perception when such deterioration occurs. Given results from research on animals that indicate cortical visual processing is more susceptible to hypoxia than earlier processing/transmission of visual inputs (e.g., Kayama, 1974; Eysel, 1978), one might have predicted that fusion of the eyes' two images would be particularly susceptible to hypoxia. However, the research reviewed above provides no indication of any heightened susceptibility to hypoxia of cortical fusion centers.

Carbon monoxide did not produce decrements in depth perception, although the levels of COHb investigated were fairly low. Some of these studies included reaction time measures and the low COHb levels did slow significantly responding and this has implications for sensitivity studies, CFF studies, and other studies where a stimulus dimension like intensity is varied in only one direction until subjects respond.

Breathing pure oxygen did not hurt or help stereopsis. No studies were found which looked at hyperbaric oxygen effects on stereopsis and depth perception. If the Behnke, Forbes, and Motley (1935) finding of a decrement in visual acuity during hyperbaric oxygenation were to hold up in additional research on hyperbaric oxygen effects on acuity, one would predict that stereopsis and depth perception also would be affected. If blood flow to the cerebral centers for binocular integration were to be severely inhibited by hyperbaric oxygen, even more dramatic effects on stereopsis and depth perception might be found. However, researchers should exhibit caution in subjecting human subjects to hyperbaric oxygen (see Chapter 20: "Oxygen toxicity").

Chapter 4

Fields of peripheral and central vision

A fairly large body of research on the effects of hypoxia and hyperoxia on visual fields has accumulated over the years. These studies are partitioned in this chapter on the basis of peripheral and central fields and on the basis of hypoxic and hyperoxic treatments.

Hypoxia and peripheral visual fields

The effects of hypoxia on size of the visual fields has received much attention by researchers. Wilmer and Berens (1918) measured the size of the peripheral fields "for form and color" in a low pressure chamber at 5,000, 10,000, 15,000, and 20,000 feet. Few details and no statistical treatment of their data were provided, but they reported there usually was a slight enlargement of the fields at 5,000 and 10,000 feet. They reported that at 15,000 feet a slight contraction which became marked at 20,000 feet. A return to normal fields occurred 5 minutes after returning to sea level or after 4 or 5 minutes of breathing pure oxygen at 20,000 feet.

According to McFarland, Evans, and Halperin (1941), Goldmann and Schubert (1933) found a large decrease in the peripheral visual fields in hypoxia when hypoxia was produced either by decompression in a low pressure chamber or by breathing low oxygen mixtures. Shrinkage was chiefly in the nasal and superior fields. A black square against a white background was used for measuring fields. Like Wilmer and Berens (1918), but without knowledge of their work (according to McFarland, Evans, and Halperin, 1941), they found initial shrinkage at about 14,000 feet which became marked at 21,500 to 23,000 feet. The effects were counteracted by breathing oxygen. According to Gellhorn and Hailman (1943), Goldmann and Schubert (1933) also found a widening of the blind spot during hypoxia.

According to McFarland, Evans, and Halperin (1941), Kyrieleis, Kyrieleis, and Siegert (1935) found no field changes during hypoxia. This was contrary to the results of Goldmann and Schubert (1933), whose work they replicated to at least some extent, including use of one of the same subjects. Like Wilmer and Berens (1918), Kyrieleis, Kyrieleis, and Siegert (1935) found a concentric widening of the field at the onset of hypoxia and no contractions

at altitudes as high as 8,000 meters (26,000 feet). The basic difference in their methodology was that they used a bright test object against a dark background instead of a dark object against a white background. They reported the bright target was easier to attend to under the distractions produced by hypoxia.

In discussing the Kyrieleis, Kyrieleis, and Siegert (1935) study, McFarland, Evans, and Halperin (1941) described a need to vary illumination levels in studies of hypoxic effects on the peripheral visual fields. The implication was that reduced sensitivity with hypoxia would take its toll on peripheral field size. Much earlier, Ferree and Rand (1922) discussed the critical effect of illumination on the breadth and shape of visual fields. They found that by manipulating the intensity of the stimulus "zones of color sensitivity may be made to have almost any breadth within the limits of the field of vision, to differ radically in shape, and even to change or reverse their order of ranking as to breadth." Given that a key effect of hypoxia is to produce retinal sensitivity changes that mimic changes produced by reducing the luminance of the stimulus, it follows that hypoxic conditions that diminish sensitivity would reduce the size of visual fields (see the discussion of a study on target luminance and field size by Kahwaji, Mateossian, and Griffin (1973) which is discussed below).

McFarland, Evans, and Halperin (1941) reported that Furuya (1937c) conducted experiments in a low pressure chamber on six subjects and found a contraction of the field which began at about 5,000 meters (16,400 feet). At first this was noted in the temporal field, especially in the upper quadrant. Continued exposure at the same altitude resulted in accentuation of the effect, which was more marked in "sympathicotonic" than in "vagotonic" subjects. No discussion of the defining characteristics of these two subject types was provided by McFarland, Evans, and Halperin.

Livingston (1944b) used a 2-mm white target to assess peripheral fields and found only small contractions following nearly an hour of exposure to altitudes as great as 19,000 feet. Like Wilmer and Berens (1918) and Kyrieleis, Kyrieleis, and Siegert (1935), Livingston also noted that sometimes the field actually enlarged, despite an increase in hypoxic exposure. When Livingston tested the visual field during the breathing of oxygen at 35,000 feet, he noted contractions of the peripheral fields plus small "islands" of insensitivity. Although this was apparently a general finding, the data presented showing large peripheral contractions came from a subject who was "susceptible to bends, who developed severe joint pains at 37,000 feet." Nitrogen bubbles were considered a possible basis for these defects.

Halstead (1945a; 1945b) studied chronic intermittent hypoxia effects on peripheral vision. Twenty male subjects meeting pilot

standards of the Air Corps were exposed to a simulated altitude of 10,000 feet in a low pressure chamber for 5 or 6 hours per day, 6 days per week for a period of 4 to 6 weeks. Subjects were tested on their ability to detect a peripheral stimulus which was exposed briefly at the same time that a foveal form/color discrimination was being made. Apparently there was no acute effect of hypoxia, but it was found that 3 or 4 weeks of exposure to 10,000 feet produced substantial decrements in peripheral fields in 13 of the 20 subjects. Briefly exposed peripheral stimuli that previously had been recognized quickly went unrecognized. Some of these subjects also experienced impaired performance on the central vision task, although no discussion of the nature of these defects was given.

Breathing pure oxygen did not immediately relieve this decrement in peripheral detection and it took a substantial number of days and weeks without the daily hypoxia for recovery to occur. Four subjects likewise were exposed chronically to higher altitudes (11,500 to 18,000 feet). Impairment of peripheral vision appeared earlier, was more marked, and recovered more slowly. One subject who had demonstrated the decrement was reexposed for a similar period, except that during the middle hour of each daily 5-hour period at altitude, he breathed pure oxygen. This prevented development of the decrements in performance on the peripheral task with repetitive exposure.

An earlier report by Halstead (1944) of decrements in performance on the same peripheral task indicated the "constriction of the visual field varied systematically with the projection distance." Performance in this instance was of a brain-damaged patient and Halstead (1945a) suggested the "cortex of the frontal lobes of the brain" was the site of these decrements in the peripheral visual fields of his normal subjects. On the other hand, the change in performance with projection distance suggests that inability to maintain accurate focus at one or more of the distances may have been a factor in performance. This raises the real possibility that the effect of hypoxia was mediated through long-term hypoxia-induced changes in the refractive state of the 65 percent of subjects who showed the "insidious" decrement in peripheral detection.

Birren et al. (1946) measured peripheral fields at 10,000, 14,000, 15,500, and 18,000 feet with a Ferree-Rand perimeter. They found a significant radial contraction of about 1.3 degrees for the three lowest altitudes and this rose to 2.6 degrees at 18,000 feet. They measured fields five times at approximately equal intervals during the 1-hour exposure to altitude. The magnitude of the constriction was related directly to duration of exposure to altitude in the chamber, except at 10,000 feet where the constriction reached maximum at the third measurement period. Field size then actually increased slightly for the final two

measures. Fatigue effects may have been confounded with exposure duration effects and recovery effects, since there was no comparable extended testing at sea level to assess possible changes in the size of the visual field as a result of seven repeated tests of the visual field without hypoxia.

Vollmer et al. (1946) replicated the Birren et al. (1946) research for 10,000 and 15,500 feet and added a condition where carbon monoxide (CO) was breathed until carboxyhemoglobin (COHb) levels of 15 to 18 percent were added to hypoxic effects. The subjects were 20 officers and enlisted Navy personnel who ranged in age from 18 to 39. Five measures of the visual fields with the Ferree-Rand perimeter were made during the exposure to altitude in a low pressure chamber. Sea level measures preceded and followed the altitude testing.

The higher altitude (15,500 feet) produced a small but significant decrease in field size compared to sea level measures both with and without CO breathing. Breathing CO did not reduce performance at sea level nor did it further reduce performance beyond the altitude decrement found at 15,500 feet. Only five subjects were tested at 10,000 feet, but they showed a stronger effect of altitude compared to their sea level performance than did subjects at the higher elevation. For this group of five subjects, COHb produced a major shrinkage of sea level fields. The radius of the field at sea level with elevated COHb was more than four degrees smaller than when CO was not breathed before testing.

The authors concluded CO at these moderate levels had no general effect on visual fields. There also was no correlation between individual levels of COHb and changes in field size. As with Birren et al. (1946), fatigue effects may have been confounded with exposure duration effects and recovery effects since no comparable series of repeated tests at sea level was carried out to assess possible effects of repeated testing without hypoxia.

Posternak (1948b) measured the size of visual fields for white, yellow, red, and blue targets in six persons at 550 meters and again during a 10-day stay at an altitude of 3,450 meters. Large variability in results occurred for the colored test targets and no conclusion could be reached about average variation with initial exposure to altitude or as a function of duration of the stay at altitude. For white, the results were less variable and it was concluded that no change in the size of the visual field occurred with altitude.

Smith (1965) measured visual fields with a Ferree-Rand simplified perimeter in five males (average age 27.4 years) at a simulated altitude of 18,000 feet in a low pressure chamber. Measures of peripheral fields were made at sea level and then following 10, 15, and 20 minutes of exposure to the altitude.

Significant decrements in relative retinal area occurred for both eyes at 18,000 feet with these averaging 11.2 percent after 10 minutes, 13.0 percent after 15 minutes, and 17.2 percent after 20 minutes.

Smith measured fields again at 5,000 feet upon recompression and again upon return to sea level. Recovery of the visual fields with recompression was rapid. The decrement from the initial sea level visual field area was found to be 3.8 percent after a rapid 3.6-minute descent from 18,000 to 5,000 feet. After a slower 10-minute descent from 5,000 feet to sea level, fields were 2.4 percent less than their initial sea level area.

Nelson (1967) measured peripheral fields of active duty Navy personnel at simulated altitudes of 8,000, 10,000, 12,500, 15,500, and 18,000 feet in a low pressure chamber. A significant contraction of the peripheral fields occurred for altitudes of 12,500 feet and above.

Kobrick (1970) provided some of the most interesting data on field size changes with hypoxia and these data may provide a key to some of the contradictions that exist in research on hypoxia and peripheral (and central) field size. Kobrick used a projection perimeter which projected 0.5 degree circles of either red, green, or blue light along 12 equidistant axes that included the vertical and horizontal. Subjects were tested with the method of limits and responded when they first saw the color as the stimulus was moved inward from the periphery and responded again when color disappeared as the stimulus was moved outward from the center. Subjects were tested at sea level and also while breathing low oxygen mixtures corresponding to oxygen tensions at 13,000, 15,000 and 17,000 feet.

Two groups of 12 subjects were tested with one group given the drug acetazolamide and one group given a placebo. The drug has been studied as a possible means for reducing mountain sickness and was expected to improve performance of subjects receiving it. Acetazolamide also has been found to produce transient myopia (e.g., Halperin and Kilvin, 1959).

Kobrick found substantial constriction of the visual field with greater constriction as altitude increased. However, this was found only for the group that did not receive the drug acetazolamide. The acetazolamide group showed almost no effect of altitude. However, and perhaps of more importance, even the sea level performance of the drug group showed sharply constricted peripheral color fields that were comparable to the fields measured at 15,000 and 17,000 feet in the no drug group. These striking group main effects were reported not to be significant in the report and the possibility exists the reduced size of the fields for the drug group just relates to random assignment of small field

subjects to the drug group. However, that these subjects showing small peripheral fields also showed no altitude effects makes this possibility highly unlikely.

Myopia reduces field size (Greve and Furuno, 1980) and an intriguing explanation of the altitude-related field constriction for the group without the myopia-inducing drug is hypoxia induced a myopic state that led to poorer visibility of targets used to measure visual fields. Since myopia reduces field size, the general constriction of fields at all altitudes of the drug group may have been because acetazolamide induced a myopic state that led to poorer visibility of targets used to measure visual fields under all altitude conditions. The Ohlbaum (1969) finding of a significant myopic shift with high altitude (18,000 feet) would provide support for such an explanation of the hypoxia effects, although the myopia that Ohlbaum found averaged only 0.12 diopters. Carapancea, Stefan, and Udrescu (1973) reported even larger myopic shifts at "altitude" for hyperopic aviators.

Kobrick (1970) suggested acetazolamide might have produced an immediate decrement on performance and it is surprising that he did not discuss the myopia explanation himself, since he provided nine references in his article on the transient-myopia-inducing effects of acetazolamide and acetazolamide-related drugs. Alternatively, if acetazolamide and hypoxia both produced constriction of the pupil, this would be another possible explanation of Kobrick's hypoxia and acetazolamide constrictions of the visual fields given the reduction of field size with pupillary constriction found by McCluskey et al. (1986) which is discussed below.

Weltman, Smith, and Egstrom (1971) found if subjects simply believed that they were engaging in a risky dive this sharply reduced their ability to detect peripheral targets that were briefly exposed while they performed a central visual acuity task. Anxiety and heart rate were elevated in the simulated dive as well, and this group also showed somewhat slower response on the central acuity task. Performance was relative to a control condition where subjects knew there was no dive in progress. Ernest and Krill (1971) found anxiety existed (and led to hyperventilation) in all three of their subjects when they first were tested in hypoxic conditions. This reduction in detection of peripheral stimuli as a function of anxiety found by Weltman, Smith, and Egstrom (1971) may well be the basis for some of the diminished peripheral fields found in studies of hypoxia if some subjects perceive the hypoxic treatment as dangerous.

Kahwaji, Mateossian, and Griffin (1973) did not investigate field size as a function of hypoxia, but they did measure field size while systematically varying target size and luminance. With small diameter targets (1, 2, and 3 mm), they found field size increased sharply as target luminance increased then decreased for

very high levels of luminance. Larger targets (6 and 9 mm) showed largest field sizes at lowest levels of luminance and produced significantly smaller fields with increasing luminance. Reduced pupil size as a function of higher target luminance was suggested as the basis for the reliable decrease in field size (for larger targets) with increasing luminance. Unfortunately, pupil size was not measured in their study.

Greve and Furuno (1980) showed that myopia, even in the absence of glaucoma, increased the size of the blind spot "due to the myopic conus" and increased supero-temporal refraction defects due to the posterior staphyloma. Thus any myopic shifts as a result of hypoxia would be expected to increase the measured blind spot and to reduce the extent of peripheral fields.

McCluskey et al. (1986) studied the effect of pilocarpine-induced miosis on the visual field in normals. Significant reductions in visual fields were found 30 and 120 minutes following administration of pilocarpine. The effect was largest for small test objects. Thirty minutes following pilocarpine, this area decrease was 64 percent for the 12e isopter, 33 percent for the 13e isopter, and 24 percent for the 14e isopter. Pupil area had shrunk from an average of 14.5 mm² to an average of 2.74 mm². Significant correlations were found between pupil area changes and visual field area changes for the 20 patients at the 30-minute test. These correlations were even more significant for the 2-hour test when constriction of the pupil had abated somewhat.¹ No hypoxic conditions were included in the research, but if pupil shifts are produced by hypoxia, as many researchers have claimed (e.g., Duguet and Mercier, 1951), these results indicate such changes can be expected to influence measures of field size.

Hypoxia and the central field

Angioscotometry (Evans, 1938) involves measurement of blind "spots" associated with retinal vessels which emanate from the blind spot of Mariotte and which typically are about the same distance or farther from the fovea than the blind spot. These are measured by having the subject carefully fixate a small fixation mark while a tiny white circular target (0.25 mm to 1.5 mm in diameter) is moved perpendicular to these vessels and points on either side of the vessel where the target disappears are noted. The width of these angioscotoma varies as a function of a number of

¹ This increase in the correlation with time probably reflected a greater range of pupil sizes (and field areas) associated with individual differences in persistence of the drug-induced miosis. However, measures of dispersion were not provided which would allow confirmation of this.

variables ranging from menstruation to fear (Evans and McFarland, 1938) and including, as discussed below, hypoxia.²

Evans and McFarland (1938) measured the size of the angioscotoma while subjects breathed oxygen mixtures corresponding to elevations of sea level, 13,000, 17,000 and 21,000 feet. For all four subjects the width of the angioscotoma increased as a direct function of altitude. The scotoma doubled in area for the subject who showed the least effect going from sea level to 21,000 feet. For the subject showing the greatest effect, the change was five-fold. However, it may not be a coincidence that this extremely large scotoma occurred when this subject (L.R.) probably was two diopters myopic and correcting this transient myopia produced a sharp reduction in scotoma size at its next measurement.

Seitz and Rosenthal (1941) confirmed the hypoxia effect found by Evans and McFarland (1938). They measured angioscotoma size at sea level and while breathing oxygen at a low tension corresponding to 17,500 feet. They also assessed effects of local application of strychnine to the eye on angioscotoma size. Their subjects were four males ranging in age from 21 to 26 with normal health and vision. A small test object (0.55 mm.) was used to plot the blind spot and two main superior angioscotomas during monocular fixation. Measures were made every 15 minutes at "altitude." Strychnine was applied to one eye after the first measurement. Angioscotomas increased in area by a factor of two as a result of hypoxia. Area returned to near normal for the eye to which strychnine was applied while the angioscotoma in the control eye showed no change in area or even showed a slight increase. It is not clear that strychnine countered the effects of hypoxia (as the authors claim) or whether it may have just increased some other visual sensitivity-related factor, since strychnine also sharply reduced the area of the angioscotoma when measured at sea level.

Rosenthal (1939) measured the angioscotoma in 15 normal persons ranging in age from 22 to 35 while they breathed 100 percent oxygen. Lloyd's stereocampimeter and charts were used with tiny white spheres as targets (0.45 to 0.52 mm in diameter). A control map of the angioscotoma was made in normal air and this was followed by a map made while breathing oxygen. Five minutes after oxygen was removed another control map was made. Every subject showed a narrowing of angioscotomata while breathing oxygen and a widening of angioscotomata after return to normal air.

Cusick, Benson, and Boothby (1940) believed the changes in the angioscotoma reflected the changes in size of the retinal vessels

² The widening of the angioscotoma as a result of fear suggests that widening of the angioscotoma with hypoxia may actually be a widening with hypoxia-induced fear or stress.

that occurred with hypoxia and hyperoxia. Evans and others sometimes found changes in the angioscotoma that were larger than these dilations and constrictions, however.

Smith, Seitz, and Clark (1946) looked at changes in size of the angioscotoma over 7.5 hours of mild hypoxia in 16 male college students ranging in age from 17 to 21. A small test object (0.4 mm.) was used to plot the superior temporal angioscotoma of the right eye. Fields were plotted at a simulated altitude of 10,000 feet and a control altitude of 1,800 feet. Altitude was simulated with a low oxygen tension in an oxygen chamber. The order of control and altitude runs was counterbalanced across subjects. Testing occurred after the following exposure times: 1.5, 3.25, 5.25, 6.5, and 7.5 hours.

Control measures were significantly lower (smaller angioscotomata) than those at altitude with the difference in campimeter chart units being about 20 percent. Small but significant increases on the order of 10 percent occurred from first to last tests at altitude, but not for corresponding control tests, indicating some cumulative effects of this relatively mild hypoxia. Tables giving the individual data showed striking individual differences in size of these angioscotomata with scores showing a range from less than 200 to more than 600 on the control runs. However, in almost all subjects, the angioscotoma increased for altitude runs compared to control runs.

Mercier and Duguet (1950) reported a brief summary of work done with Bailliart where they tried to replicate the results of Evans and McFarland (1938) using a decompression chamber. Their "Evan's angioscotometer was modified by Magitot," although no discussion occurred about what this modification was except that the test object was 0.3 mm in diameter for Mercier, Duguet, and Bailliart and 0.4 mm in diameter for Evans and McFarland.

Mercier, Duguet, and Bailliart could not even find the large upper temporal scotomata mapped by Evans and McFarland. Instead of an increase in the size of the angioscotomata, Mercier and Duguet (1950) found a substantial reduction of the blind spot and this reduction first was noted at measures made at about 3,500 meters. The shrinkage continued up to 6,000 meters (apparently as high as they went). This contraction of the blind spot apparently occurred for all eight of their subjects with the contraction ranging from 6 to 80 percent when measured at 6,000 meters. One possibly significant difference between the study of Mercier, Duguet, and Bailliart and the study of Evans and McFarland was that the former used a decompression chamber to induce hypoxia and the latter used low oxygen mixtures.

Mercier, Duguet, and Bailliart measured the blind spot again upon return to normal pressure. For two of the subjects the blind

spot was of normal size, for three it was enlarged, and for the remaining three it maintained the high altitude contraction. Mercier, Duguet, and Bailliart also looked at the effects of pure oxygen on the size of the blind spot. Unlike Rosenthal (1939) who found the angioscotoma to contract when the subject breathed oxygen, they found oxygen to expand the blind spot to 165 percent of its original area. They used the same apparatus and appear to have used the same subjects they had used to demonstrate the contraction of the blind spot with altitude.

Brognoli and Boles Carenini (1952) reported in their English summary that the blind spot and angioscotomata increased with hypoxia. They found the vasodilating drugs amyl nitrite and nicotinic acid reduced these increased scotomata. Dilated vessels would be expected to increase the angioscotoma, according to Cusick, Benson, and Boothby (1940), and it appears that angioscotomata changes are more than just changes in vessel size.

Bietti (1953), who headed the laboratory where the Brognoli and Boles Carenini research originated, noted that 20 percent of cases he had observed actually had shown a reduction in size of the angioscotomata with hypoxia. Bietti (1953) also described research on an "artificial angioscotoma" where similar techniques to angioscotometry were used to measure the width of a slit of light that was viewed perifoveally. A small bright spot was projected on the darker background of the slit and moved perpendicular to it until the subject noted that it disappeared (because it could not be seen due to a lack of contrast). The width of this "Goldmann slit" was found to increase with hypoxia and to decrease with hyperoxia compared to its width in a normal atmosphere.

A wide-measured slit would imply that a larger fraction of the measuring spot was needed at the edge of the bright slit to be visible. A narrow-measured slit would imply that only a small fraction of the measuring spot was needed at the edge of the slit to be visible. Thus, a measure of the width of this Goldmann slit would appear to be largely a measure of visual acuity with a narrow slit indicating higher acuity. Wide slits would be expected (and were found) as a result of hypoxia which degrades acuity. The narrow slits found with hyperoxia suggest hyperoxia increased acuity.

Bietti (1953) stressed when measures of both this Goldmann slit and the angioscotoma were made at the same session, there was considerable independence between the measures. Wide slits sometimes went with narrow angioscotomata and vice versa. Apparently, the measured size of the Goldmann slit was related more reliably to hypoxia and hyperoxia than angioscotoma size.

The width of a retinal vessel might change as a result of hypoxia (and hyperoxia), but at least its shadow would not be

altered by optical changes of the eye. However, optical changes of the eye would alter the retinal image of the tiny white targets used to measure the angioscotomata. Defocus of these small targets probably would enlarge the diameters of their effective retinal images if the targets were bright (with strong contrast to the background) and cause a narrowing of the angioscotoma because they would have to be projected further into it before they would disappear. If the targets were dim (or the contrast with the background were low) the defocus instead would reduce their effective retinal size and they would disappear sooner as they were moved into the vessel shadow and the scotomata would be enlarged. With either dim or bright targets, if hypoxia were to increase refraction of the eye and improve the focus of these small measuring targets for hyperopic subjects and were to reduce the focus of these targets for emmetropes and myopes, this could produce the varying results with hypoxia for different subjects during angioscotometry that Bietti noted.

Rosenthal (1939) always found a contraction of the angioscotoma when pure oxygen was breathed. According to Bietti (1953), Dugué, Dumont, and Bailliart (1947) always found that breathing of pure oxygen dilated the angioscotoma. If a consistent refractive shift (increased focus or increased blurring of the retinal image) were to occur with hyperoxia, a different level of brightness of the measuring target in a different experiment might account for these contradictory results. If we assume a consistent improvement of focus with hyperoxia. The researcher with dim (or low contrast) targets would have "larger" (less blurring of their extremities) targets that would have to penetrate more deeply to disappear, producing narrower measured angioscotoma. The researcher with bright (or high contrast) targets would have "smaller" targets (again less blurring of their extremities but reduced effective width as well) that would more quickly disappear as they approached the vessel "shadow," producing wider angioscotoma. This explanation would predict that Rosenthal used relatively dim (or low contrast) targets and Dugué, Dumont, and Bailliart (1947) used relatively bright (or high contrast) targets.

Unlike the shadow of the retinal vessel which would not be altered by changes in focus of the eye, Goldmann's slit would be affected by changes in the focus of the eyes with hypoxia as well as the measuring dot. Given their probable similarity in luminance, slit and dot would be affected similarly. Improved focus of both Goldmann's slit and its measuring dot would be expected to narrow the slit since acuity would be increased with less of the dot required to be external to the slit in order for it to be seen. Blurring of both Goldmann's slit and its measuring dot would be expected to widen the slit since acuity would be reduced with more of the dot required to be external to the slit in order for it to be seen.

Hyperoxia and peripheral visual fields

Behnke, Forbes, and Motley (1935) measured visual fields before and after breathing oxygen under pressure in four "healthy young men." The subjects breathed pure oxygen via a mask or helmet in a large pressure chamber at a pressure of three atmospheres for a period of at least 3.5 hours and up to 4 hours. Measurements were regularly made of leucocyte count, blood pressure, heart rate, respiratory rate, minute volume, visual acuity, area of the visual field, and duration of a negative afterimage formed by viewing a red and green cross for 20 seconds. Changes in visual fields were not noted during the first 3 hours of hyperoxygenation. During the 4th hour, contraction of the visual fields began. Contraction ranged from one half the initial area for one subject to as much as the 10-degree circle of the perimeter chart for another subject. Recovery following exposure to air took 50 minutes in one extreme contraction. In one session, the contraction suggested left temporal hemianopsia and the right pupil was dilated to a greater degree than the left.

Miller (1958) was concerned that the Behnke, Forbes, and Motley (1935) result might indicate field reduction for pilots who breathed pure oxygen for extended periods. He measured peripheral fields of six male Navy enlisted personnel while they breathed 100 percent oxygen at normal ground level pressure for 4 hours. Miller found that hourly measures during hypoxia showed near identical fields to those measured over comparable periods in air. The blind spot also was outlined and it remained essentially the same for all measurement conditions. Inspection of Miller's Figure 1 largely supports these claims of no effects of hyperoxia for large test objects (6/333) and for a small red test object (9/1000) which caused the smallest measured field. The one possible exception is that there is a one- to three-degree constriction of fields for oxygen compared to air for all hourly tests when a small white (9/1000) test object was used to measure fields on a tangent screen. This greater constriction with oxygen than air increased with exposure time.

According to Paulson and Ryan (1981), Gallagher et al. (1965) investigated the effects of breathing 100 percent oxygen at sea level for 24 hours and found no significant changes in a wide variety of visual functions including perimetry.

Rosenberg, Shibata, and Maclean (1966), found that inhalation of oxygen at three atmospheres for up to 3 hours produced bilateral constriction of the visual fields in two of seven human subjects. Little discussion of these defects occurred, but the field reductions were accompanied by lights that "appeared too bright" and a distortion in the appearance of objects. Vision returned in both cases to normal 40 minutes after the experiment. Hyperven-

tilation and hypocapnia occurred in five of the six subjects for whom blood samples were obtained. Arterial CO₂ tension began to decrease during the first 5 minutes of oxygen breathing and continued until it reached 35 mm Hg after about 90 minutes and remained at that level for the 3 hours of exposure to hyperbaric oxygenation. Although we have noted hyperventilation frequently in the research on hypoxia, this hyperventilation during hyperoxia indicates that it is probably anxiety associated with chambers and/or breathing masks that produces much of the hyperventilation for both hypoxia and hyperoxia.

Anderson (1968) also measured fields while oxygen was breathed under pressure but hyperbaric oxygen was presented for only a relatively brief period. He reported no effects on visual fields of 20 minutes of exposure to 100 percent oxygen at a pressure of 3.04 atmospheres. He also tested subjects after breathing pure oxygen at normal pressure for 15 minutes and after breathing air at 3.04 atmospheres for 8 minutes. In none of these conditions was there any deviation in peripheral fields from fields measured while breathing air at normal atmospheric pressure and he concluded that only with extended exposures like those of Behnke, Forbes, and Motley (1935) would the field defects appear.

Conclusions and research needs

The occasional expansions of visual fields with initial exposures to hypoxia or with low levels of hypoxia may be spurious, but a number of studies reported them. They may have their parallel in research on sensitivity that showed nonlinear sensitivity decrements and even some increases in sensitivity as hypoxia became more severe. Refraction and pupil size both have effects on the size of peripheral fields and some studies have reported hypoxia effects on refraction and pupil size. Hypoxic changes in refraction and/or the pupil may explain these unexpected field changes.

The single study found that investigated carbon monoxide effects on peripheral fields produced mixed results with a decrement in the size of fields at sea level and no decrement at altitude. Studies using hyperbaric oxygenation found reduced field size, but apparently only when exposures were for long periods and only for susceptible subjects. Hyperventilation occurred in one study of hyperbaric oxygenation and may have influenced field size. No studies were found which looked at the effects of hyperventilation during normal air breathing on visual fields.

Peripheral and central fields do not appear to lend themselves readily to research on hypoxia. The multitude of influences other than hypoxia make interpretation of results difficult. One study showed that peripheral detection deteriorated sharply when there

was only a make-believe dive. Hypoxia may influence diverse ocular systems with contradictory effects on field extent. Until there is better understanding of effects of hypoxia and hypocapnia on retinal sensitivity, the pupil, and refraction, there will be difficulties of understanding the effects of hypoxia on visual field size which is strongly influenced by illumination, pupil size, and refractive errors.

Chapter 5

Critical flicker/fusion frequency

Humans and other animals have a limited ability to resolve the separate flashes of a flashing light as the flash rate increases. The increasing flash rate which causes this flashing stimulus to no longer be seen as flickering is known as the critical fusion frequency. The critical flicker frequency is the decreasing flash rate that causes a "fused" flashing light (or illuminated surface) to first be perceived as flickering. The critical flicker/fusion frequencies have been used widely as a measure of visual and brain sensitivity. Landis (1954) and Simonson and Brozek (1952) have provided reviews of the critical flicker/fusion frequency (CFF).

Hyperventilation reduces alveolar and arterial CO_2 levels and this hypocapnia has marked effects on the CFF and absolute visual sensitivity (Alpern and Hendley, 1952). Hyperventilation is included in the review because it frequently is stimulated by hypoxia (e.g., Ernest and Krill, 1971). Any discussion of the effects of low CO_2 levels on the CFF also requires consideration of the effects of elevated levels of CO_2 on visual performance and a few of the following studies deal with the effects of elevated CO_2 on the CFF.

There is a large volume of research on the CFF and studies of the effects of hypoxia and hyperventilation are discussed first in this review. Research on carbon monoxide effects and research on effects of hyperoxia are discussed in later sections.

Hypoxia and hypocapnia and the CFF

The CFF apparently was first used to assess the effects of hypoxia on visual sensitivity by Seitz (1940), who obtained extensive data from one undergraduate student and three graduate students. A six-degree circular flashing area with a small central fixation spot was viewed through a two-mm artificial pupil at a range of illuminations. Testing occurred in an oxygen chamber while subjects breathed air or lower oxygen concentrations ranging from air down to 10.57 percent oxygen for some sessions and down to 9.5 percent oxygen for others. The stimulus distance was 20 cm. Each session was begun with 2 minutes of light adaptation followed by 30 minutes of dark adaptation. Measurements began at the lowest illumination with adaptation to the particular luminance for 2 minutes prior to measures of the fusion frequency.

Subjects always adjusted the flicker rate upward until fusion occurred. Later experiments used only a single luminance target for the entire session.

The first experiments of Seitz used gradual "ascents" requiring 7.5 hours to reach an oxygen tension equivalent to the tension at 22,000 feet and they did not show consistent effects of hypoxia on the CFF. Faster ascents to 17,500 and 20,000 feet (15 minutes from sea level to 17,500 feet and 18 minutes from sea level to 20,000 feet) did show decrements in CFF, but then it took about an hour at this altitude before the maximum decrement occurred. Both rod and cone levels of luminance showed decrements in the CFF during hypoxia, although the decrement with hypoxia typically was larger for the cone luminance levels. During the testing session with rapid reductions in oxygen tension, two series of measurements occurred and the second series of measurements at altitude typically showed larger effects than the first series, indicating a cumulative effect of hypoxia. However, it is puzzling that while the earlier gradual 7.5-hour "climb" to 22,000 feet prevented decrements in the CFF, the rapid exposure to hypoxia that occurred in the later experiments required at least an hour of exposure to hypoxia to produce a maximum effect.¹ Subjects did not spend more than 2 hours at "altitude" in these later experiments and it would be interesting to see if longer periods would have produced adaptation such as that in the earlier 7.5-hour exposure to a gradually decreasing oxygen tension.

Seitz found recovery of the CFF upon return to normal air typically took much longer than the few minutes required for recovery of visual sensitivity in absolute sensitivity experiments (e.g., McFarland and Evans, 1939). Recovery of the CFF to prehypoxia levels typically required at least 30 minutes. Strychnine applied to the eye improved CFF for that eye, both in normal air and with reduced oxygen tension.

All measures made by Seitz were of fusion, i.e., frequencies always were varied in an increasing direction from low flickering levels. This may have masked some of the hypoxia effects if, as would be expected, subjects' responses indicating fusion were slowed by hypoxia (e.g., McFarland, 1937b) and the flash frequency actually was increased to a level greater than the point required for fusion.

¹ Hyperventilation may have occurred early in this rapid reduction of oxygen tension and the resultant hypocapnia and boosted arterial oxygen may have initially countered hypoxic decrements.

Gellhorn and Hailman (1944) measured both CFF and the occipital EEG during 6- to 17-minute exposures to severe hypoxia and during exposure to hypoxia with elevated CO₂. Subjects were medical students aged 20 to 25 who viewed a two-degree visual field through an artificial pupil. As with Seitz, only fusion thresholds were measured. A small decrement in the CFF was found while breathing 8.4 percent oxygen and this became a substantial effect when tension dropped to 7.8 percent in the same session. Gellhorn and Hailman found that occipital EEG changed when the CFF was reduced sharply with the alpha rhythm typically being replaced by slower wave activity.

Gellhorn and Hailman also found administration of 3 percent or 3.6 percent CO₂ along with the low oxygen mixtures typically reduced or prevented decrements in the CFF, except when even lower levels of oxygen were breathed (6.2 percent). These improvements in the CFF when breathing CO₂ are somewhat surprising since hypercapnia typically reduces the CFF and hypocapnia increases it (see below). It is highly probable hyperventilation was generated by the three percent CO₂ and that this actually reduced alveolar and blood CO₂ levels, despite the slightly increased levels of CO₂ in inspired air. Schaefer and Carey (1953) found that CO₂ levels had to be above five percent to reduce the CFF. The probable hyperventilation also would boost oxygen levels countering some of the effects of severe hypoxia.

These remarkably low levels of oxygen tension corresponding to altitudes of about 25,000 feet apparently were withstood well by the subjects of Gellhorn and Hailman. However, exposure periods were short relative to more typical experimental hypoxic treatments. Severe symptoms were noted by Gellhorn and Hailman when the oxygen concentration was lowered further to five percent, even in the presence of three percent CO₂.

Birren et al. (1946) also assessed the effects of hypoxia on the CFF. They tested 4 subjects at 18,000 feet, 17 subjects at 15,500 feet, 11 subjects at 14,000 feet, and 24 subjects at 10,000 feet. No discussion of sex or age of subjects was given, but they probably were males of pilot age. A one-degree test object was viewed at a distance of 18 inches. The method of limits was used with the threshold approached alternately from above and below. Averages were obtained of 10 readings at sea level and 4 readings at altitude. Unlike Seitz (1940) who presented low oxygen mixtures at ground level, Birren et al. (1946) used a low pressure chamber and exposed subjects to normal air at the four simulated altitudes with a separate 1-hour session at each altitude. They also measured the size of peripheral visual fields in their experimental sessions.

Both field size and the CFF decreased with hypoxia with effects related to the degree of hypoxia. The perimetry results were

discussed in the previous chapter. Decompression to 18,000 feet produced a substantial decrement in the CFF compared to the decrement from sea level observed at 14,000 feet and 15,500 feet. The decrements in the CFF appeared at the first of five measurements at altitude and increased slightly over the course of testing. Testing immediately after recompression to sea level showed a decrement of the CFF compared to the initial sea level readings. Although 8 subjects either collapsed or approached collapse and were unable to complete testing at 18,000 feet, their average CFF change prior to leaving the experiment actually was less than those who completed the hour at 18,000 (1.16 flashes per second vs. 2.49 flashes per second). However, the small number of subjects (four) at 18,000 feet prevented generalizations about these reversed altitude effects.

Vollmer et al. (1946) assessed both altitude and CO effects on the CFF (also on field size and body sway) using a highly similar testing procedure to that of Birren et al. (1946). Twenty officers and enlisted Navy personnel, 18-39 years of age, viewed a one-degree CFF test object at a distance of 18 inches. Thresholds were approached alternately from above and below. A low pressure chamber was used to simulate altitudes of 10,000 and 15,500 feet. Altitude (15,500 feet) produced a small but significant decrease in the CFF and field size both with and without CO breathing. As will be discussed later in the section on CO-breathing effects, CO did not reduce performance beyond the decrement with hypoxia alone.

Lillienthal and Fugitt (1946) also assessed the effects of altitude and low levels of COHb on sensitivity to flicker. Five 18-year-old males who had been examined and accepted for flight training viewed a five-mm neon glow tube through a 12-inch viewing tube which made a CFF stimulus of 0.94 degrees visual angle. Rapid rates of flicker that produced fusion were presented and the rate was decreased steadily until flicker onset was observed. Then the rate was abruptly increased and the measurement repeated. Three such determinations were made within 10 to 15 seconds. At that point, the subject withdrew his eye from the viewing tube, rested for 2 to 3 minutes, and the three determinations were repeated. No mention was given of an artificial pupil in the viewing tube and probably none was used.

Without elevated COHb, decompression to 10,000 feet produced a significant decrement in the CFF for two of the five subjects, decompression to 11,000 feet produced a significant decrement for four of the five, and decompression to 12,000 feet produced a significant decrement for all five. No discussion of the possible bases for the individual differences in CFF decrements with hypoxia was given. Ten minutes of breathing pure oxygen at 11,000 and 12,000 feet restored the CFF to sea level values. The detrimental effects found as a result of breathing CO at altitude are described in a later section of this chapter.

Adler et al. (1950) studied the effect of various drugs on psychomotor performance at ground level and at simulated altitudes up to 18,000 feet in a low pressure chamber. Sixteen subjects viewed a constant light source that was not described, but given the methodology of research by some of the same researchers (Krasno and Ivy, 1950) it was probably a 0.75 degree by 0.92 degree rectangle viewed at 100 cm. This light source was interrupted by a sector disk. Subjects began viewing at fusion levels and reported when flicker was first seen. Testing occurred in a decompression chamber at ground level then at 10,000, 15,000, and 18,000 feet. Numerous other tests were given as well. Various drugs and a placebo were compared.

The placebo condition at sea level produced a significantly higher CFF than at the two higher altitudes with the maximum decrement in the CFF found at the maximum altitude of 18,000 feet. Drugs reduced, but typically did not eliminate the hypoxia effects. A figure provided in the report indicated flicker thresholds that are different, perhaps five per second greater, than presumably the same data presented in their Table 1. However, the differences between sea level CFF and altitude CFF appear to be the same in the figure and the table. The use of only decreasing flash rates (to flicker) would produce apparent CFF decrements if subjects' reactions to indicate flicker were delayed by hypoxia or drugs.

This research of Adler et al. (1950) was carried out over an extended period of about 10 weeks and subjects were exposed to 18,000 feet without oxygen two or three times a week. The CFF showed a progressive decline over this long period both when measured at sea level and at altitude. There was an 8.6 flashes per second average drop over the long period at sea level. This drop was significant, but the corresponding 2.9 flashes per second average drop over the long period at 18,000 feet was not significant. This decrement in the CFF with exposures to hypoxia over many days appeared to parallel the long-term decrements in visual field size which were described by Halstead (1945a; 1945b) following repeated exposures to altitude (see Chapter 4: "Fields of peripheral and central vision").

Scow, Krasno, and Ivy (1950) studied the immediate and cumulative effects on psychomotor performance of exposure to hypoxia, high altitude, and hyperventilation. The subjects were 11 medical and graduate students who provided measures of the CFF, pursuit meter performance, tapping rate, and tremor both at ground level and at 18,000 feet. They also performed these tasks following hyperventilation at ground level and with supplemental oxygen at 35,000 feet. No description of the CFF stimulus or task was given, but they probably used the Krasno and Ivy (1950) apparatus for measuring the CFF (0.75-degree by 0.92-degree rectangle when viewed at 100 cm) and probably followed the Krasno and Ivy procedure of use of all descending trials (flicker

threshold). Significant decrements at 18,000 feet without oxygen were found on all measures. The CFF was more than four flashes per second lower when measured at altitude than when measured at sea level. Hyperventilation did not produce any changes in the CFF or in other measures nor did breathing pure oxygen at 35,000 feet.

Simonson and Winchell (1951) studied the effects of low oxygen and high CO₂ on the fusion frequency of flicker. Thirteen normal healthy men aged between 21 and 35 viewed a one-cm-diameter test patch subtending a visual angle of one degree (57 cm viewing distance). The illumination was 50 fl and the dark-light ratio was 60:40. The exposure time of this flickering stimulus was only 1 second (to prevent adaptation effects). The schedule of gas breathing was 3 to 5 minutes of room air, followed by 12 minutes of 5 percent CO₂ and 95 percent oxygen. This was followed by 10 minutes of normal air which was followed by 14 percent oxygen for 12 minutes. Oxygen saturation was measured with a Millikan oximeter.

Eleven of the 13 subjects showed a drop in the CFF while breathing the low oxygen mixture with the average drop being 2.3 flashes per second. Arterial oxygen saturation during breathing of the 14 percent oxygen dropped 6.3 percent, on the average, with no correlation found between this drop for individuals and their drop in the CFF. The CO₂ mixture caused a drop in the CFF for all subjects, despite the high oxygen tension of this mixture. This drop averaged 3.9 flashes per second. This drop was not only greater than for 14 percent oxygen, it was much more rapid, with a three-flash-per-second drop already present at the fourth minute.

Large individual differences were found in the decrements in the CFF associated with breathing both gas mixtures. CO₂-breathing increased pulmonary ventilation by 129 percent, on the average, but there was no correlation between individual ventilation levels and individual CFF levels. A high correlation ($r=.87$) was found between the initial CFF and the drop in the CFF during breathing of CO₂. This suggests those subjects who had engaged in some initial hyperventilation prior to breathing CO₂ and who had an elevated CFF as a result of hyperventilation-induced hypocapnia (Alpern and Hendley, 1952) were responsible for the high correlation with subsequent CFF drops produced by the CO₂ breathing. A much smaller correlation was found between the initial CFF level and the drop in the CFF during low-oxygen breathing ($r=.42$) and this may simply reflect regression to the mean. Problems with the research included a critical missing control condition with similarly extended testing of the CFF while breathing normal air. Studies have shown that there is a "vigilance" decrement in the CFF (Waller and Levander, 1980) and this may have accounted for part of the drop in the CFF with both gas mixtures.

Alpern and Hendley (1952) determined the effects of metabolically-induced blood pH changes and respiration-induced blood pH and blood CO₂ changes on visual sensitivity and the CFF. Their subjects included a total of 28 normal young adults for various conditions of the study. Visual thresholds were discussed in an earlier chapter. The CFF was measured while viewing (with an artificial pupil) a circular 2.3-degree test field against an annular background with an external diameter of 6 degrees. Talbot luminances of the flashing stimulus were 0.25, 4, 400, and 4,500 ml. Annular backgrounds were equated in luminance for lower luminances, but held at a maximum of 35 ml. Metabolic acidosis was produced by oral administration of ammonium chloride. Metabolic alkalosis was produced by oral administration of sodium bicarbonate. Respiratory acidosis was produced by having the subject breathe a mixture of 7 percent CO₂ and 93 percent oxygen. Respiratory alkalosis was produced by having the subject hyperventilate voluntarily.

Respiratory acidosis significantly reduced the CFF at the two luminance levels tested (4 and 400 ml). Respiratory alkalosis significantly increased the CFF at all four luminance levels where it was tested. Neither metabolic acidosis nor metabolic alkalosis significantly changed the CFF. The implication of these results was that it was levels of blood CO₂ and not pH levels in the blood that altered vision. One problem with the research was that metabolic serum pH changes were somewhat less than respiratory serum pH changes and this could account partly for why metabolic changes did not significantly influence the CFF (and absolute sensitivity). It was not clear why such wide fluctuations existed in numbers of subjects for different conditions or why there was a failure to assess respiratory acidosis effects at all luminances at which respiratory alkalosis was assessed.

Schaefer and Carey (1953) measured the CFF and EEG in 10 subjects who were exposed to 1.5, 3.4, 5.4, and 7.5 percent CO₂ over a period of 20 minutes. They used the Krasno and Ivy (1950) apparatus for measuring the CFF (a 0.75-degree by 0.92-degree rectangle when viewed at 100 cm). They found that a concentration of five percent CO₂ or higher produced a significant drop in the CFF, a decreasing qualitative blocking effect, and an increased alpha blocking time. There was too little discussion in this abstract to determine if problems existed in the research. However, if they followed the Krasno and Ivy procedure of use of all descending trials (flicker thresholds), any decrement produced by CO₂ on response speed partially could account for these effects.

Bietti (1953) described research by Bietti, Grignolo, and Boles Carenini which apparently showed a reduction in the CFF during hypoxia. This occurred both at low luminance levels affecting only rods and higher luminance levels affecting cones.

Rokseth and Lorentzen (1954) looked at the combined effect of alcohol and hypoxia on the CFF. They tested 25 healthy male students and Norwegian Medical Corps personnel. The CFF was measured under conditions of hypoxia alone, alcohol alone, both hypoxia and alcohol, and neither hypoxia nor alcohol. The CFF stimulus was 1.5 cm in diameter and viewed at 75 cm (1.15 degrees). Hypoxia was produced by decompression to an altitude of 10,000 feet with hypoxia lasting for 4 hours. Measures of the CFF involved both a decrease of flash frequency until flicker was detected and an increase in flash frequency until fusion was detected with 10 such frequency measures averaged.

Hypoxia reduced the CFF and this decrement became larger over the 4-hour session. Blood alcohol levels of 0.03 to 0.04 percent also produced significant CFF decrements. The effect of alcohol decreased over the 4-hour session as the blood alcohol level dropped. The combined effects of alcohol and hypoxia on the CFF largely were equivalent to adding the separate decrements for alcohol alone and hypoxia alone. Oxygen saturations of the blood with hypoxia alone ranged from 83 to 90 percent. Oxygen saturations of the blood when hypoxia and alcohol were combined ranged from 75 to 85 percent. No blood oxygen saturation measure was reported for alcohol at sea level.

Jorgensen (1955) studied the effects of hyperventilation on the CFF with foveal images of different sizes. It is not clear whether the subject was one young emmetrope with normal vision and no eye diseases or whether there were more subjects with this profile. However, it appears that only a single subject's data was presented. A wide range of sizes of flickering targets were used from smallest visible to "covering the entire rod-free zone." Testing occurred with and without a white background for the flickering stimulus.

Hyperventilation increased the rate at which flicker was seen over the rate without hyperventilation for virtually all sizes of targets. Testing began after 5 minutes of hyperventilation and the maximum increment in the CFF with hyperventilation typically occurred 15 to 30 minutes after hyperventilation was begun.

When this hyperventilation increment in the CFF was plotted as a function of retinal size of the target, it took the form of a double-peaked curve as retinal size of the targets increased. This double-peaked function undoubtedly was related to the fact that the series of increasing sized targets was presented twice, once at a distance of 7 meters, providing the small retinal images, and again at 70 cm, providing the large retinal images. The two peaks were near the midpoint of each of these two series of actual target sizes and the smallest and largest actual targets produced minimum or near-minimum CFF increments with hyperventilation at both presentation distances.

It is obvious the different presentation distances had an independent effect on the CFF that largely overrode the continuum of retinal image size generated by presenting the series of targets twice. This effect of target distance is most interesting, and it would be good to see a replication of this hyperventilation-CFF study where all retinal sizes were presented at the same distance, where several stimuli of constant retinal size are presented at several distances ranging from the near point to optical infinity, and where a number of subjects are tested.

Granger and Ikeda (1961) provided an extraordinary study of the effect of hyperventilation on foveal CFF that has numerous implications for effects of hypoxia on the CFF, given that hyperventilation is a fairly normal consequence of hypoxia (e.g., Ernest and Krill, 1971). Their objectives were to assess effects of hyperventilation on the CFF for different luminances and different target sizes in order to gain insight into the mechanism of these well-established CFF improvements with hyperventilation. Subjects for the most part were the two authors with additional data collected from five other subjects. No subject suffered from any visual disorder or other pathological condition known to affect the CFF and any refractive errors were corrected fully.

Thirty seconds of hyperventilation at a little more than twice the normal respiration rate was used for experimental sessions and no hyperventilation for control sessions. The CFF was measured immediately after hyperventilation. Stimulus sizes ranged from 2.5 minutes of visual angle to two-degrees-11-minutes of visual angle. Stimulus intensities varied from zero to five (log intensity in Trolands). Only one to four log Trolands were used for most sizes of stimuli, since very dim and very bright stimuli made for difficult or impossible flicker determinations. An artificial pupil was used throughout data collection.

Hyperventilation elevated CFF when stimuli were larger than 5 minutes of visual angle, with this increase gradually going from 0 for a field subtending a few minutes, to 2 to 3 flashes per second for fields of 1 to 2 degrees. The CFF typically increased linearly as a function of target luminance. However, for the largest targets, the CFF leveled off and then dropped at highest luminance levels. The elevation of the CFF by hyperventilation applied to the linear rise and applied also to the leveling off and drop of this CFF as target luminance increased (i.e., the two rising and falling curves were parallel). This indicated the hyperventilation increment could not be accounted for as a shift to the left of the curve on the illumination axis in the same way that a shift to the right of data curves on the illumination axis accounted for hypoxia decrements in contrast discrimination (McFarland, Halperin, and

Niven, 1944) and visual acuity (McFarland and Halperin, 1940). Unfortunately blood oxygen, blood CO_2 , and blood pH were not measured during hyperventilation and control trials.

There are at least two reasons that the Granger and Ikeda (1961) research has numerous implications for effects of hypoxia on the CFF. One is that hypoxia often induces hyperventilation (e.g., Ernest and Krill, 1971) and the resultant hypocapnia would operate to increase the CFF, countering to some extent decrements from hypoxia. The other is that it is probable hypoxia effects on the CFF directly are related to the size of the stimulus as Granger and Ikeda have clearly shown is the case for hyperventilation. If so, it may provide an explanation of many contradictory results in research on hypoxia and the CFF which have used a large range of target sizes. It also suggests any new research on respiratory effects with CFF as the dependent variable should use flashing targets of large area in order to increase the sensitivity of the experiments.

Baer (1967) measured effects of hyperventilation on the CFF in 45 college males with equal numbers of heavy smokers, moderate smokers, and nonsmokers. A test patch of 12.7 mm (luminance of 25 ml) was viewed at an unspecified distance through an artificial pupil of 2 mm. Both ascending (fusion) and descending (flicker) thresholds were measured. A 2-minute period of hyperventilation decreased the CFF. This decrease was contrary to the increase found in previous research where hyperventilation was only for 30 seconds and the CFF was measured immediately afterward (Granger and Ikeda, 1961). Baer measured the CFF six times over a 4-minute period following hyperventilation and it is possible that they failed to measure the CFF quickly enough following hyperventilation to show the hypocapnia effects. Another possibility is that their stimuli may have been smaller than those shown by Granger and Ikeda (1961) to produce hyperventilation increases in the CFF.

Kobrick (1968) assessed a variety of visual functions at altitude with and without the drug acetazolamide which may help to prevent altitude sickness. Subjects were 36 male soldier volunteers ranging in age from 19 to 36 who were divided into acetazolamide and placebo groups. Vision was normal and there were no physical defects which might be aggravated by hypoxia. The CFF was measured with a Grayson-Stadler apparatus (Model E622) with three ascending and three descending trials averaged. Testing occurred at sea level and again about 3 days later after 24 hours of exposure to an altitude of 12,800 feet. Hypoxia did not produce any changes in the CFF (or any other dependent variables). The absence of change in the CFF did not replicate the CFF decrements found by Birren et al. (1946) at similar altitudes. This may have been because Kobrick provided longer exposure to hypoxia before testing with resultant acclimatization. According to Kobrick, it

may have reflected use of a flashing red stimulus by Birren et al. vs. Kobrick's use of a white stimulus.

Kobrick and Appleton (1971) assessed a variety of visual functions under extended hypoxia including the CFF. Subjects were 8 healthy soldier volunteers ranging in age between 18 and 25 with normal near and far acuity, normal stereopsis, and normal peripheral vision. The CFF was measured at sea level and after 1, 18, 24, and 48 hours of exposure to an altitude of 15,000 feet in a decompression chamber. Dark adaptation, near and far acuity, depth perception, stereopsis, and peripheral visual reaction time also were measured. A Grayson-Stadler (Model E622) flicker apparatus was used to measure the CFF with three ascending and three descending trials averaged. Three light-dark ratios of 0.95 on-0.05 off, 0.50 on-0.50 off, and 0.05 on-0.95 off (per cycle) were used to measure the CFF.

Changes occurred in the CFF, dark adaptation, and peripheral visual response as a result of hypoxia with maximal changes at the initial 1-hour test and some recovery over 24 or 48 hours. Strongest and most persistent effects of hypoxia on the CFF were for the 5-95 light-dark ratio.² This may reflect the greater oxygen consumption of the retina in darkness (e.g., Linsenmeier, 1986).

In their discussion, Kobrick and Appleton (1971) indicated the initial drop in the CFF showed complete recovery by the end of exposure. However, they appear to be victims of an optical illusion that exists in their Figure 2. Despite appearances, the CFF was lower than in preexposure trials for all light-dark ratios at the end of 48 hours and this difference was nearly five flashes per second for the 5-95 light-dark ratio.

Nair, Malhotra, and Gopinath (1972) assessed the effects on the CFF of 6 weeks acclimatization to an actual altitude of 11,000 feet with 3 weeks of adaptation to cold also occurring during the 6-week stay. There were 20 healthy subjects ranging in age from 20-28. A Grass photostimulator presented a 1-cm square stimulus which had a visual angle of 0.4 degrees at the viewing distance of 150 cm. Stimulus intensity was 30 lux at the source and room illumination was kept at 20 lux. The CFF was recorded at the same time of day for each subject after the subject relaxed for 1 hour in a warm

² This parallels research of McFarland, Warren, and Karis (1958) who found the greatest age decrement on CFF to occur for the shortest light-dark-ratios. Given the Granger and Ikeda (1961) finding that large stimulus areas enhanced hyperventilation effects and this light-dark ratio result, both stimulus features probably should be included in any research investigating oxygen tension or other respiratory effects on CFF.

room. Flickering stimuli were increased in flicker rate until fusion was noted. Baseline measures at sea level were taken, then subjects were flown to altitude and tested 6 to 8 hours after arrival. Subjects were tested weekly for 6 weeks, then returned to sea level and retested. Half of the group spent 3 weeks in cold temperatures with inadequate clothing followed by 3 weeks in a heated room. The other half spent 3 weeks in the heated room followed by 3 weeks in cold temperatures with inadequate clothing.

A small (1.15 flashes per second), but apparently significant drop in the CFF occurred after arrival at altitude for both groups.³ Cold temperatures reduced the CFF for both groups and this was the major change noted during the 6 weeks at altitude. A sharp four flashes per second rise in the CFF above initial sea level testing was found for both groups upon return to sea level, indicating that adaptations ("Hematological, cardiorespiratory and probably metabolic adjustments") to the 6 weeks of altitude and 3 weeks of cold improved performance with normal oxygen tension at sea level. The confound of cold and altitude prevented identification of whether this acclimatization effect that substantially boosted subsequent sea level performance was due to hypoxia, low temperature, or both.

Aisenberg et al. (1974) studied hypoxemia and the CFF in congenital heart disease. Cyanotic heart disease patients (blood oxygen saturations less than 90 percent) were found to have significantly lower CFFs than acyanotic heart disease patients (blood oxygen saturations exceeding 90 percent). The average CFF for the cyanotic group was 43.2 flashes per second compared to 46.6 for the acyanotic patients. In the cyanotic group, blood oxygen levels were associated significantly with the CFF. There apparently was no correlation between blood oxygen levels and the CFF for the acyanotic group. The CFF was associated directly with age in both groups.

Seki and Hugon (1976) found striking decrements in the CFF associated with a very deep dive (62 ATA). Helium-oxygen mixtures were breathed and the oxygen partial pressure was maintained between 0.38 and 0.42 ATA during the 11 days of compression and 50 hours of saturation. The oxygen partial pressure was maintained between 0.49 and 0.52 ATA during the 10 days of decompression. The CFF was measured with a target 0.5 degree in diameter at an unspecified distance using the SHIBATA-FL-AO flicker apparatus. Only flicker thresholds were measured with the flash rate reduced for each trial from 60 flashes per second.

³ The table of results does not indicate that the initial drop noted at altitude was significant for both groups, although the text does.

The CFF for one subject changed from 42.5 flashes per second on the surface to 32.8 flashes per second at 62 ATA to 42.5 flashes per second upon return to the surface. For the other subject, the corresponding changes were from 44.9 to 37.7 to 43.3 flashes per second. The correlations between depth and the CFF for both subjects was -0.93 . Depth and ambient temperature were also correlated ($r=.74$) as were the CFF and temperature ($r=-.71$ for one subject and $r=-.66$ for the other). The much higher correlation between depth and CFF than between temperature and CFF indicated it was depth and not temperature that produced the major change in the CFF. The constant slightly hyperoxic oxygen tension indicated changes in pressure and not changes in oxygen tension produced the CFF changes.

No discussion of CO_2 levels was provided by Seki and Hugon (1976). However, at these huge pressures, even a minuscule quantity of CO_2 in the breathing mixture might produce CO_2 tensions that exceeded the greater than five percent CO_2 tensions that caused the reductions in the CFF found by Alpern and Hendley (1952) and Schaefer and Carey (1953).

Sen Gupta, Mathew, and Gopinath (1979) assessed acclimatization to high altitude with and without heavy exercise during the acclimatization period at a moderate altitude. They used time of useful consciousness (TUC) following exposure to air at 7,260 m and the CFF (measured at more moderate altitudes and sea level) as dependent variables. The subjects were 20 healthy soldiers (20-26 years old) who were given training on the CFF apparatus prior to testing at altitudes. A Lafayette Flicker Fusion Apparatus (Model 1202 A) with a binocular viewing chamber was used. Frequencies always were presented in ascending order and subjects signalled the fusion point. Four measurements were made and if there was variation in the settings, the average was used. The CFF was measured in a decompression chamber at sea level, 1,850, and 3,500 meters. Thirty minutes of adaptation occurred at each altitude prior to testing. Subjects then spent 8 weeks at 1,850 meters with one group receiving only 20 minutes of physical training per day and another receiving 40 minutes plus another 60 minutes of compulsory games. The CFF was measured weekly during these 8 weeks. Subjects were returned to Delhi and the TUC and the CFF recorded. Subjects then were flown to 3,500 meters and stayed there for 4 weeks. TUC was measured upon return to Delhi. For unexplained reasons, the CFF was not measured at 3,500 or upon return.

Both the TUC and the CFF improved with acclimatization. The TUC measure showed a significant and marked improvement as a result of acclimatization at 1,850 meters for the high exercise group (ranging from 202.2 to 280.6 seconds) which was significantly greater than for the low exercise group (ranging from 198.3 to 227.2 seconds). Four weeks at 3,500 meters produced a further

increase for the high exercisers and a very large increase in TUC for the low exercisers. Although the high exercisers still had a higher average TUC (314.7 seconds) than the lows (276.6), the difference now was not significant.

The CFF measured at 1,350 meters in the decompression chamber was not significantly reduced from sea level. Measures of the CFF at 3,500 meters in the decompression chamber were significantly lower than sea level measures. Readings upon arrival at an actual 1,850 meters also were significantly lower for both groups than at sea level. Following a stay at altitude, the CFF returned to sea level values for both groups, but this occurred at the 16th day for the high exercisers and not until the 40th day for the low exercisers. Following return to sea level after the 48 days at 1,850 meters, both groups had higher CFF levels than their initial CFF levels at sea level. The high exercisers had significantly higher postaltitude CFF levels than the low exercisers. No explanation was provided for the failure to collect additional CFF data during and following exposure to an actual altitude of 3,500 meters.

A recent study did not examine low oxygen tension effects on the CFF, but did look at probable restrictions of blood flow to the retina that may emulate effects of breathing low oxygen. Langan and Watkins (1987) determined the effects of tight collars and neckties on the CFF. Preliminary observations had indicated tightening a collar band to 1.27 cm less than the subjects unrestricted neck measurement caused an observable reduction in pulsing of "the retinal vein" upon examination with an ophthalmoscope. Subjects for the investigation of possible visual sensitivity effects were 32 men with 10 in a no-neck-bind control group. The flicker source was viewed at 84 cm and there was no discussion of stimulus size, although it appears to have been small. Both fusion and flicker thresholds were measured (ascending and descending trials) and these were averaged. Three such averages were collected under conditions with no neckwear pressure, with neckwear pressure, and with neckwear pressure removed.

Tightening the collar significantly reduced CFF in the experimental group and these measures did not immediately return to normal after the tie was loosened. The control group did not have any neckwear pressure and showed no CFF changes over three sets of measurements. This study could stand replication with inclusion of ear oximetry or other measures of blood oxygen saturation and with measurement of possible respiration and blood CO₂ changes induced by neckwear pressure. Other dependent variables such as contrast sensitivity, auditory acuity, and measures of cognitive performance also would be of interest.

Carbon monoxide and the CFF

Asphyxia via carbon monoxide is a less traumatic death than asphyxia via hypoxic hypoxia and this relative lack of distress associated with hemic hypoxia may be a factor in differences in effects of the two types of hypoxia on visual and other performances. Although hypoxic hypoxia produces its share of contradictory effects on vision and other behaviors, there probably is a larger percentage of contradictions in research on the effects on the CFF of hypoxia that is generated by breathing CO (hemic hypoxia).

Even as McFarland et al. (1944) found that low oxygen saturation produced by breathing oxygen at low tension and low oxygen saturation produced by a buildup of COHb were additive in effects on contrast sensitivity, Lillenthal and Fugitt (1946) made a largely similar finding for the CFF. Lillenthal and Fugitt assessed the effects of low levels of COHb on visual sensitivity at altitude using the CFF as their measure of visual sensitivity. Five 18-year-old males who had been examined and accepted for flight training served as subjects. A 5-mm neon glow tube was viewed through a 12-inch viewing tube which presumably would make for a stimulus with a visual angle of 0.94 degrees. Fusion flash rates were presented initially with the rate decreased steadily until flicker onset was observed. Following the recording of this rate, it was abruptly increased and the measurement repeated. Three such determinations were made within 10 to 15 seconds. The subject then withdrew his eye from the viewing tube and rested for 2 to 3 minutes after which rest the three determinations were repeated.

As discussed earlier, without elevated COHb, decompression to 10,000 feet produced a significant decrement in the CFF for two of the five, decompression to 11,000 feet produced a significant decrement for another two and decompression to 12,000 feet produced a significant decrement for the fifth. Ten minutes of pure oxygen breathing at 11,000 and 12,000 feet restored CFF to sea level values.

Measurements of CFF without decompression while breathing CO-air mixtures of 0.15 to 0.2 percent did not lead to decrements in the CFF, even when levels of 13.8 to 17.4 percent COHb were attained by the different subjects. However, when decompressed to 5,000 feet, all subjects showed COHb depression of the CFF with the COHb levels causing this decrement ranging from 5.1 percent for one subject to 9.2 percent for another. Results were similar at 6,000 feet, although, paradoxically, it took somewhat higher levels of COHb to produce depression of the CFF. The moderately low levels of 5 to 10 percent COHb (measured above the COHb existing before CO

exposure) were seen as equivalent to adding 7,000 feet of altitude in terms of the effect on flicker sensitivity.

Vollmer et al. (1946) also assessed both altitude and CO effects on the CFF. Twenty officers and enlisted Navy personnel, 18-39 years of age, viewed a one-degree CFF test object at a distance of 18 inches. Thresholds were approached alternately from above and below and measures averaged. A low-pressure chamber was used to simulate altitudes of 10,000 and 15,500 feet. As discussed earlier, altitude (15,500 feet) produced a small but significant decrease in the CFF (and field size) both with and without CO breathing. However, unlike the results of Lillenthal and Fugitt (1946) for lower altitudes, CO breathing did not reduce performance beyond the decrement with hypoxia alone.

Von Post-Lingen (1964) assessed the effects of exposure to small concentrations of carbon monoxide by determining whether a decrement in the CFF became more likely following hemic hypoxia. CFF decrements were indicated by an increase in the intensity required to produce subjective flicker of a constant on-off-rate stimulus. A 1.9-degree stimulus was presented at an intensity that provided clear perception of flicker. Intensity was lowered until flicker disappeared and the intensity level recorded. After that intensity was raised until flicker appeared and the intensity level was again recorded. These ascending and descending intensity settings were averaged. It was found CO exposure increased susceptibility to the transitory fall in the CFF produced by intravenous injection of the anesthetic drug Evipan. This CFF drop was shown by Berg (1949) to indicate reduced viability of the nervous system.

Von Post-Lingen (1964) found when double-blind experiments were conducted this largely eliminated significant effects of CO. Undoubtedly, the starting point from which intensity increases influences the intensity level that leads to perceived flicker in much the same way that the starting flicker rate influences flicker/fusion thresholds (Ginsburg, 1967). With single-blind procedures, experimenters may unintentionally alter starting points to make results fit with their preconceptions.

Beard and Grandstaff (1970) studied the effect of low COHb levels on the CFF and found significant decrements which have failed to be replicated by a number of researchers. Among these, Guest, Duncan, and Lawther (1970) looked at carbon monoxide and phenobarbitone effects on the CFF and also on the auditory flutter fusion threshold. Subjects viewed a stimulus 0.68 degree in diameter at 60 cm. Descending frequencies were presented on each trial until flicker was noted. Phenobarbitone produced a significant drop in the CFF, but there was no change in the CFF with elevated COHb (about 10 percent) compared to air breathing.

O'Donnell, Chikos, and Theodore (1971) also studied the effect of carbon monoxide exposure on the CFF using COHb levels of 5.9 and 12.7 percent. The CFF was measured with ascending trials with the fusion point being identified by the subject. A red stimulus 0.375 inch in diameter was viewed at approximately 16 inches (visual angle of approximately 1.34 degrees). CO exposure (75 ppm and 150 ppm) did not cause changes in the CFF.

Fodor and Winneke (1972) also studied the effect of low COHb concentrations (5.3 percent) on the CFF. Subjects were tested with a Bettendorf 40256 flicker device. A continuously descending frequency was used, starting with 60 flashes per second. Subjects reported when flicker first appeared. No effect of CO on the CFF was observed.

Seppanen, Hakkinen, and Tenkku (1977) studied the effect of gradually increasing COHb on visual perception and psychomotor performance of smoking and nonsmoking subjects. The 22 smokers and 22 nonsmokers viewed a large (compared to most other studies) 5.76-degree stimulus at a distance of 50 cm. Both ascending and descending trials were used with the average taken as the CFF. CO-air mixtures were breathed with CO equal to 1,100 ppm CO. A significant linear decrease in the CFF was found as COHb increased. Even the small difference in the CFF between 4 percent COHb and 5 percent COHb was found to be significant. As with the results of Beard and Grandstaff (1970), many researchers have wondered why these surprisingly strong effects of low COHb levels were found. However, it may just reflect a large amount of carefully collected data. Also, a large stimulus appears to be much more sensitive than small stimuli to respiratory effects on the CFF (See Granger and Ikeda, 1961).

Winneke (1974) studied the effects of methylene chloride and carbon monoxide on the CFF using a Bettendorf 40236 flicker device. A descending frequency was used with subjects reporting the appearance of flicker. CO was breathed at two levels and in a third condition methylene chloride was breathed. Methylene chloride produced significant decrements in the CFF, but CO percent did not decrease the CFF at either level, despite COHb levels as high as 10 percent.

Hyperoxia and the CFF

Bennett and Cross (1960) found increasing the pressures at which air was breathed up to seven atmospheres led to distinct shifts in the CFF for each subject. The oxygen tension would have been somewhat greater than that obtained by breathing pure oxygen at one atmosphere. They used the same apparatus used by Simonson and Winchell (1951) which was described earlier in this chapter. For the majority of subjects, this reliable change was a decrease

of one or more flashes per second. For some, however, it was an increase in the CFF of similar magnitude. Although details were not provided, this changed state was reached quickly at high pressures and less quickly at lower pressures. These alterations in the fusion frequency of flicker were correlated with a change in the electroencephalogram described as abolition of alpha blocking. Individual differences in hyperventilation are a likely explanation of the consistent individual differences in CFF change.

No other studies were found looking at the effects of hyperoxia on the CFF in humans, except studies described earlier that looked at recovery from hypoxic decrements while breathing pure oxygen (e.g., Lillenthal and Fugitt, 1946). However, Burns (1971) used rhesus monkeys who were trained to respond to flicker and investigated the effects of breathing 100 percent oxygen at 0.8, 1.4, and 2.0 atmospheres on the CFF. Oxygen reduced the CFF with the reduction directly proportional to pressure. The results are intriguing and suggest a need for human data on the CFF as a function of hyperbaric oxygenation.

Conclusions and research needs

Despite the large number of studies of CFF and hypoxia, a number of questions remain unanswered. The absence of effects of hypoxia on the CFF with long periods of adaptation to the low oxygen tension found by Seitz (1940) and the apparently contradictory need for extended exposure to hypoxia for rapid changes in oxygen tension in later experiments by Seitz remains a mystery. One suspects that hyperventilation may have operated to increase CFF at late stages of the slow decrease in oxygen tensions and hyperventilation may have been prevalent early in the later series of experiments and this reduced immediate hypoxic decrements in the CFF. Replication of some of Seitz's experiments with measurement of blood CO_2 and with control of respiration might explain his contradictory findings.

The large stimulus-size effect found by Granger and Ikeda (1961) when hyperventilation boosted the CFF also probably would be found when effects of hypoxia and carbon monoxide on the CFF were studied. The unusually strong effects on the CFF of COHb found by Seppanen, Hakkinen, and Tenkku (1977) may well reflect his unusually large flickering target. Research exploring this stimulus size effect for different respiratory conditions would appear to have relevance for explaining retinal and central flicker perception mechanisms. If size effects were found, such research also would identify research procedures that would be more apt to show effects of respiratory or related independent variables. Should the stimulus size effect be confined to hypocapnia, this would be of even more theoretical interest.

Kobrick and Appleton (1971) found that hypoxia had its greatest effect when the light portion of the light-dark interval was small. Researchers probably would maximize hypoxia effects and other respiration effects when the flash is brief relative to the off time. Probably both large stimuli and brief stimulus flashes are needed for maximally sensitive research on the CFF.

One of the most interesting findings of Ernest and Krill (1971) was their demonstration of sharply increased scalloping for ascending and descending thresholds during hypoxia compared to normoxia in their study of absolute sensitivity. A parallel study of the effects of hypoxia (and perhaps hypocapnia) on scalloping of successive fusion and flicker thresholds would appear to have many methodological benefits. It is critical that the starting point for ascending thresholds and the starting point for descending thresholds be the same for all pairs of trials (Ginsburg, 1967).

As with absolute visual sensitivity, contrast sensitivity, and acuity, the CFF changes with hypoxia showed large individual differences that have not been well explained. The CFF would provide an important dependent variable for studying individual differences in visual response to hypoxia. The strong possibility that different visual performances (CFF, visual sensitivity, contrast sensitivity, acuity, etc.) all would show correlated decrements with hypoxia would have large implications for selection and/or training of hypoxia-tolerant personnel. If hypoxic decrements in these different visual performances were not found to be correlated, this result could provide keys to understanding basic differences among these visual performances.

The decrements in the CFF with hyperoxia for monkeys (Burns, 1971) may be an artifact associated with measurement of behavioral responses. On the other hand, measurement of the CFF in humans in conditions of hyperbaric oxygenation would appear to be a worthwhile effort. However, it would be best if subjects were used who were being exposed to the potentially toxic environment for other reasons that did not interfere with CFF data collection.

Although Kobrick (1968) apparently did not find any CFF differences with hypoxia for a group receiving the drug acetazolamide or any difference between the drug group and a placebo group, additional research with this drug might be informative. As will be noted throughout this review, acetazolamide has mimicked the effects of hypoxia on visual field size, intraocular pressure, etc. Acetazolamide also has operated synergistically with hypoxia to sharply decrease intraocular pressure (Mercier et al., 1964). No studies were found which looked at the effects of acetazolamide on the CFF. Given the above links between acetazolamide effects and hypoxia effects and given the benefits associated with the drug for reducing altitude sickness, research on its effects on the CFF might be of benefit.

This could be achieved easily by including the drug and a placebo as a between-groups factor or as a repeated-measures factor in research on the effects of stimulus size, hypocapnia, etc., on the CFF. However, the vasodilation caused by the drug (Lassen et al., 1987) would preclude its use in any hyperbaric oxygen environments since it probably would operate like CO₂ and increase the probability of convulsions.

The Jorgensen (1955) finding of bimodal image-size changes in the effects of hyperventilation on the CFF raised many more questions than it answered. A replication and extension of this hyperventilation-CFF study is needed where all retinal sizes are presented at the same distance, where several stimuli of constant retinal size are presented at several distances ranging from the near point to optical infinity, and where a number of subjects are tested.

Chapter 6

Color vision

A number of researchers have investigated whether or not color vision might be affected by changes in oxygen tension. If one receptor type or one or more visual pigments were more affected by changes in oxygen tension than others, a hue shift might occur. At least one study (Paulson and Ryan, 1981) was conducted in the hope that this was the case, since hypoxia-induced or hyperoxia-induced failures to see figures on Ishihara-type color plates would allow a person to identify when he was experiencing potentially dangerous oxygen-deficiencies or oxygen-toxicities.

Hypoxia and color vision

Wilmer and Berens (1918) included color vision in their extensive study of visual performance under hypoxia. They used "Stilling's plates" and found no change in color vision for 10 subjects who were tested at 20,000 feet. Wilmer and Berens also found hypoxia produced decrements in sensitivity for spectrally pure red and green lights, no decrements for white lights, and apparently improved sensitivity for a wide band blue light. However, these were rather crude experiments on visual sensitivity where adjustments were made of an optical wedge held between the subject's eye and a distant target and it is doubtful these effects would be reproduced with or without more refined testing procedures.

According to McFarland, Evans, and Halperin (1941), Wischnewsky and Zirlin¹ (1935) found low oxygen tensions led to a greater decrease of retinal sensitivity to red, green, and blue light compared to white light and found colors to lose saturation at threshold, particularly blue and green. However, McFarland, Evans, and Halperin (1941) indicated the apparatus of these Russian researchers was crude and so was their understanding of rod and cone function, since they did not seem to know that rods are insensitive to red and that, even when breathing air, colors lose their saturation when they are so dim that they are only seen by the rods.

¹ McFarland, Evans, and Halperin (1941) provided a different spelling of Wischnewsky and Zirlin, namely, Vishnevskiy and Tsyrlin.

Using the sensitive Hecht-Shlaer apparatus (Hecht and Shlaer, 1938), McDonald and Adler (1939) found oxygen deprivation had an equal effect on rod vision and cone vision. For cone vision they used a centrally fixated test flash subtending two degrees of visual angle. Unfortunately, they did not indicate size of the target used for rod vision testing or its location relative to the fixation point. They used only one healthy well-trained observer who breathed a mixture of air and nitrogen with approximately 10.4 percent oxygen for from 15 to 20 minutes before testing. A decrease in sensitivity of 0.4 log units as a result of hypoxia was found for both rods and cones.

According to Mercier and Duguet (1950), Malmejac et al. (1944) investigated intensity matches of two red or two green plates during a prolonged stay at 6,000 meters in a decompression chamber. No decrement in the ability to make these matches occurred during the stay at altitude.

Schmidt (1950) provided an extensive review of early German research on the effects of oxygen deficiency on color vision. Much of the research involved use of an anomaloscope where a yellow produced by an additive mixture of red and green is matched to a spectrally pure yellow by adjusting the relative brightness of the green and/or the red. Velhagen (1936) was reported by Schmidt to have published the first report on the effects of high altitudes on color vision. He found persons with normal color vision at sea level developed a pathologically increased color adaptation above 9,800 feet. He referred to this as color asthenopia. He also claimed persons with minor color vision anomalies at sea level may show an aggravation of this anomaly with oxygen deficiency or a change in the form of their deficiency.

According to Schmidt (1950), Schmidt (1937) did not find color asthenopia in persons with normal color vision, although he did find this in subjects with defects at sea level. Schmidt (1937) also differed from Velhagen in finding "the characteristic differences between the various forms of color deficiency also exist in the presence of oxygen deficiency." Schmidt (1950) presented a figure that indicated a decrease in color sensitivity (presumably for normals, but perhaps only for color defectives), since there was a larger scatter of anomaloscope settings at 13,000 feet than at lower elevations and in some cases increased scatter appeared at 9,800 feet. This increase in scatter with low oxygen particularly was marked when subjects fixated on the color target for 1.5 seconds during adjustments and less marked when subjects maintained adaptation to a neutral white area and only viewed the color "for an instant."

According to Schmidt (1950) both Velhagen and he found low oxygen changes in color vision were reversed by breathing pure oxygen, but he specifically noted this was not an abrupt reversal.

However, no actual time for recovery of normal color vision was provided in the Schmidt (1950) review.

Schmidt (1950) also discussed research by Fichter (1940) who also studied the problem of hypoxic "color asthenopia." Fichter tested 57 normal trichromats, 10 deuteranomalous subjects, and 3 protanomalous subjects. In most cases he found decreasing color sensitivity, i.e., increased scatter of anomaloscope settings with increasing altitude. When subjects did not fixate on the color stimulus, but only glanced at it briefly during adjustments, normal trichromats remained normally trichromatic at high altitudes.

According to Schmidt (1950), Velhagen used the anomaloscope and found a shifting of the Rayleigh equation in some normal trichromats under hypoxia and, according to Schmidt, this indicated a decrease of red sensitivity. Velhagen found a decrease in green sensitivity in other subjects. According to Schmidt (1950), Both Schmidt (1937) and Fichter (1941) reported that, on the average, anomaloscope measures indicated a slight decrease in green sensitivity at 19,700 feet. Schmidt (1939) followed up with another study of absolute thresholds for red and green targets under low oxygen tension. Normal trichromats showed an increase in the red threshold above 13,000 feet, but no change in the green threshold.

Schmidt and Bingel (1953) studied the effects of hypoxia on color saturation thresholds. They presented adjacent stimulus fields with one white and the other white with a small amount of red, green, or blue light added. The threshold amounts of color required to detect the presence of the color in the "colored" half field were determined in air and in reduced oxygen tensions. Sensitivity to green and blue showed a small but significant decrement at 13,000 and at 18,000 feet. There was some suggestion of an improvement of performance over baseline when testing occurred after 20 minutes of air breathing that followed the hypoxic testing at 18,000 feet. This occurred for the color green. Color-saturation thresholds for the color red did not change at either "altitude" and this differential effect of hypoxia for different wavelengths indicated more than a general loss of color sensitivity was involved.

Boles-Carenini and Cima (1952) studied color sensitivity with Nagel's anomaloscope under normal, hypoxic, and hyperoxic conditions in subjects who breathed normal air, breathed low-oxygen mixtures, underwent pressure ischemia, breathed pure oxygen, and breathed pure oxygen while undergoing pressure ischemia. The low-oxygen tension corresponded to the oxygen tension at 6,000 meters. According to the English-language summary, hypoxia created or worsened anomalies of the anomaloscopic quotient. Inhalation of oxygen reduced the variance of anomaloscope settings compared to settings while breathing air. Eyeball pressure leading to partial

ischemia always generated an anomaly in the red-green chromatic sensation. Combining pressure ischemia and oxygen breathing led to a neutralization of their opposite effects.

Frantzen and Yusfin (1958) assessed hypoxic shifts in color discrimination sensitivity at different "altitudes" and the effects of breathing 100 percent oxygen following hypoxia. There were 25 subjects whose characteristics were not described. A special anomaloscope was used where the right of two identical half circles was varied on either red, blue, or green wavelength until the difference was noted and the change recorded. Each subject was tested 30 times (30 ascents). The dependent variable was the amount of wavelength change. Color discrimination was reduced from normal atmospheric pressure baseline by a factor of 2.0 at 5,000 meters for blue. Color discrimination was reduced by a factor of 1.7 at 5,000 meters for red. Color discrimination was reduced by a factor of 1.3 at 5,000 meters for green. Large variability in color discrimination under hypoxia was reported between subjects and even for the same subject on different ascents. One highly-emphasized finding was that high baseline scores led to big drops in discrimination performance and low baseline scores led to small drops. However, this could be largely the result of random errors in baseline measurements and regression to the mean during later testing.

In one of the conditions of their extensive study of hypoxia and sensitivity, Ernest and Krill (1971) examined relative effects of hypoxia on rod and cone vision. Under hypoxia (10 percent oxygen), red targets five degrees in diameter presented at an eccentricity of five degrees required a significantly larger increase in luminance for detection (0.42 log units) than similar size/eccentricity blue targets (0.15 log units). This slowing of hypoxic performance occurred relative to performance in air. The authors viewed this as a greater effect of hypoxia on cones than rods in this area of the retina, but were unsure why this was the case. As will be discussed later, Koblrick et al. (1984) found no effect of hypoxia on peripheral (and central) red targets, but did find a decrease in sensitivity for green targets.

Wolbarsht, White, and Anderson (1973) studied "colors" generated by a revolving achromatic figure (Benham's Top) and looked at the effects of hypoxia on matching of actual chromatic colors to these entoptic colors. Any respiratory effects found for color matches could be the result of changes in the afterimages that generate the entoptic colors or changes in the chromatic colors that match them. It thus should be a highly sensitive indicator of changes in visual function, even though further research might be needed to pin down the source of the change. Wolbarsht, White, and Anderson (1973) found some systematic differences appeared, but the single hypoxic condition among the otherwise constant oxygen tension conditions (in all but the one

hypoxic condition, altitude and oxygen tension were covaried to maintain a normal sea level oxygen tension) did not stand out from the others.

Smith, Ernest, and Pokorny (1976) studied the effect of hypoxia on FM 100-hue test performance. In normal test illumination (1,670 lux), breathing 10 percent oxygen did not increase errors on the test and performance at both low and normal oxygen tensions was nearly error free. At 37 lux, hypoxia significantly increased errors in red and blue-green "quadrants" over errors in air at this illumination. At very low illuminations, normal observers also produce maximum errors in these quadrants. The effect of hypoxia thus appeared to be to reduce effective illumination and not to have any other specific effect on color vision.

Kobrick et al. (1984) found no decrement in sensitivity to a red stimulus as a function of prolonged stays at altitude, but did find decrements in sensitivity to green. As is discussed in the chapter on absolute sensitivity, this may have been related to an interaction of hypoxic changes in refraction with the chromatic aberration of the eye and not to any differential effect of hypoxia on receptors.

Hyperoxia and color vision

As discussed earlier, Boles-Carenini and Cima (1952) studied color sensitivity with Nagel's anomaloscope under normal, hypoxic, and hyperoxic conditions in subjects who breathed normal air, breathed low-oxygen mixtures, underwent pressure ischemia, breathed pure oxygen, and breathed pure oxygen while undergoing pressure ischemia. According to the English-language summary, inhalation of oxygen reduced the variance of anomaloscope settings compared to settings while breathing air.

According to Paulson and Ryan (1981), Gallagher et al. (1965) found no effects on color vision of breathing 100 percent oxygen at sea level for 24 hours. However, they used six photographic reproductions of the Ishihara plates which apparently quickly were memorized by subjects and there is some question whether the tests were suitably sensitive during the repeated testing that occurred.

Bogetti and Molfino (1965) indicated in the English abstract of their Italian-language report that hyperbaric oxygenation at 2.5 atmospheres actually reduced the number of errors on the Farnsworth-Munsell 100 Hue Test. The improved performance occurred after 45 minutes of exposure to the hyperbaric oxygen. However, it was not clear from the abstract whether the control performance occurred prior to hyperbaric oxygenation or during the first minutes of hyperbaric oxygenation. All 20 of the 20 subjects showed this improved performance following 45 minutes of hyperoxia.

Paulson and Ryan (1981) used the F-M 100-Hue Test for assessing the effect of air under high atmospheric pressure on color vision. Subjects were 12 Navy divers aged 26-36 with normal color vision plus three nondivers who were tested with a similar schedule, but without changes in pressure. Each diver was tested with the F-M 100-Hue test on seven occasions. These were twice pre-dive in the chamber, three times during the dive, and twice post-dive. One or more days separated administrations. Subjects breathed normoxic nitrogen mixtures at pressures of five atmospheres for 4.5 days. The oxygen tension thus was equivalent to 100 percent oxygen at one atmosphere. Five 1-hour excursions occurred three times with air being breathed at seven atmospheres. Decompression occurred over 3 days while breathing air. Although it was anticipated that there would be decrements in performance as a result of the long-term exposure to oxygen at above-normal tensions, the only changes in color vision were a few unexpected improvements in performance after long exposure in one of the dives.

Conclusions and research needs

Hypoxia appeared to have few effects on color vision other than at low illuminations where it exaggerated the normal effect of low illumination on color-sorting tasks. Hyperoxia, on the other hand, seemed to have a beneficial effect and color vision may be the area of visual performance which most benefits from higher-than-normal oxygen tensions. Research is needed to confirm and elucidate this possible improvement in color vision during hyperbaric oxygenation, although it would be advisable to limit testing to patients undergoing hyperbaric oxygenation treatments, due to the potential toxic effects of this environment.

Striking color shifts in the retina occur with hypoxia and hyperoxia (see Chapter 12: "Ocular vessels and blood flow"). These differently colored vascular networks might act somewhat like color filters and differentially influence the photoreceptor response to colors during hypoxia, normoxia, and hyperoxia. If hyperoxic effects on color vision were matched by the effects of wearing rose-colored glasses during normoxia, the fundus color change during hyperoxia might be the explanation.

Surprisingly, no studies were found which looked at the effects of hypocapnia or hypercapnia effects on color vision. The same was true for carbon monoxide. One suspects that such research has been carried out, but negative results were found which were either not published or were not even submitted for publication. Research on carbon monoxide effects would appear to be particularly important. If a pronounced defect were found to be associated with carbon monoxide poisoning, an "Ishihara" plate could be developed that was

readable only when carbon monoxide was being breathed.² This could be posted at conspicuous locations to warn persons in environments where CO poisoning is possible.

² Such a plate might read DANGER! HIGH LEVEL OF CARBON MONOXIDE.

Chapter 7

Afterimages and other entoptic phenomena

Early aviators described persisting afterimages at high altitudes without oxygen which caused problems for viewing of real images. Other entoptic phenomena (e.g., "red veils") were associated with use of oxygen in aircraft. A number of early investigations were made of the effects of hypoxia on these entoptic phenomena.

Hypoxia and afterimages

In a classic piece of vision research, Craik (1940) demonstrated visual afterimages originated from the primary visual image on the retina without any major contribution from "lower and higher visual centers." One eye was rendered temporarily blind by pressure on the eyeball at a level which totally cut off blood flow to the retina.¹ The functioning eye fixated a light source and the image fell on the nonfunctioning eye as well. After 2 minutes, the subject looked away from the light source and a distinct afterimage was visible in the functioning eye. Pressure then was removed from the other eyeball and when vision returned in a few seconds, an afterimage also was seen with this eye. This afterimage typically was not exactly coincident with the afterimage of the other eye due to a slight misdirection of the ischemic eye as a result of the application of pressure. However, this was a benefit for this demonstration, since it confirmed the fact that both eyes had afterimages. The pressure-induced anoxia did not prevent the afterimage and this not only showed the afterimage was not produced in the brain it also showed that photochemical processes involved in generation of the afterimage were not substantially changed by this temporary lack of oxygen.

Although Craik showed temporary ischemia did not prevent afterimage formation, there is evidence that afterimage processes may be influenced by hypoxia. Gellhorn and Spiesman (1935) studied the influence of hypoxia, elevated CO₂, and hyperventilation on latency of negative afterimages. Eight people were used as subjects. They had undergone several weeks of training in observation of afterimages and reporting of afterimage latencies. Afterimages were formed by fixating a bright stimulus against a

¹ This temporary ischemia is still frequently referred to as "Craik Blindness."

darker background. Ten-minute intervals separated the formation and viewing of these afterimages. Afterimages were viewed with closed eyes and a positive afterimage preceded the appearance of the negative afterimage. Only the time from stimulus offset to the appearance of the negative afterimage was measured. The low oxygen condition was typically 9.2- to 11-percent oxygen with the oxygen mixed with nitrogen. CO₂ concentrations were from 4.8 to 6.4 percent for different subjects. Hyperventilation occurred at rates of 66 to 88 inhalations per minute for from 3 to 6 minutes with shorter periods associated with higher inhalation rates.

Oxygen concentrations of 13 to 16 percent did not influence the latency of negative afterimages. However, oxygen tensions of 9.2 and 11 percent greatly delayed the negative afterimage and in several instances prevented its appearance altogether. CO₂ had a similar effect although the latency increase typically was less than during hypoxia and nonappearance of the afterimage was less likely. Hyperventilation also increased latencies and in some instances prevented appearance of the afterimage, although short periods of hyperventilation had no effect on afterimage latency. Recovery from all three latency-extending treatments was typically slow, requiring 20 minutes or more.

If fixation were impaired by these treatments, this could account for increased latencies and hypoxia has been shown to influence eye movements (McFarland, Knehr, and Berens, 1937a) and so has hyperventilation (Fenn, et al., 1949). On the other hand, Gellhorn and Spiesman (1935) mentioned this possibility and noted that although a shortened fixation time during air breathing did increase latency of the negative afterimage, this never led to the afterimage not appearing at all, as occurred in some of their experiments on low oxygen, high CO₂, and hyperventilation

According to McFarland, Evans, and Halperin (1941), Wischnewsky and Zirilin² (1935) found a lowered atmospheric pressure produced a decrease in both the light sensitivity and the electrical excitability of the eye, although no details of oxygen tensions or testing procedures were provided. Wischnewsky and Zirilin concluded since entoptic visual phenomena produced by electrical stimulation do not involve the photochemical system, hypoxia had its primary effect on the neural tissue of the visual mechanism.

McFarland (1937b) noted that "aviators and mountaineers at high altitudes have frequently mentioned the increased latency and unusual quality and intensity of after-images." McFarland (1937a) included measures of both "time to appearance" and "time to

² McFarland, Evans, and Halperin (1941) provided a different spelling of Wischnewsky and Zirilin, namely, Vishnevskiy and Tsyrlin.

disappearance" of negative afterimages at sea level and at a height of 14,890 feet in the Andes mountains. Subjects closed their eyes for 3 minutes then opened them and fixated a 2-inch yellow square on a blue background at a distance of 18 inches for 15 seconds. The subject then closed his eyes again and indicated when the negative afterimage first appeared, first disappeared, reappeared, and again disappeared. These intervals were recorded on a stopwatch.

At sea level, the afterimage appeared at 3.3 seconds, disappeared at 10.6 seconds, reappeared at 13.1 seconds, and disappeared at 18.7 seconds. At altitude, the corresponding average times were 3.6, 13.1, 18.1, and 24.9 seconds. Although times were longer at altitude, the differences were not quite significant and McFarland did not claim any altitude effects were found on these afterimage parameters.

In another study, McFarland (1937b) used the same procedure at sea level and several different altitudes in the Andes of 9,200, 15,400, 17,500, and 20,140 feet. Although there was a direct association with altitude for the various afterimage parameters, only at 20,140 feet were the increases in times for appearance, disappearance, reappearance, and second disappearance of the negative afterimage significantly lengthened in comparison to sea level. No reports of an absence of afterimage ever occurred as was reported by Gellhorn and Spiesman (1935). Several subjects reported qualitative changes in brightness and hue of the afterimages at the two highest elevations compared to sea level and the lower elevations.

The most extensive study of the effects of hypoxia on afterimages was carried out by McFarland, Hurvich, and Halperin (1943). They also varied the stimulus intensity of the forming stimulus and studied the effect on recovery of breathing pure oxygen after hypoxia. In all cases, the time following stimulation before the negative afterimage appeared was the dependent variable. Three highly-trained subjects (including Hurvich and Halperin) were used. A two-degree diameter stimulus was exposed for 0.2 seconds while fixation was maintained on a small red fixation dot at the center of this "forming" stimulus. Viewing was monocular through a 1-mm pupil at a distance of 35 cm. Prior to viewing the series of afterimages, subjects viewed a 50-degree by 65-degree white matte adapting field which was approximately 10 footcandles in brightness. Subjects viewed this adapting field for 3 minutes and this was followed by 5 minutes of dark adaptation. Afterimages were then formed of the test stimulus and the latency of appearance of the afterimage was determined while the afterimage was viewed in complete darkness. Test stimuli were presented at different intensities of 1.16, 1.48, 2.13, and 2.79 log photons although there was some variation in these levels and for one subject dimmer stimuli of 0.6 and 0.93 log photons were used. Trials were

separated by at least 30 seconds. Trials in air preceded trials at low oxygen. Finally, "recovery" measures were made with pure oxygen.

The latency of afterimage appearance was related inversely to the intensity of the forming stimulus. These latencies typically ranged from 0.7 to about 1.7 seconds while breathing air. Low oxygen levels produced a small additional delay in their appearance, but even at lower stimulus intensities, the increase in time was typically only 0.25 second or less. For the single subject who was tested with a range of oxygen levels (10.8, 12.1, and 13.7 percent), there was an inverse relationship between oxygen tension and latency. Breathing pure oxygen produced a return to latencies obtained with air. However, the recovery was not rapid as is the case for recovery of visual sensitivity when pure oxygen is breathed following hypoxia (e.g., McFarland and Evans, 1939), and required as much as 50 minutes of exposure to pure oxygen for complete recovery.

Given these very small increments in afterimage latency with hypoxia, there is a possibility that these were not perceptual changes with hypoxia, but response time changes with hypoxia. There are well documented effects of hypoxia on simple reaction time and choice reaction time (e.g., McFarland, 1937b) and the reaction time for reporting the appearance of the afterimages would probably have been slowed by nearly the fraction of a second increase McFarland, Hurvich, and Halperin (1943) found as the effect of hypoxia on "afterimage appearance."

Whiteside (1957) was aware of the McFarland, Hurvich, and Halperin (1943) study of afterimage latency, but apparently was not aware that McFarland (1937a; 1937b) already had looked at afterimage duration. Whiteside felt the important aspect of hypoxia effects on afterimages was that it caused them to persist longer than normal and, as a result, to interfere with viewing of actual visual stimuli. Whiteside studied afterimage durations by presenting a 0.2 second flash of a white disk that subtended a visual angle of two degrees. The viewing distance was unspecified. The subject then viewed the positive afterimage in complete darkness and reported to the experimenter when it disappeared. Measures were made in a decompression chamber at sea level, 5,000, 10,000, 15,000, and 20,000 feet.

Whiteside found afterimage durations for the five altitudes were 17.3, 18.1, 19.5, 20.4, and 22.7 seconds. Despite the longer afterimage duration with hypoxia, hypoxia also led to problems of seeing the afterimage and this was true even during exposure to the lowest 5,000 feet altitude. There was "intrinsic light" in nonstimulated areas of the retina which interfered with seeing of afterimages. The afterimage also was less bright and its edges were not so sharply defined. It is possible refractive changes

produced by hypoxia (e.g., Ohlbaum, 1969) may have blurred the retinal image of the forming stimulus and caused less bright and less sharp images.

Dyer and Allen (1968) studied the size of afterimages at different projection distances. Between measurements, subjects frequently reported the negative afterimage of a bright white figure took on a regular sequence of distinct colors over time. The influence of hypoxia on latency of the appearance or disappearance of afterimages, augurs for an influence of hypoxia on the latency of appearance of different colors.³ What is more, the qualitative nature of a color shift might make for easier identification of afterimage changes than the criterion of afterimage sharpness which was used by Gellhorn and Spiesman (1935) or the criteria of afterimage appearance and afterimage disappearance that were used by McFarland (1937a; 1937b) and Whiteside (1957).

Wolbarsht, White, and Anderson (1973) studied "colors" generated by a revolving achromatic figure (Benham's Top) and looked at the effects of hypoxia on matching of actual chromatic colors to these entoptic colors. Some systematic differences appeared, but the single hypoxic condition among the otherwise constant oxygen tension conditions (in all but one hypoxic condition, altitude and oxygen tension were covaried to maintain a normal sea level oxygen tension) did not stand out from the others.

Hyperoxia and afterimages

McFarland, Hurvich, and Halperin (1943) studied the effect of breathing pure oxygen after hypoxia and found afterimage latencies returned to normal, although the return was slow. Apparently, they did not look at the effects of breathing pure oxygen on afterimage latency without prior hypoxia.

Only a single study was found which described effects of hyperbaric oxygen on entoptic phenomena. Behnke, Forbes, and Motley (1935) measured visual fields and other visual performances before and after breathing oxygen under pressure in four "healthy young men." The subjects breathed pure oxygen via a mask or helmet in a large pressure chamber at a pressure of three atmospheres for a period of at least 3.5 hours and up to 4 hours. Measurements

³ McFarland (1937b) found subjects reported qualitative changes in brightness and hue of the afterimages at the two highest elevations compared to sea level and the lower elevations.

were made at intervals of leucocyte count, blood pressure, heart rate, respiratory rate and minute volume, visual acuity, area of the visual field, and the "appearance time" of a negative afterimage formed by viewing a red and green cross at a distance of one meter for 20 seconds. No change in afterimage onset times was reported for the first 3 hours of exposure. In the fourth hour of oxygen breathing at three atmospheres, visual acuity decreased by as much as 60 percent. The onset of the afterimage was delayed during the same period as this large reduction of visual acuity with this delay being 50 to 100 percent. Other results of this important early study of hyperbaric oxygen effects on vision are described elsewhere in this report.

Other entoptic phenomena

Wald et al. (1942) in their study of low oxygen effects upon the visual threshold discussed "subjective light" which appeared when air was breathed following a period of hypoxia. Every subject reported red subjective light starting about 15 to 30 seconds after the return to room air. This lasted for 2 to 3 minutes. A less reliable phenomenon, but one frequently observed was "flickering subjective light and color sensations" during periods of hypoxia. It was reported these entoptic phenomena did not interfere with visual thresholds.

Livingston (1944b) described visual sensations associated with an ascent to 17,000 feet in complete darkness and the effects of oxygen breathing following this hypoxia.

"The first visual sensation is one in which a series of light flocculent grey-red clouds pass in waves from near the centre of vision to the periphery. They are not at first dense enough to shut out the stimulus provided by a self-luminous test object of low brightness, but they cause it to lose some of its sharpness. These clouds become more pronounced and faster in movement as anoxaemia proceeds, being denser towards the periphery, until perception is adversely affected. If oxygen is administered during such a test the first visual sensation is the appearance of an intensely blue truncated cone situated at and around the fixation point. Outside this cone, wave after wave of grey-red clouds move with increasing rapidity. These are last observed near the periphery, eventually dispersing and leaving in their place a deep blue field. Five full breaths of oxygen, within 45 sec, delivered at the correct rate for the altitude of the experiment, have restored function, as judged by the complete elimination of areas of defect. The targets previously dull or below perception

become intensely bright and easy to follow. Plotting of the field can be undertaken with speed and accuracy. These phenomena add weight to the contention that cone vision resists oxygen-want better than rod vision."

Rose (1950b) noted that red "veils" appeared before the eyes when oxygen breathing was started following mild hypoxia. The strong possibility this entoptic phenomenon could interfere with vision caused Rose to recommend that aviators not breathe oxygen intermittently nor to wait until high altitudes have been reached before breathing oxygen.

Whiteside (1957), like Livingston (1944a), provided an extensive description of visual field changes during complete darkness that were associated with hypoxia and with hypoxia followed by breathing of oxygen. Not only did increases and decreases of oxygen produce entoptic phenomena, these varied in fairly striking ways in the periphery and in the center of vision. Subjects were seated in a completely dark decompression chamber and dark adapted at ground level for 15 minutes to eliminate all afterimages. Prior to decompression, the visual field was reported to be uniformly dark with a "normal amount of entoptic light." There was more such light in the periphery than in the center of the visual field. Subjects were decompressed to 10,000 feet and during the ascent there was an increase of entoptic light with took on the appearance of a flickering pattern. At 10,000 feet, the light increased but lost its flickering pattern appearance and appeared steady and uniform. At 15,000 feet, the field was uniformly bright and remained that way for the 4.5 minutes the subject remained at that altitude. After 3 minutes at 20,000 feet, there was a barely detectable difference with the central field somewhat darker than the periphery.

Oxygen then was switched on at 20,000 feet and the subject reported a large increase in brightness of the field with the central field darker "like a five-degree afterimage." The brightness of the peripheral field then quickly decreased until the whole field was much darker and uniform. After only 40 seconds of oxygen the periphery became nearly black but a five-degree area in the central field was a bright spot which became quite marked. This then declined in brightness until it was difficult to discriminate the central spot from the periphery. This oxygen scenario lasted only 1 minute and then oxygen was turned off. The whole field was uniformly dark and then splashes of light appeared uniformly across the visual field. After a minute of this increasing light, the lower half of the field appeared darker than the upper. Another minute at 20,000 feet without oxygen led to brighter flickering light "like an aurora borealis." After another minute, the central field of five degrees seemed a little darker than the periphery and the flickering had disappeared. Another minute led to equal brightness of the upper and lower field and a

darker central field than the periphery. At this point, the subject was feeling light-headed from hypoxia and had some problems turning the oxygen back on. Switching on oxygen produced a transient increase in luminosity accompanied by great flickering splashes of light with the entire effect over in 30 seconds. The increase appeared first in the central field followed by a decrease in that area and an increase in luminance of the periphery. The periphery then faded and merged into the central field and the entire field became quite black. Continued breathing of oxygen only led to a slight brightening of the entire field.

Whiteside also looked at the effects of Craik blindness on entoptic phenomena while the subject was in complete darkness. The palms of the hands were pressed over the eyes for 50 seconds with enough pressure to cause temporary blindness. After the onset of pressure, the normal amount of entoptic light over the field increased. After 20 seconds, the uniform field appearance changed to a slightly darker central field. A momentarily darker central field was seen at 50 seconds, then it merged into the periphery to give a uniformly bright field. Pressure was then released and the subject reported:

"Whole field clears from centre outwards--central bright, peripheral bright--central bright, peripheral dark--central vanishes merging into the blackness of the periphery. The entire field is very black and seems to be getting still blacker. The central area is now becoming a little brighter than the periphery--the periphery is still black, but the central area is now distinctly brighter. The difference between central and peripheral field luminosity is increasing. The central field is still bright, but seems to be spreading out towards the periphery. At first the apparent 'texture' of the central bright area was speckled, but now it is a smooth 'texture.'"

The central bright area then spread to the periphery and the intensity simultaneously diminished until the entire field became "uniformly grey as with normal entoptic light."

There are obvious similarities in these discussions by Whiteside of entoptic effects with hypoxia followed by oxygen and entoptic effects of Craik blindness followed by a return to visual function. Differences might reflect pressure phosphenes produced by pressure against the eyeball. Unfortunately, the reports appear to be only those of a single subject. Color predominated in subjective light descriptions reported by Wald et al. (1942), Livingston (1944a), and Rose (1950b) and the absence of any red veils or other reports of color (with the possible exception of the aurora borealis) makes one wonder whether this Whiteside subject perhaps was color blind.

After presenting the afterimage duration results and the subjective light results, Whiteside (1957) went somewhat beyond these data to make the case that hypoxia-prolonged positive afterimages of bright sky were the culprit in the "subjective haze" that is present in high altitude flight with low degrees of hypoxia resulting either from breathing air at lower altitudes or while breathing oxygen at altitudes up to 40,000 feet in the absence of pressurization.

Conclusions and research needs

Given that hypoxia sometimes influences refraction of the eye and the size of the pupil, the changes in duration, intensity, and sharpness of afterimages as a result of hypoxia could have reflected hypoxic deterioration of the images that formed the afterimages and not any change in the afterimage process. There is an even simpler explanation of the tiny hypoxic effects on afterimage latency reported by McFarland, Hurvich, and Halperin (1943). These fraction of a second latency increases easily could have been the result of a hypoxic slowing of the verbal response that indicated the appearance of the afterimage and not changes in the appearance time.

For most subjects, the color of negative afterimages is highly salient. The latency and duration of the successive color phases that afterimages typically exhibit might be easier to report than sharpness or presence or absence of afterimages. If these phases were to be lengthened or shortened with hypoxia or if hypoxia produced qualitative changes in hue or saturation of these afterimage colors, this might be worth learning. The improvements in color vision with hyperoxia might augur for even larger changes in the afterimage color sequence with oxygen at greater-than-normal tensions.

Extensive discussion of the "red-veils" and related entoptic phenomena occurred in this review, since these apparently are striking low-oxygen visual effects that can interfere with processing of real images. These pronounced visual phenomena occur in the total absence of any visual stimulation, yet they exhibit form and movement. The red veils and other spontaneous entoptic phenomena would appear to have much relevance to research on neural processes of the eye.

It is possible these red veils are pressure phosphenes associated with mechanical changes in the eye, such as those noted by Alder and Cringel (1985) in cats when respiratory gases were changed. These eye changes caused large movements of electrodes inserted into the eyes and were believed by Alder and Cringel to be related to retinal circulation changes and changes in blood volume. If the red veils are a form of pressure phosphene, they also may

provide a subjective indicator of ocular pressure changes that could be used during research on respiratory factors and other factors that cause changes in intraocular pressure.

It appears that research on the hypoxic thresholds for these entoptic phenomena could provide particularly important data on the effects of hypoxia. For example, it would be important to identify the degree of hypoxia, the duration of hypoxia, and various combinations of degree and duration of hypoxia that must exist before resumption of air breathing produces the "red veils." It also would be of interest to know whether pure oxygen at normal or increased atmospheric pressure produces the red veils without any previous hypoxia.

Chapter 8

Persistence of vision following ischemia

Applying pressure to the eyeball cuts off the flow of blood to the retina and, within a few seconds, this leads to a state of blindness that is quickly reversible when the pressure is released (Craik, 1940). As discussed below, respiratory conditions which increase and decrease the amount of oxygen available within the eye, reliably increase and decrease the latency of this "Craik blindness." This variable of persistence of vision following ischemia is an important index of ocular oxygenation, particularly for "hyperoxic" conditions that increase persistence well above the normal brief time to blackout.¹

Lambert and Bjurstedt (1952) probably were the first to measure the effect of variation of respiratory gases on the latency of blackout produced by pressure on the eyeball. To increase pressure, a Bailliart tonometer was applied to the eyeball through the lower lid. They noted in their brief report increasing the oxygen tension in inspired air prolonged the latency of blackout associated with retinal ischemia and CO₂ mixtures also prolonged this latency. The "onset of dimming of vision" averaged 4.7 seconds when the 10 subjects breathed air, 5.4 seconds when they breathed 60 percent oxygen, and 6.4 seconds when they breathed 100 percent oxygen. Another experiment involved breathing of pure oxygen at two atmospheres pressure and a further prolongation of the time to "dimming" occurred, although no time was reported. A hypoxic mixture of 10 percent oxygen temporarily reduced the period to 4.3 seconds, but 3 minutes of breathing the low-oxygen mixture increased the latent period to 4.7 seconds, indicating probable adaptation to the hypoxic stimulus. Five percent CO₂ in air increased the latency to 5.2 seconds. Five-percent CO₂ and 95 percent oxygen increased it to 7.8 seconds.

Carlisle, Lanphier, and Rahn (1964) determined the duration of vision after the blood supply to the retina was cut off while subjects breathed oxygen at a range of elevated pressures. The subjects were three normal adults who breathed oxygen from a mouthpiece in a compression chamber in which atmospheric pressure was increased up to as much as four atmospheres. The subject

¹ The short latencies of vision following pressure ischemia at normal oxygen tensions and lower make this technique less useful for studying effects of hypoxia on vision than it is for studying hyperoxia effects.

started a stopwatch then applied digital pressure to his eyeball. As soon as a scotoma in any part of the paracentral field of vision appeared, he stopped the watch. Four or five determinations of scotomata latency were made while breathing oxygen at each of seven atmospheric pressures. The series was repeated for each subject at a second session.

Carlisle, Lanphier, and Rahn found persistence of vision was related linearly to alveolar oxygen pressure for each subject. Average persistence was 4.3 seconds in air and ranged from 5.8 seconds for oxygen at one atmosphere to 49.3 seconds for oxygen at four atmospheres of pressure which was the maximum hyperbaric pressure used.

Saltzman et al. (1965a) measured the time that vision was retained during retinal ischaemia induced by a plunger-type ophthalmodynamometer that interrupted retinal blood flow until all vision was lost. Hyperbaric oxygenation strikingly prolonged the time to blackout. Delay of blackout was related linearly to gauge pressure for 0 (sea level), 3, 12, 20, and 30 PSIG with visual persistence times of about 12, 14, 19, 28, and 40 seconds. At 40 PSIG, vision persisted for 58 seconds and this represented about a 10-second additional increment in visual persistence beyond the linear increase from 30 PSIG that would be predicted from the nearly straight line fitting persistence times for 0 through 30 PSIG. Saltzman et al. (1965a) also found that additional persistence of vision occurred when a low concentration of CO₂ was included in the inspired mixture.

Anderson (1968) studied a number of ocular effects of changes in oxygen and carbon dioxide tension, including visual persistence following eyeball pressure that interrupted the retinal blood supply. The relationship of "time to blackout" to the atmospheric pressure of pure oxygen was linear from 760 to 2311 mm Hg and then there was a somewhat longer latency associated with an increase from 2311 to 2828 mm Hg similar to that reported by Saltzman et al. (1965a).

Anderson (1968) used these times to blackout for different eyeball quantities of oxygen prior to ischemia to calculate retinal oxygen uptakes. Average values for three groups of subjects were 7.0, 8.7, and 9.7 ml O₂/100 ml wet retina/minute. Anderson pointed out these were extremely high oxygen uptakes and "reflect the prodigious retinal capacity for energy production."

Anderson (1968) also reported the time it took for the retina to recover from pressure-induced ischemia. Vision always returned almost instantaneously upon pressure release, but if pressure were reintroduced within a few seconds, blackout returned quickly. Complete recovery was defined as the minimum interval required that would cause times to blackout following a second pressure-induced

ischemia to be as long as times to blackout for the initial ischemia. It typically required about the same length of time for complete recovery as the original length of time to blackout. Since for high pressures this sometimes involved times of nearly 1 minute, it suggests hyperbaric oxygen travels a long distance into the structures and humors of the eye and takes some time to get there. The large gradients of oxygen tension in the vitreous at normal oxygen tensions (e.g., Jacobi and Driest, 1966) would probably be much shallower under hyperbaric oxygenation.

Anderson (1968) noted the accumulation of CO₂ could be a factor in production of ischemic blackout. However, when CO₂ was added to the oxygen under pressure, Anderson found a significant lengthening of the time to blackout, not the shortening that would be predicted if CO₂ accumulation were a factor in production of the blackout. The probable explanation was the CO₂ prevented some of the vasoconstriction associated with hyperoxia and allowed greater perfusion of retinal tissues with oxygen during the "preoxygenation" period. Acetazolamide increases CO₂ concentrations in retinal tissue and this drug was found by Anderson to prolong the time to blackout in the same way that adding CO₂ to inspired gases prolonged time to blackout. This similar effect of inspired CO₂ and acetazolamide strongly supports the explanation that increased CO₂ concentrations in the retina improve perfusion of ocular tissues with hyperbaric oxygen.

As discussed earlier, this positive effect of inspired CO₂ on visual persistence was shown by Lambert and Bjurstedt (1952) to occur even with air-CO₂ mixtures at a pressure of one atmosphere. It is puzzling that CFF and visual sensitivity are reduced by breathing CO₂ mixtures (e.g., Alpern and Hendley, 1952). However, the key to the difference in results for this persistence measure and the more traditional sensitivity measures may be the quantity of CO₂ in the mixture. Lambert and Bjurstedt used a 5 percent mixture and Anderson maintained CO₂ partial pressures at about 30 mm Hg., despite a wide variation in the total atmospheric pressure of the inspired mixtures. At sea level, a CO₂ partial pressure of 30 mm Hg. corresponds to about 4 percent CO₂. Alpern and Hendley administered a 7 percent CO₂ mixture. It is possible increasing CO₂ mixtures above five percent would reduce visual persistence following pressure ischemia. If so, it would show the common link of the visual persistence variable to other measures of visual performance.

Flower and Patz (1971) used the ERG response (b-wave) to assess effects of hyperbaric oxygenation when retinal blood supply was cut off and also when both retinal and choroidal blood supply were cut off. The subjects were nine cats and one rhesus monkey. ERG recordings to a 0.02-second white light flash (that produced a midrange b-wave response) were recorded with flashes every 20 seconds. Retinal and choroidal blood supply were cut off in seven

cats by increasing intraocular pressure via a tube within the anterior chamber of the eye connected to saline under pressure. For two of the cats and the monkey, only the retinal blood supply was cut off by laser coagulation of retinal arteries as they emerged from the edge of the disk.

Breathing 100 percent oxygen at 50 PSIG prolonged the ERG b-wave following pressure ischemia compared to the b-wave duration following pressure ischemia during air breathing. Switching from air to 100 percent oxygen at 50 PSIG reinstated the ERG b-wave when pressure ischemia already had eliminated the ERG b-wave during air breathing. Breathing air at 50 PSIG prolonged the ERG b-wave following pressure ischemia compared to its survival time following pressure ischemia when the animal breathed air at sea level pressure.

For animals where the retinal blood supply was occluded by photocoagulation, the ERG b-wave was nonexistent during air breathing. Breathing 100 percent oxygen at sea level pressure restored the ERG b-wave to about 45 percent of the level recorded 24 hours earlier before coagulation. Breathing of 100 percent oxygen at 20 PSIG restored the ERG b-wave to 70 percent of the earlier level. However, oxygen breathing with further pressure increases to 50 PSIG did not further increase ERG b-wave levels. These latter results showed how hyperbaric oxygenation can allow the choroidal circulation to supply oxygen to inner retinal layers normally only oxygenated by the retinal circulation.

Conclusions and research needs

Although it has been claimed that pressure ischemia is harmless, even when applied for several minutes, this 50-year-old literature reviewer is much less willing to give his eye the finger than he was at 32 when he unsuccessfully sought a Pulfrich stereo effect by producing moderate ischemia in one eye during binocular viewing. It is somewhat of a relief that no important extensions of these persistence-of-vision experiments following Craik blindness come to mind. Even one detached retina or other serious visual problem that conceivably might result from producing pressure ischemia would be too many.

Chapter 9

Oxygen and eye potentials

The standing potential (SP) of the eye, also known as the corneoretinal potential, is measured from the front to the back of the human eyeball and is approximately six millivolts (Drummond and Rebusck, 1981). If that sounds small, consider that the potentials measured at the scalp in electroencephalography (EEG) are on the order of a few microvolts. In fact, there is often a problem of inadvertently picking up the large potential changes associated with eyeball movement during recording of the EEG at scalp locations far from the eyes. The SP is influenced by visual stimulation, but changes are slow and typically occur over several minutes. The SP also is affected by respiratory conditions, including hypoxia, and much of this chapter deals with research on these changes.

Much more rapid changes in voltage across the eye also occur as a result of visual stimulation. For example, exposing the eye to a flash of light produces rapid distinct voltage patterns which make up the electroretinogram (ERG). This electrical activity is linked to the activity of photoreceptors, the pigment epithelium, and other retinal structures. Some of the activity is correlated with optic nerve signals going to the brain and this makes the ERG a useful and convenient tool for studying vision in animals and in man. Given that hypoxia influences visual phenomena, it is not surprising numerous studies have shown the rapid potential changes recorded in the ERG also are influenced by hypoxia.

This chapter is divided into three sections. The first section deals with the effects of hypoxia, hypocapnia, and moderate hyperoxia on the SP. The second deals primarily with influences of hypoxia and hypocapnia on the ERG. The third section deals with the effects on the ERG of higher-than-normal oxygen tensions including oxygen tensions produced by breathing pure oxygen at pressures of more than one atmosphere. The effects of hypocapnia are discussed because hyperventilation-produced hypocapnia reliably accompanies hypoxia for most subjects, as has been pointed out by numerous investigators (e.g., Ernest and Krill, 1971; Fenn et al., 1949). The section on the ERG also includes several studies on animals that looked at visual signals or potentials at various points in the visual pathway from the eye to the brain. Typically, the ERG was a key response measure in these studies of the effects of hypoxia on different stages of processing of visual inputs.

The standing potential

Fenn et al. (1949) probably were the first researchers to assess the effects of hypoxia on the SP. They assessed this voltage through measurement of the horizontal electrocuculogram (EOG).¹ Fixation points for alternate eye movements were located about 45 degrees on each side of the center of view. Several different subjects were used, including most of the investigators. The EOG was recorded at ground level and during decompression to 18,000, 20,000, or 23,000 feet. Decompression was replaced by inhalation of nine percent oxygen at ground level for some experiments. In later experiments, hyperventilation occurred for 20 to 30 minutes with recording of the EOG at intervals during this period. Alveolar samples also were taken during these intervals to monitor PCO_2 . Hyperventilation was facilitated with a "pneumolator" that provided positive pressure during inspiration and ambient pressure during expiration.

Most subjects showed increases in the SP during hypoxia in the initial experiments where hyperventilation was not controlled, although there were large individual differences. One subject showed increases in the SP of about 70 percent on five of seven experiments, but the increase was typically much less for other subjects. When large increases occurred they appeared to be largely because of the strong hyperventilation and substantial hypocapnia (low arterial CO_2) that accompanied hypoxia for these subjects with increased SPs. As the authors noted, the observed effects "might be due to the acapnia which inevitably accompanies anoxia in varying degrees."

Hypocapnia was controlled and measured in later experiments on hypoxia of Fenn et al. (1949). They found a sharp reduction of alveolar CO_2 to 18 mm Hg increased the SP by about 20 percent. They also looked at hypocapnia without hypoxia and found this showed little difference in effect on the SP from hypocapnia with hypoxia, although there were a few individuals for whom hypoxia and hypocapnia led to higher SPs than hypocapnia alone. The SP typically was somewhat slow to recover to levels that existed prior to hyperventilation. An incidental finding was hypocapnia caused a slowing of the lateral eye movements which generated the EOG and also caused them to become "erratic." This made EOG measurements difficult.

¹ Electrooculography involves measurement of voltage changes associated with horizontal eye movements with electrodes located on the skin at the sides of the eye. When eye movements are constant, any change in the EOG probably reflects a change in the potential across the eye.

Noell (1952) studied the large rapid increase in the SP of the rabbit when sodium azide (NaN_3) was administered intravenously. Hypoxia induced by breathing pure nitrogen abolished this heightened SP within 7 minutes. Switching from nitrogen to oxygen during this abolishment of the SP rise, produced sharp increases in the SP, much like the initial rise following azide infusion. Removal of the cornea, lens, iris, corpus ciliare, and the anterior rim of the retina only reduced the azide response by 30 percent. On the other hand, detachment of the retina abolished the response. The pigment epithelium was found to be critical for the azide response, but the optic nerve, ganglion cells, or a retina sensitive to illumination were not. According to Gouras and Carr (1965), Noell (1953) later showed azide not only increased the SP, but also the a-, b-, and c-waves of the ERG.

Kolder (1959) investigated the effects on the SP of breathing oxygen at low concentrations (7, 9, and 12 percent) for brief periods (3 to 15 minutes). Measurement of hypoxia effects were made after the SP had become relatively stable following 30 minutes of dark adaptation. Although the article was not fully translated, it appeared hypoxia caused a rise in the SP beginning at the onset of hypoxia which lasted for several minutes and reached approximately 125 percent of original SP levels. This rise was followed by a sinusoidal variation that included a drop after about a dozen more minutes to a substantially lower level than when hypoxia began (approximately 70 percent of the original SP). Blood-oxygen saturations were measured and drops of 20 to 30 percent occurred during these severe hypoxic conditions. Kolder apparently did not observe hyperventilation during hypoxia or measure any resultant drops in alveolar or arterial CO_2 , which Fenn et al. (1949) indicated were the basis for most of the SP increases during hypoxia in their research.

Arden and Kelsey (1962) observed the effects of pressure ischemia on the SP. In one experiment, they found that Craik blindness led to a drop in the SP to dark-trough levels, regardless of the point during the slow SP oscillation when pressure was applied. Eye movements used to generate the SP apparently were not impeded seriously by the pressure on one eye. They produced an ischemia of several minutes in another experiment and found this delayed the light rise associated with an increase in illumination. Intermittent ischemia following this light rise produced a sharp drop in the SP, but in this experiment the SP typically did not drop to dark-trough levels. A patient with partial occlusion of the central vein in one eye showed a near absence of light rise in that eye and this supported the pressure ischemia findings. The rapid drop in the SP with pressure ischemia and its rapid recovery when eyeball pressure was removed both indicated the eye is not carrying a long-lasting charge like a capacitor, but instead the SP constantly is being generated by normal activity in the eye during both light and darkness.

Yonemura and Kawasaki (1979) studied the effects of osmotic stress and acetazolamide on the SP. Both produced large SP decrements which were shown to originate in the retinal pigment epithelium in both instances. Acetazolamide may have effects parallel to the effects of hypoxia on aqueous-humor secretion (Mercier et al., 1964), visual fields (Kobrick, 1970), and refraction (Halperin and Kilvin, 1959; Ohlbaum, 1969). This finding that the drug strongly depressed the SP of the eye appeared to deserve inclusion in this review, despite the fact hypoxic changes and related respiratory changes in the SP are less clear cut than the sharp decrements produced by acetazolamide.

Taumer, Tohde, and Pernice (1976) provided an experimental and theoretical investigation of the slow oscillation of the SP. They concluded rod and cone processes independently contributed to the SP oscillation. Any differential effects of hypoxia on cone and rod function might be expected to alter the characteristics of the oscillation. The same would be true should pure oxygen at more than one atmosphere influence the receptor types differently. As will be discussed below, oxygen at one atmosphere did not influence the sinusoidal character of the SP. However, one atmosphere of oxygen had only a minimal effect on persistence of vision following pressure ischemia, whereas hyperbaric oxygenation prolonged persistence by as much as five times that obtained at one atmosphere (e.g., Anderson, 1968). SP changes with hyperbaric oxygenation apparently have not been investigated and this may be an area needing research.

Drummond and Rebuck (1981) studied the effect of hypoxia, hypocapnia, and moderate hyperoxia on the SP in man. Subjects were eight males and seven females between the ages of 22 and 47. No subject had visual abnormalities other than simple refractive errors. A rebreathing device was used to produce hypoxia and CO₂ was removed from the inspired mixture. Oxygen saturation of the blood was monitored continuously and maintained at 80 percent by addition of oxygen to the rebreather. In a first series of experiments, natural fluctuations in the SP appeared, despite a long period of adaptation to a constant light and these interfered with measurement of hypoxia effects. They reported hypoxia may have had the effect of dampening this sinusoidal variation.

In a second series of experiments, the sinusoidal SP variation more or less was brought under control. "Light off" and "light on" periods (12 minutes each) were alternated and the "light on" periods then produced a steep sinusoidal rise in the SP and the "light off" periods corresponded to and increased the fall of the sinusoid. In the hypoxia condition, the first dark-light cycle began and was 4 minutes from completion when hypoxia began. Thus the second dark-light cycle began 4 minutes following the onset of hypoxia and these 4 minutes were about the time it took for blood oxygen saturation to drop to 80 percent.

The dark trough following hypoxia was lower than that during a control condition consisting of a similar repetition of the two dark-light cycles, but with air breathing throughout. Another change with hypoxia was found for the second light-onset-induced SP peak which was lower than in the control condition.

A similar dark-light/dark-light sequence was used to study effects of hyperoxia and hypocapnia on the SP. Hyperoxia was produced by breathing pure oxygen at the normal atmospheric pressure. Hypocapnia was induced by hyperventilation. Hypocapnia and hyperoxia began 4 minutes before completion of the first dark-light cycle.

Breathing pure oxygen did not change the light peaks and troughs from those obtained during constant air breathing. The series of tests on hypocapnia was cut short when the sixth subject tested experienced dysarthria (speech impairment) and an apparent left facial weakness. However, hypocapnia also did not consistently change the light peaks and troughs and this is surprising since Fenn et al. (1949) had found hypocapnia to produce larger SP changes than hypoxia. In summary, only hypoxia was found to have an effect on the SP and inspection of the figures in the Drummond and Rebeck indicates even this was a fairly small effect compared to the sinusoidal variation in the SP induced by the dark-light cycle. As discussed earlier, hyperbaric oxygenation might be expected to produce an effect on level of the SP or on SP oscillation, even though breathing pure oxygen at one atmosphere did not.

Marmor, Donovan, and Gaba (1985) assessed changes in the SP as a function of hypoxia, and assessed the effects when hypoxia was followed by 100 percent oxygen and air breathing. One subject was a 33-year-old emmetropic male without retinal pathology and with large easily recordable ERG c-waves. The other subject was a 42-year-old male with 3.75 diopters of myopia, tigroid fundus pigmentation, a flat nevus in the left eye, and minimal or nonrecordable ERG c-waves. Recordings were made in darkness with the exception of red LED fixation lights. For 15 seconds out of each minute, LEDs subtending a visual angle of 45 degrees were alternated back and forth every 1.5 seconds. The oxygen levels were near 10 percent and hemoglobin oxygen saturation was lowered to values near 80 percent. These low levels were achieved gradually (over a period of 5 to 10 minutes) to minimize possible systemic effects.

Both subjects showed a slow, but reproducible rise in the SP as a result of reduced oxygen saturation. Raising the lowered oxygen saturation by breathing 100 percent oxygen or room air caused a sharp fall of the SP by 20-30 percent of its amplitude. After 5-10 minutes, the SP began to drift back upward toward baseline levels. The SP changes always were similar in both eyes. They were reproducible within the same session and also when repeated on

different days. Control conditions with air and 100 percent oxygen were alternated with hypoxia and these led to a SP baseline that was effectively stable and showed neither gas-related shifts nor slow (two-per-hour) oscillations. However, the hypoxia condition never led to such stability. When CO_2 was monitored there was only a small shift over 20 minutes of ventilation (from 40- to 36-mm Hg). Thus the subject was not particularly hypocapnic and CO_2 changes were unlikely to have caused the SP shifts with hypoxia. The authors indicated this was only a pilot study with a restricted range of hypoxic conditions. They indicated this range needed to include more severe levels of hypoxia which they anticipated would produce substantial SP shifts.

Kreienbuhl and Niemeyer (1985) studied the SP and c-wave of the perfused cat eye while varying the oxygen content and also the flow rate of the perfusate. Increases in flow rate with oxygen constant often increased the SP, but produced no changes in the c-wave. Decreases in flow rate with oxygen constant produced inconsistent changes in the SP, but produced no changes in the c-wave.

Kreienbuhl and Niemeyer also found changes in oxygen with flow rate constant were related inversely to changes in the c-wave. Increasing oxygen increased the SP, but decreasing oxygen left the SP unchanged. These results showed a general lack of correlation between the ERG c-wave and the SP in the perfused eye.

Linsenmeier and Steinberg (1986) investigated the mechanism of hypoxic effects on SP and DC ERG of the cat. The subjects were anesthetized or decerebrate cats. SPs and DC ERGs were measured between a reference electrode behind the eye and a silver wire in the vitreous. The transepithelial potential (TEP) was measured between the reference electrode behind the eye and a microelectrode in the subretinal space. Stimuli were periods of white light having an illumination at about rod saturation presented in most cases to an initially dark-adapted retina. Air or gas mixtures were breathed, with the latter reducing arterial oxygen tension to various levels. The SP increased upon the onset of hypoxia and decreased at the end of hypoxia. The SP change with hypoxia onset was greatest for dark-adapted eyes and was much reduced if hypoxia occurred during exposure to steady light (with hypoxia onset occurring after the SP had stabilized following shifts resulting from light onset). TEPs always showed the bulk of the SP shifts and this indicated the SPs were produced largely in the retinal pigment epithelial cells and not by the neural retina. ERG c-wave changes with hypoxia mimicked SP changes and large SP changes almost always were accompanied by large c-wave changes. Subsequent to the c-wave, there is a drop in voltage in the ERG known as the fast-oscillation trough. This was lower significantly during hypoxia than during normoxia. A light peak follows this trough after several minutes, and this also was much reduced during hypoxia.

Linsenmeier, Smith, and Pokorny (in press) determined the effects of hypoxia on the light rise of the SP in humans. Three observers were used, two of whom were authors plus a student volunteer. The subjects viewed a large 70- by 30-degree white screen which varied from an initial luminance of 7.5 cd-m₂ (approximately 350 td. for the 8-mm dilated pupil). This screen decreased in luminance by 0.0333 log unit every 20 seconds so the screen luminance reached a minimum of 0.35 td after 30 minutes. The screen luminance was then raised to 6,250 td in a single step. During the prior decreasing luminance, 10 repeated left-right-left eye movements occurred for 10 seconds every minute with the movements stimulated by a chime that accompanied illumination of first a red LED 20 degrees to the left and then illumination of a red LED 20 degrees to the right. Observers breathed gas from a bladder that contained either air or a mixture of 10 percent oxygen with 90 percent nitrogen. Arterial oxygen saturation was monitored continuously with an ear oximeter. A 4-minute sequence of eye movements was recorded 2 minutes prior to the end of the period of decreasing luminance and 2 minutes after the step change in luminance to 6,250 td. After that a 10-second eye-movement sequence was recorded every minute for 8 minutes. The observer started breathing through the mask or breathing tube 10 minutes before the light step and continued until the end of the test. In another protocol aimed at exploring prolonged hypoxia effects, the observers remained in the dark for a period of 10-15 minutes at the end of the "ramp" prior to the light step, although reduced oxygen was started at the same point on the decreasing illumination "ramp."

Hypoxia occurring during the "ramp" caused an earlier rise of the SP than when normal air was breathed, with the rise occurring shortly after the low-oxygen mixture was introduced. In the later experiments where the step increase was delayed, there was less increase in the SP following the step increase in luminance during hypoxia than without hypoxia. Thus hypoxia onset increased the SP and prolonged hypoxia tended to reduce peaks of the SP and the peak/trough ratio.

Hypoxia and hypocapnia and the ERG

In their research on failure of the rabbit visual pathway during hypoxia, Noell and Chinn (1950) found breathing pure nitrogen quickly reduced the ERG b-wave. On the other hand, a small b-wave persisted into late stages of hypoxia after the optic-tract response had disappeared. They interpreted this to indicate the retinal ganglion cells become nonexcitable sooner after the onset of hypoxia than the bipolar cells and photoreceptors. Visual cells in the cortex and geniculate were found to be even more sensitive to hypoxia than ganglion cells.

Alpern et al. (1955) reported Dodt (1951) found the ERG generated by flicker was changed by hyperventilation. Since the flicker stimulus used by Dodt prevented any identification of how the different components of the ERG produced by a single flash were influenced, Alpern et al. (1955) assessed the effects of reduced alveolar CO₂ tension on the a-wave and b-wave of the human ERG as these were generated by single flashes at two flash intensities. The subjects were two young observers who were dark-adapted prior to testing. Stimulus flashes of 81-millisecond duration were presented under conditions of normal breathing and also during "rather marked" hyperventilation. Two intensity flashes were used, one moderate intensity flash (0.011×10^5 trolands) which did not produce an a-wave and one brighter flash ($.1 \times 10^5$ trolands) which did.

Alpern et al. found the b-wave showed an increase in amplitude with hyperventilation for both intensities. The a-wave was reduced greatly following hyperventilation and sometimes disappeared. All effects were reversed once normal breathing was resumed. No actual measures of blood pH or levels of CO₂ in the blood were made to determine the degree of respiratory alkalosis, but, according to Alpern et al., this strong effect of hypocapnia on the ERG argued for effects of hypocapnia on visual phenomena such as metacontrast and alpha adaptation which normally covaried with ERG changes.

Arden and Greaves (1956) studied the reversible alterations of the rabbit ERG after occlusion of the retinal circulation. Intraocular pressure was raised above the arterial pressure, causing a total cutoff of blood flow into the eye. As a result, the ERG was extinguished rapidly with the c-wave going first, followed by the a-wave, and finally the b-wave. Restoration of blood flow caused a rapid return of the waves with the c-wave larger than normal. Other experiments where no ERG was measured during the period of ischemia also showed the rapid return of the ERG after blood flow was reintroduced, but under this circumstance, the c-wave returned at normal levels.

Subsequent experiments were conducted to elucidate these c-wave differences after recovery. It was found shining a light on the eye just prior to ischemia, or early in the period of blood cutoff before ischemia was complete, caused the enhanced c-wave and also an enhanced a-wave in ERGs obtained after ischemia. No enhancement occurred for these potentials when the light was presented late in the period of ischemia. This effect of a light prior to or early during the period of ischemia, but not later in ischemia, indicated the effect was on neural processes halted by ischemia and not on photochemical processes which continue in the absence of circulating blood (e.g., Craik, 1940).

Horsten and Winkelman (1957) studied the effect of temporary occlusion of the aorta on the ERG of cats. They found the b-wave

quickly was reduced to half height following clamping of the aorta and then disappeared after about another similar period (with a bright 50 lux stimulus). The negative potential of the ERG was much more resistant to clamping of the aorta. A stimulus intensity of 1.5 lux produced a substantially longer lasting b-wave than the 50 lux stimulus. This 1.5-lux stimulus was too weak to generate a negative potential. When the clamp on the aorta was removed, and a stimulus of 50 lux was used, the negative potential returned within a very few seconds and the b-wave followed after about 1 minute (or more). The b-wave reached 100 percent of its original levels after about 3 minutes. Complete recovery of the b-wave did not occur for the longest period of aorta occlusion. During recovery, ERG responses to successive bright stimuli (3-second interval between stimuli) diminished in amplitude and a period of total darkness was required to restore ERG amplitude. With a dim stimulus, no such decrease in ERG amplitude occurred. Thus, several of their findings indicated greater perseveration of ERG responses during hypoxia when the stimulus was less intense.

Brown, Hill, and Burke (1957) studied the effect of hypoxia on the human ERG for red, blue, and white flashes. Breathing oxygen at a concentration of 15 percent had little effect on any of the waves. Breathing nine percent oxygen, however, produced an immediate decrement in the initial positive wave for the red stimulus (x-wave) and its amplitude continued to drop to one-half the normal value following 10 minutes of breathing the nine percent oxygen mixture. Much smaller decrements with hypoxia occurred for the qualitatively different initial positive waves (b-waves) produced by blue and white stimulation.

Recovery of the hypoxia-attenuated x-wave following air breathing was not complete in 10 minutes. Control experiments indicated the x-wave reduction with nine percent oxygen could have been only partially the result of reduced transmission of light through the hypoxia-reduced hemoglobin in the retinal vessels through which light must pass to reach receptors. A decrement in cone function under conditions of low oxygen was believed to be the basis of the x-wave changes.

Pearlman (1962) did not study effects of hypoxia on the ERG, but he did provide evidence the c-wave (late positive deflection) in the human ERG, which is altered by hypoxia (e.g., Arden and Greaves, 1956), is not produced in the retina, but has a "pupillo-ciliary" origin. The c-wave was measured in both eyes even though one was covered and not stimulated. When a mydriatic-cycloplegic agent (one percent Cyclogel) was introduced, the c-wave was eliminated. The same was true for a miotic (two percent Pilocarpine). In both cases, the b-wave was present. The untreated eye continued to demonstrate the c-wave even (as noted above) when it was covered and only the treated eye was stimulated.

Pearlman judged the source of the c-wave somewhat more likely to be the pupil than the ciliary body.

According to Mitari and Takagi (1965), Nagaya and Muneoka (1963) found the critical concentrations of inspired oxygen to produce nonexcitability of the human visual pathway were 14 percent for the cortex, 12 to 13 percent for the retinal ganglion cells, and 10 percent for the bipolar cells and photoreceptors.

Mitari and Takagi (1965) themselves gradually decompressed rabbits to 10,000 meters and then gradually returned them to sea level. ERG a-waves and b-waves were reduced in amplitude as elevation increased. Latencies increased for the ERG with decompression and also for evoked responses recorded at the lateral geniculate, superior colliculus, and cortex. The increases in latency at altitude were more pronounced for the ERG than for the various evoked responses. Recovery of latency upon recompression was slowed for the ERG b-wave and for the cortical evoked responses. This was not the case for the ERG a-wave and for evoked responses from the lateral geniculate and superior colliculus.

Fujino and Hamasaki (1965) studied the effect of occluding the retinal and choroidal circulation on the electroretinogram of monkeys. When both retinal and choroidal circulations were blocked, there was an immediate loss of the b-wave. The P I component of the ERG was lost after 5 minutes and the P III after 20 to 40 minutes. When just the retinal circulation was interrupted, there was an immediate depression of the b-wave followed by its abolition in 60 seconds. The P I and P III components were maintained for at least 60 minutes. Choroidal occlusion with retinal circulation intact resulted in b-wave loss in times comparable to when only the retinal circulation was interrupted. The P I and P III components could not be maintained by the retinal circulation and disappeared after 20 to 40 minutes.

Gouras and Carr (1965) found large differences in light-induced DC responses of the monkey retina before and after central retinal artery interruption. The effect of eliminating retinal circulation was to destroy inner retinal layers while leaving outer layers which receive oxygen from the choroidal circulation intact. The effect of this was to eliminate or greatly reduce the normal positive DC response to light. The ERG b-wave also was reduced greatly and the a-wave dominated ERG records. However, despite the destruction of inner retinal layers, the sodium-azide response (Noell, 1952) still was present.

Massopust, Wolin, and Barnes (1966) studied the ERG in cats exposed to severe hypoxia (9.1 percent oxygen). They found both the a-wave and b-wave amplitudes decreased. The latency of the b-wave increased in all cases. The latency of the a-wave did not change.

Fujino and Hamasaki (1967) studied the effect of intraocular pressure on the electroretinogram of monkeys and determined it was ocular ischemia caused by the pressure and not pressure per se that caused the disappearance of the ERG.

Karlberg, Hedin, and Bjornberg (1968) measured the human ERG during a short-term intraocular tension rise produced by a transparent suction cup electrode applied to the eye. Low suction pressures of 80 and 100 mm Hg produced no ERG changes. Suction of 120 mm Hg produced a 25 percent reduction of the b-wave that remained constant for the full 20 minutes of suction. A suction of 150 mm Hg decreased the b-wave to one-half its amplitude in 50 to 60 seconds and abolished it after 100 to 110 seconds.

Van den Bos (1968) studied the effects of hypoxia on the ERG in cats. Oxygen tensions ranging from 21 down to 10 percent showed little effect on the b-wave amplitude. With tensions lower than 10 percent, the amplitude of the b-wave dropped sharply, although occasionally early in hypoxia a larger-than-normal b-wave was observed. Such supernormal responses occurred with spontaneous breathing, but not with controlled respiration, and may have reflected hypocapnia effects associated with hyperventilation. When blood-oxygen saturations were very low, the ERG lost its characteristic form and became a biphasic curve.

Carapancea (1971) explored the effects of decompression to high altitudes on the ERG. He found the latency of the b-wave almost always increased, its amplitude frequently decreased, and there were "irregular variations of culmination time and of duration." Disrupted "metabolism of visual neuroepithelial cells [associated] with rods" was seen as the hypoxic consequence that caused these changes in the ERG b-wave. No specifics about altitude were provided in this brief report.

Tazawa and Seaman (1972) measured the ERG of the living extracorporeal bovine eye as it was influenced by hypoxia and hypothermia. Reduction of ERG components as a function of anoxia (interruption of perfusion) occurred first for the b-wave, next for the slow positive component, and finally the a-wave. During recovery from anoxia, enhancement occurred first for the a-wave, then the positive component, and finally the b-wave.

Sipperley, Anderson, and Hamasaki (1973) studied the short-term effect of intraocular pressure elevation on the human ERG using a suction cup procedure similar to that of Karlberg, Hedin, and Bjornberg (1968). Results basically were similar with no b-wave reduction until the IOP approached or exceeded the diastolic ophthalmic artery pressure. However, even pressures higher than the systolic artery pressure for 5 minutes sometimes did not completely abolish the b-wave.

Gerstle, Anderson, and Hamasaki (1973) studied the effects of raising IOP on the ERG and optic nerve conduction of visual impulses in owl monkeys. IOP levels that cut off ocular blood flow, quickly abolished the ERG b-wave. However, the responses of the optic tract required about twice as long to be abolished. With a slightly lower IOP, the b-wave was abolished in less than 2 minutes, but the optic-tract response remained at a low level for 10 minutes. With slightly lower IOPs, the b-wave always was attenuated more as a result of the reduced perfusion of the eye than the optic-tract response. IOPs which allowed a perfusion pressure of 30 mm Hg had almost no effect on either the ERG or the optic tract response.

Adams et al. (1977) looked at the effects of hypoxia on visual function and its moderation by chemotherapy. They found a strong rapid deterioration of the ERG, responses evoked at the optic tract, and responses evoked at the striate cortex when animals breathed 8 percent and 10 percent oxygen levels. On the other hand, 12 and 15 percent oxygen did not produce decreases in retinal and neural function, despite periods of testing of up to 8 hours. In line with Gerstle and Anderson (1973), ERG-b-wave decrements exceeded optic-tract decrements and this indicated the b-wave was not closely correlated with retinal output. They claimed it was more likely a measure of the metabolic state of the retina.

In a second series of experiments, Adams et al. (1977) looked at effects of hypoxia on blood pH and the ERG b-wave. There was a large increase in acidosis at later stages of exposure to nine percent oxygen² and b-wave amplitude was typically inversely related to blood acidity during hypoxia and during the slow recovery that occurred during normal air breathing. On the other hand, blood acidity increased relatively slowly during hypoxia while an immediate decrement in the b-wave was noted. Metabolic buffering of blood pH was found to reduce the decrement in the b-wave during hypoxia.

In experiments with cats breathing normal air, Adams et al. (1977) found respiratory alkalosis induced by hyperventilation had little effect on the ERG, but that metabolic alkalosis produced by intravenous infusion of bicarbonate produced a significant increase in amplitude of the ERG b-wave that was reversed by injection of acid. This contrasts with research of Alpern and Hendley (1952) who found respiratory alkalosis had a major effect on absolute visual sensitivity and CFF while metabolic alkalosis had little

² The basis for this acidosis may have been reduced respiration of the anesthetized animals. On the other hand, arterial CO₂ apparently did not show parallel increases to pH decreases.

effect. The low correlation between b-wave changes and changes in neural output from the retina may help explain these contrasting results.

Eysel (1978) investigated the susceptibility of the cat's visual system to hypoxia, hypotonia, and circulatory arrest. Simultaneous measures of responses to flash stimuli were made at the retina (ERG), optic tract, lateral geniculate, superior colliculus, and visual cortex. Hypoxia induced by pure nitrogen first effected the b-wave of the ERG, then the postsynaptic components of the visual cortex, then the superior colliculus and lateral geniculate nuclei, then the response of the optic tract to electrical stimuli and the less susceptible receptor component of the ERG.

Ingenito and Durlacher (1979) studied the effects of carbon monoxide on the b-wave of the cat ERG and compared them with effects of nitrogen hypoxia, epinephrine, vasodilator drugs, and changes in respiratory tidal volume. Low COHb levels reduced the b-wave, whereas hypoxia-reduced HbO₂ levels of comparable magnitude did not. In fact, low-oxygen-high-nitrogen hypoxia led to hypocapnia and an enhancement of the b-wave. Some toxic CO effect on the retina was believed to have produced the CO decrement in the b-wave and not a tissue hypoxia associated with the reduction of HbO₂ as a result of the 7.5 percent COHb.

Howard and Sawyer (1975) studied the ERG in six dogs who underwent hypoxia and in four of these six dogs who were subjected to increased intraocular pressure. Lowering the arterial oxygen to 45 torr by increasing the nitrogen content of the respiratory mixture, caused a sharp decrease in b-wave amplitude in all dogs. Arterial CO₂ was monitored and maintained at 38 +/- 2 torr. Drops in the b-wave occurred for arterial O₂ levels above 45 torr, but these were small relative to the drop at 45 torr. Reducing the intraocular perfusion pressure to 45 mm Hg (by increasing the intraocular pressure to within 45 mm Hg of the arterial blood pressure) produced a similar diminution of the ERG b-wave to that obtained by reducing arterial O₂ levels to 45 torr. For both treatments, the b-wave was reduced or disappeared much more quickly than the a-wave.

Niemeyer, Nagahara, and Demant (1982) studied the effects of changes in arterial O₂ and CO₂ on the ERG in the cat. Cats breathed different gas mixtures of 100 percent oxygen, 10 percent oxygen-90 percent nitrogen, 5 percent oxygen-95 percent nitrogen, 5 percent CO₂ in air, 10 percent CO₂ in air, and 5 percent CO₂-95 percent oxygen. The period of exposure to these gases was 10 minutes except for 5 percent oxygen which was only for 5 minutes.

The ERG b-wave showed no change during breathing of pure oxygen, showed a small decrease with 10 percent oxygen, and showed

a much larger decrease with 5 percent oxygen. None of the CO₂ mixtures had any effect on the b-wave. The c-wave dropped slightly during breathing of pure oxygen. The c-wave showed a sharp rise with 10 percent oxygen and this was followed by a several minute drop upon return to air breathing. An even sharper rise in the c-wave occurred with breathing of 5 percent oxygen followed by a nearly instantaneous drop on return to air. This drop was to a point well below prehypoxia levels. The c-wave rose and then dropped for all CO₂ mixtures with the steepest rise for 10 percent CO₂.

Arterial blood pressure dropped at the beginning of breathing of all gas mixtures, except 100 percent oxygen. It then rose during the gas-breathing period with a further rise upon return to air breathing. Arterial blood pressure then returned to normal levels after 5 to 10 minutes. Arterial blood pressure typically was correlated negatively with the c-wave and it was believed the increased choroidal blood flow directly affected (reduced) the c-wave. The authors claim their b-wave findings offer electrophysiological evidence for autoregulation of the retinal vessels. However, they noted this vasculature cannot quite cope with the low arterial oxygen tensions of 30 and 26 mm Hg associated with 10 percent and 5 percent oxygen, respectively. This finding for the ERG corresponds closely to ganglion-cell results of Enroth-Cugell, Goldstick, and Linsenmeier (1980), who found ganglion-cell function was affected sharply at an arterial oxygen tension of about 35 mm Hg, but also found that ganglion-cell function largely was unaffected for higher oxygen tensions.

Papst, Demant, and Niemeyer (1982) studied the effects of changes in perfusate oxygen levels on the b-wave and on perfusate flow in the perfused cat eye. Flow of perfusate changes when vessel size changes. Hypoxia reduced the b-wave and increased the flow of perfusate. Hyperoxia (increases in perfusate oxygen tension of from 7 to 38 percent) increased the b-wave and reduced the flow of perfusate. During hypoxia the diameter of arteries increased by up to 22 percent and the diameter of veins increased by up to 14.3 percent.

Linsenmeier, Mines, and Steinberg (1983) studied the effects of hypoxia and hypercapnia on the light peak and ERG of the cat. Adult cats breathed gas mixtures that reduced arterial oxygen tension in some experiments and increased arterial blood acidity in others. The DC ERG was recorded at different levels of hypoxia and hypercapnia to a 5-minute stimulus of diffuse white light about a log unit above rod saturation.

They found the light peak of the DC ERG was found to be sharply reduced by both hypoxia and hypercapnia with the change occurring for hypoxia at much lower levels of hypoxia than the hypoxic level required to reduce retinal response. Although the magnitude of

changes of the light peak induced by hypoxia and hypercapnia were similar, there were some differences in the wave forms for the two conditions. Changes in arterial pH with hypoxia were minimal and although pH changes within the eye itself produced by hypoxia may have accounted for the reduced light peak, it was not via hypoxic changes in arterial pH. ERG b-wave changes did not occur until much higher levels of hypoxia than required to alter the light peak. However, even low levels of hypercapnia (arterial pH = 7.2) reduced the b-wave. Increases in the c-wave typically occurred with small reductions in arterial oxygen tension, but the results were more variable than those produced by low oxygen for the light peak. Hypercapnia also increased the c-wave with the changes beginning at a blood pH of about 7.3.

Linsenmeier and Steinberg (1984) studied the effects of hypoxia on potassium homeostasis and on pigment epithelial cells in the cat retina. They were seeking a mechanism to explain the effects of moderate levels of hypoxia on the DC ERG and other ocular potentials. Subjects were 26 anesthetized adult cats. K^+ levels in the subretinal space and apical/basal membrane hyperpolarizations in retinal pigment epithelium cells were recorded during various illumination levels (including darkness) and with different arterial oxygen tensions. Hypoxia led to a rapid buildup of potassium in the subretinal space during dark adaptation which caused a depolarization of first the apical and then the basal membranes of retinal pigment epithelium cells. Hypoxia slowed light-evoked potassium and membrane responses, increased their amplitudes, and slowed and reduced their recovery.

Steinberg (in press) provided a review of studies of the effects of mild hypoxia on the ERG, SP, and underlying processes in the photoreceptors and pigment epithelial cells. Hypoxia was seen to slow the Na^+K^+ pump of the rods. This leads to an excess of K^+ in the subretinal space which depolarizes apical and basal membranes of the retinal pigment epithelium. This depolarization increases the SP of the eye. This slowing of the Na^+K^+ pump by hypoxia (and light) reduces oxygen consumption of the rods and undoubtedly contributes to the survival of these photoreceptors during hypoxia.

Hyperbaric oxygenation and the ERG

Several of the studies reviewed above included pure oxygen breathing at normal atmospheric pressures as one condition among conditions that also included lower than normal oxygen tensions. In most cases, there was no particular change in either the SP of the eye or in the ERG as a result of increased oxygen tensions above normal air.

Noell (1962), on the other hand, found that long exposures of rabbits to oxygen at one atmosphere led to death of the visual cells. In fact, exposure to 55 to 60 percent oxygen for 7 days produced cell death in almost half the animals, although no evidence for visual cell death was obtained with 50 percent oxygen for 12 days. A significant attenuation of the ERG preceded the manifestation of visual cell death. Continued exposure to 100 percent oxygen for 5 to 8 hours beyond the first ERG decrement led to irreversible cell death.

As would be expected, given the toxic effects of oxygen he found at one atmosphere, Noell (1962) also reported that oxygen at hyperbaric pressures led to very rapid declines of the ERG b-wave of the rabbit. For example, at three atmospheres it was abolished in 200 minutes and at seven atmospheres the b-wave was abolished in about 45 minutes.

Bridges (1966) also assessed electroretinographic changes of rabbits during hyperbaric oxygenation (pure oxygen administered at pressures of 2.5, 3, 4, 5, 6, and 7 atmospheres). An atmosphere 2.5 times normal greatly reduced the a-wave at 5 hours of exposure, but did not abolish it. This condition did abolish the b-wave at about 3.5 hours. ERG b-waves and a-waves were abolished following exposure to three atmospheres of pure oxygen and following exposure to all pressures above three atmospheres. With a pressure of seven atmospheres, this abolishment occurred in less than 2 hours for the a-wave and in less than an hour for the b-wave. When pressure was sufficient to abolish both waves, the a-wave always survived longer than the b-wave. The ratio of a-wave to b-wave survival times increased in direct proportion to the atmospheric pressure.

While pure oxygen at high pressures eventually abolished the a-wave and b-wave, early exposure to the hyperbaric oxygen increased the magnitude of both these waves over those obtained at atmospheric pressure. These peak responses were reached rapidly with seven atmospheres of pressure and more slowly as the pressure was reduced. Latencies of these peak responses were similar for the two waves.

Kozousek (1967) studied the human ERG under conditions of normal and hyperbaric oxygenation and this was the only report found which provided human ERG data during hyperbaric oxygenation. The English summary of their Czechoslovakian language report indicated both the positive and negative ERG potentials were increased with hyperbaric oxygenation. The ERG quickly returned to normal and sometimes to somewhat lower than normal levels when hyperbaric oxygenation ended.

Conclusions and research needs

Although a total retinal ischemia produced dramatic drops in the SP, reduced oxygen tensions had a much more subtle effect on this potential. On the other hand, moderate levels of hypoxia that have little or no effect on the ERG do alter the SP. Contradictory results existed on the effects of hypocapnia on the SP with the early research of Fenn et al. (1949) finding hypocapnia boosting the SP more than hypoxia and Drummond and Rebuck (1981) finding effects of hypoxia and no effect of hypocapnia.

A number of studies have shown the ERG b-wave is affected strongly by hypoxia only when oxygen levels are around 10 percent or below and the b-wave generally is unaffected by slightly higher oxygen tensions. This corresponds closely to the hypoxic levels required to influence visual sensitivity (see Chapter 1: "Absolute sensitivity and dark adaptation") and ganglion cell responses (see the next chapter). On the other hand, research has indicated that even when the b-wave is much attenuated or abolished, that substantial optic-tract responses still may be occurring to the visual stimulation.

As was discussed earlier, no studies were found which looked at the effects of hyperbaric oxygenation on the SP in man or animals. This would appear to be an important area for future research. It is true pure oxygen at a single atmosphere had negligible effects on the SP (Drummond and Rebuck, 1981), but persistence of vision following retinal ischemia also showed little difference between air breathing and pure oxygen breathing at one atmosphere. On the other hand, dramatic increases in persistence of vision occurred for pressures above one atmosphere (see Chapter 8: "Persistence of vision following ischemia"). The Kozousek (1967) finding of enhanced positive and negative ERG potentials with hyperbaric oxygenation also may augur for substantial SP changes.

Chapter 10

Ganglion cell and optic-tract responses

The ganglion cells in the retina form the optic tract that leaves the eye en route to the lateral geniculate. The optic tract provides a convenient site for monitoring of visual functioning in animals and both individual nerve firings and average activity have been recorded. These optic-tract responses are related more directly to visual stimulation than the potentials recorded in the electroretinogram and often appear even when ERG activity is nonexistent (see below).

In their research on failure of the rabbit visual pathway during hypoxia, Noell and Chinn (1950) found the retinal ganglion cells to become nonexcitable much sooner after the onset of hypoxia than the bipolar cells and photoreceptors. As discussed in the previous chapter, this was based on a persistent ERG b-wave that survived nitrogen breathing longer than the optic tract response. On the other hand, visual cells in the cortex and geniculate were found to be even more sensitive to hypoxia than ganglion cells.

Noell (1951) compared rabbits, cats, monkeys, and man and found large differences in the time following onset of asphyxiation before there was loss of vision for humans or loss of optic-tract responses for the other mammals. This time to asphyxial block was 312 seconds for rabbits, 209 seconds for cats, 112 seconds for monkeys, and 50 seconds for man. Noell also concluded the sites of asphyxial block in mammalian retinæ showed variation for these different species. In the rabbit, cat, and man the site was determined to be neurons of the ganglionic cell layer. Early processes of retinal excitation were judged to produce the initial block to vision for the cat.

Massopust, Wolin, and Barnes (1966) studied optic tract and visual evoked cortical potentials, along with potentials at other points of the visual system (ERG, and superior colliculus) in cats exposed to severe hypoxia (9.1 percent oxygen). Small variable increases in the latency of evoked potentials were found with hypoxia at the optic tract and other recording sites. The amplitude of these various potentials was reduced substantially during hypoxia, although variability in these changes was large. They also found the waveforms evoked while the animal breathed air were more complex than those evoked during hypoxia.

As discussed in the previous chapter on the ERG, Gerstle, Anderson, and Hamasaki (1973) studied the effects of raising

intraocular pressure (IOP) on the ERG and optic nerve conduction of visual impulse in owl monkeys. IOP levels that cut off ocular blood flow, quickly abolished the ERG b-wave. However, the responses of the optic tract required about twice as long to be abolished. With a slightly lower IOP that allowed a small amount of blood to flow in the eye, the b-wave was abolished in less than 2 minutes, but the optic-tract response remained at a low level for the full 10 minutes over which it was measured. IOPs that attenuated the optic tract response always attenuated the b-wave to a greater extent and at some perfusion pressures there was b-wave attenuation, but the optic-tract response remained unchanged. IOPs which allowed a perfusion pressure of 30 mm Hg had almost no effect on either the ERG or optic tract response.

Adams et al. (1977) looked at the effects of hypoxia on visual function and its moderation by chemotherapy. They found a strong rapid deterioration of ERG, optic-tract responses, and striate-cortex responses when cats breathed 8 percent and 10 percent oxygen levels. Hypoxia-produced decrements in the ERG b-wave exceeded hypoxia-produced decrements in the optic tract. As mentioned, Adams et al. (1977) believed this indicated the b-wave is not closely correlated with retinal output, but is more likely a measure of the metabolic state of the retina.

Eysel (1978) investigated the susceptibility of the cat's visual system to hypoxia, hypotonia, and circulatory arrest. Simultaneous measures of responses to flash stimuli were made at the retina (ERG), optic tract, lateral geniculate, superior colliculus, and visual cortex. Hypoxia induced by pure nitrogen first affected the b-wave of the ERG, then the postsynaptic components of the visual cortex, superior colliculus, and lateral geniculate nuclei. Only after these sites were inhibited strongly by hypoxia was there any major decrement in the response of the optic tract to electrical stimuli or any major decrement in the receptor component of the ERG.

Enroth-Cugell, Goldstick, and Linsenmeier (1980) assessed effects of hypoxia on the contrast sensitivity of retinal ganglion cells and on the oxygen tension of the inner retina itself. Adult cats were used with 19 providing data for ganglion-cell recordings alone, 7 providing data for measurements of retinal oxygen tension alone, and 5 providing data for both types of measurements. Electrodes were placed in the optic tract and ganglion-cell spikes were recorded while the animals viewed sinusoidal gratings. Measurements of retinal oxygen tension were made with bipolar polarographic oxygen electrodes.

Enroth-Cugell, Goldstick, and Linsenmeier found that as long as the arterial oxygen tension was greater than 35 mm Hg, the sensitivity of ganglion cells seldom changed. On the other hand, lower oxygen tensions almost always reduced sensitivity. This

generally was true of both the receptive field center and its surround. Retinal oxygen tension (oxygen tension in the vitreous humor near the retina) was directly related to arterial oxygen tension, although the slope of the function relating retinal oxygen tension to arterial oxygen tension was much steeper for arterial tensions below 35 mm Hg than above.

Grehn (1981) studied the sensitivity of the retinal nerve fiber layer to elevated intraocular pressure and graded hypoxia in the cat. An electrode was placed in the nerve fiber layer and antidromic responses were measured to electrical stimulation of the ipsilateral optic tract. IOP pressures equal to the arterial pressure reduced responses to antidromic stimulation with a fixed number of responses occurring almost regardless of the frequency of antidromic stimulation. Asphyxia of the animal produced results comparable to increasing IOP. Repeated elevations of the IOP led to a shortening of the duration (reduction of the number) of responses to the antidromic stimulation. However, this new response pattern did not change following the fourth such repeat IOP elevation. Alternating antidromic electrical stimulation and light stimulation indicated the antidromic impulse conduction along the axons survived hypoxia longer than the ERG b-wave

Alder and Constable (1981) studied the effect of hypoxia on the mean firing rate of retinal ganglion cells in cats. Oxygen levels of 4, 5, 6, 7, 8, 10, 15, 20, and 30 percent were breathed by the cats. Recordings were made from electrodes inserted into ganglion cells. Cells typically showed an initial increase in mean firing rate for the oxygen tensions from 4 to 10 percent, followed by a decrease in firing rate for cells for oxygen tensions from 4 to 8 percent. Only when oxygen percentages were less than 10 (oxygen tensions less than 45 mm Hg) was there an effect on retinal function. The results indicated ganglion-cell function may be strongly affected by hypoxia and this may be relevant to the visual loss associated with a variety of retinal disorders.

Grehn, Grusser, and Stange (1984) studied the effects of short-term increases in intraocular pressure on cat retinal ganglion cell activity associated with spots of light or annuli of light directed at the receptive field of the ganglion cell. Sharp drops in impulse rate occurred as intraocular pressure increased, but these threshold pressures were different for on-center responses than for off-center responses. This wide variation in responses to on-center and off-center stimulation suggested the site of ischemia effects was closer to the receptors than to the ganglion cells. Similar effects would be expected if retinal ischemia were induced by reduced oxygen tensions instead of increases in intraocular pressure.

Conclusions and research needs

These studies of responses of individual ganglion cells and averaged responses from the optic tract support studies reviewed in previous chapters that showed the ability of the mammalian eye to almost fully compensate for reduced oxygen concentrations until levels of about 10 percent or lower are reached. The different hypoxic thresholds for responses of single ganglion cells to dots and their fitted annuluses provide indications of substantial visual processing that occurs in the retina itself and of the relatively high susceptibility of this processing to hypoxia. Use of these ganglion cell recording techniques during hypercapnia, hypocapnia, and carbon monoxide poisoning, might provide insights into the effects on the retina of these different respiratory conditions which influence vision.

Chapter 11

EEG and visual evoked potentials

Cortical processing of inputs from the eye might be abolished by hypoxia even if signals were present throughout the pathway from the eye to the brain. As will be discussed in this chapter, some research indicates the cortical responses to visual stimulation typically are more sensitive to hypoxia than their antecedents. On the other hand, the absence of cortical potentials does not necessarily imply that vision is absent even as the absence of the ERG b-wave did not necessarily imply an altered or absent optic-tract response (Adams et al., 1977).

Gellhorn and Hailman (1944) measured both the CFF and the occipital EEG during 6- to 17-minute exposures to severe hypoxia and to severe hypoxia with elevated CO₂. Subjects were medical students aged 20 to 25 who viewed a two-degree visual field through an artificial pupil. As was discussed in Chapter 5: "Critical flicker/fusion frequency," a small decrement in the CFF while breathing 8.4 percent oxygen became a substantial effect when the concentration of oxygen dropped to 7.8 percent in the same session. Gellhorn and Hailman found whenever the CFF was reduced sharply, the occipital EEG was changed during these periods. Typically, this change involved replacement of the alpha rhythm by slower wave activity.

In their research on failure of the rabbit visual pathway during hypoxia, Noell and Chinn (1950) found the retinal ganglion cells to become nonexcitable much sooner after the onset of hypoxia than the bipolar cells and photoreceptors. On the other hand, evoked responses measured at the cortex and geniculate were found to be even more sensitive to hypoxia than those measured at the optic tract. When the optic tract was stimulated electrically, the responses to this stimulation at the cortex disappeared somewhat more quickly following nitrogen breathing than the responses at the lateral geniculate.

According to Mitari and Takagi (1965), Nagaya and Muneoka (1963) found the critical concentrations of inspired oxygen to produce nonexcitability of the human visual pathway were 14 percent for the cortex, 12 to 13 percent for the retinal ganglion cells, and 10 percent for the bipolar cells and photoreceptors. The susceptibility to hypoxia of these points on the visual pathway paralleled the susceptibilities found by Noell and Chinn (1950).

Massopust, Wolin, and Barnes (1966) studied visual evoked cortical potentials, along with potentials at other points of the visual system (ERG, optic chiasm, and superior colliculus) in cats exposed to severe hypoxia (9.1 percent oxygen). Small and variable increases in the latency of cortical evoked potentials were found with hypoxia. In addition, the amplitude of these potentials was reduced substantially, although these changes showed considerable variability between animals. They also found the waveforms evoked in air were more complex than those evoked during hypoxia.

Kayama (1974) studied visual evoked potentials and EEG activity of the central visual system during and after hypoxia in cats. An exceedingly low oxygen mixture was administered ($PO_2 = 18-20$ mm Hg). There was a transient elevation of all electrical activity at the onset of hypoxia. This electrical activity then declined and disappeared. Visual cortex potentials were reduced earlier than responses in the lateral geniculate body. Postsynaptic lateral geniculate responses declined sooner than presynaptic responses. Both results indicated more distal locations were hit hardest by hypoxia ala Noell and Chinn (1950).

Smith and Strawbridge (1974) studied the effects of breathing pure oxygen at one atmosphere of pressure on auditory and visual evoked potentials and on the contingent negative variation (CNV) in seven subjects. Three sessions occurred with air breathing for 20 minutes, followed by pure oxygen breathing for 20 minutes, followed by a second air breathing session for 20 minutes. Visual inspection of both auditory and visual evoked potentials indicated no systematic changes in amplitude or latency of waveform components over the three sessions and quantitative waveform analyses provided a similar conclusion. Data on the CNV were available from only three of the seven subjects, but there was no indication of any CNV differences between air breathing and pure oxygen breathing.

Forster et al. (1975) studied effects of acute and prolonged exposure to an altitude of 4,300 meters on the electroencephalogram and the visual evoked potential. Seven healthy males provided data within 2 or 3 hours of the onset of hypoxia ($PaO_2=40$ mm Hg) and at 24- to 48-hour intervals for the next 9 to 12 days. No changes were found at the first testing for any subjects and it was only after 5 days at altitude that changes were noted. These were increases in EEG frequency and decreases in VEP amplitude. These changes were viewed as indications of cortical excitation as a result of prolonged hypoxia.

Petajan et al. (1976) found carbon monoxide had little effect on the visual cortical evoked response in rats until COHb levels reached a remarkably high level of nearly 70 percent and these levels had to be maintained for an hour before any changes were noted. Blood pressure changes resulting from hypoxia were seen as

a critical factor in the evoked response changes and also in changes in ventral caudal nerve motor conduction velocity which was highly correlated with the evoked response changes.

Shelburne, McLaurin, and McLaurin (1976) studied the effects of graded hypoxia on the VEP and the EEG of rhesus monkeys. They found the VEP was more persistent than the EEG following hypoxia and returned faster with air breathing as well. The shape of the VEP waveform shifted during hypoxia. With pO_2 values less than 39 mm Hg there was an upward positive shift of late components of the VEP. This upward shift was the only VEP change noted for oxygen tensions between 29-39 mm Hg.

Shelburne, McLaurin, and McLaurin found severe hypoxia greatly prolonged latencies of various components of the VEP, particularly the first negative component (N_1). However, this occurred only for pO_2 values below 29.7 mm Hg. Above this tension, N_1 latency remained constant for 2 hours. Amplitude changes of the P_1 - N_1 VEP complex also were closely related to pO_2 when pO_2 was very low. With a pO_2 of 37.5 there was no diminution of VEP amplitude over 100 minutes. With a pO_2 of 24.5 mm Hg, the VEP gradually declined and disappeared in 62 minutes. With a pO_2 of 20.5 mm Hg, the VEP rapidly declined and disappeared in 17 minutes.

Adams et al. (1977) looked at the effects of hypoxia on visual function and its moderation by chemotherapy and ERG and ganglion-cell changes have been discussed in earlier chapters. They also found a strong rapid deterioration of striate cortex responses when animals breathed 8 percent and 10 percent oxygen levels. However, they found these potentials recorded at the striate cortex showed no significant reduction until the 60th minute of hypoxia. Responses at the optic nerve already had been diminished by 25 percent at that time, and ERG b-waves were only 10 percent of their original values.

This result appears contrary to several earlier studies, such as Noell and Chinn (1950) that have shown disappearance of signals occurs first at more distant points in the visual pathway from the retina. However, both results may be compatible. The Adams et al. (1977) result of greater attenuation earlier in the visual pathway, suggests if a signal is present at a synaptic junction along the visual pathway at some threshold level, the signal is transmitted to the next level and somehow amplified. If the threshold level were not met, no signal would be transmitted to the next level and this would describe the Noell and Chinn finding of distal locations losing the visual signal first in severe hypoxia.

Eysel (1978) investigated the susceptibility of the cat's visual system to hypoxia, hypotonia, and circulatory arrest. Simultaneous measures of responses to flash stimuli were made at the retina (ERG), optic tract, lateral geniculate, superior

colliculus, and visual cortex. As discussed in earlier chapters, hypoxia induced by pure nitrogen first effected the b-wave of the ERG, then the postsynaptic components of the visual cortex, then the superior colliculus and lateral geniculate nuclei, then the response of the optic tract to electrical stimuli and the less-susceptible receptor component of the ERG.

Kinney et al. (1978) reported sizeable and significant changes in latency and amplitude of VEP components as a function of compression to depths as great as 1,600 feet. The helium-oxygen mixtures were maintained at a constant 0.3 atmosphere of oxygen pressure at each depth and these differences probably cannot be considered either hypoxia or hyperoxia effects. However, such intense pressures could cause even a small percentage of CO₂ to have a sizable tension and hypercapnia may have been a factor in the reduced amplitudes and increased latencies of the VEPs.

Sohmer, Freeman, and Malachi (1986) looked at cortical potentials evoked by visual, auditory, vestibular, and somatosensory stimuli in as severe a hypoxia as they could maintain in cats without causing the animals to collapse. For some reason, there was a decrement in auditory evoked potentials (at a pO₂ of 27 mm Hg; oxygen saturation equal to 24 percent) that left visual, vestibular, and somatosensory potentials unchanged. With even lower hypoxia (pO₂=21.2 mm Hg; oxygen saturation equal to 24.5), the VEP actually was augmented instead of depressed as expected. This was believed to have occurred because of a pupil dilation that was observed at these severe hypoxic levels which would have augmented the retinal stimulation.

Conclusions and research needs

There may be a contradiction between the Adams et al. (1977) result of greater hypoxic attenuation of optic tract responses than cortical responses to the same visual stimuli and the typical finding that visual signals drop out first at more distal points on the visual pathway (e.g., Noell and Chinn, 1950). A possible reconciliation was suggested earlier which involved signals below threshold not crossing synaptic junctions and signals above threshold crossing the junction and also being amplified or reconstituted in some manner.

No studies were found which looked at the effects of hyperbaric oxygenation on the VEP. Pure oxygen at one atmosphere did not produce changes in the VEP (Smith and Strawbridge, 1974), but hyperbaric oxygenation sometimes is qualitatively different in its effects than oxygen at concentrations from 21 to 100 percent at sea level. For example, air and pure oxygen at sea level produced nearly identical persistence of vision following Craik blindness, whereas oxygen at four atmospheres increased persistence by a

factor of eight (Carlisle, Lanphier, and Rahn, 1964). The potential dangers associated with the hyperbaric oxygen environment probably would require more reason than this for carrying out research on the VEP in human subjects, however.

Chapter 12

Ocular vessels and blood flow

The eye provides a window on the blood circulation associated with neural networks that in many ways are an extension of the brain. Changes in vessel size and changes in blood flow as a result of hypoxia, hyperoxia, hypocapnia, and hypercapnia not only shed light on regulation of oxygen in the eye, but also on the brain's regulation of oxygen. Ocular circulation thus has been a fertile area of research on effects of hypoxia and this long chapter reflects this scientific attention.

Cusick, Benson, and Boothby (1940) were among the first to study the effects of hypoxia and hyperoxia on the size of the retinal vessels. They noted a 10 to 20 percent dilation of both arteries and veins when observations were made in a low-pressure chamber at altitudes from 18,000 to 21,000 feet. They reported both arteries and veins appeared dark and the entire retina "appears dusky" during hypoxia and these brightness and color changes were related directly to the degree of hypoxia. When 100 percent oxygen was breathed by another group of subjects, a significant decrease in size of the vessels was found. This decrease varied between 10.5 and 37.7 percent for the arteries and between 16.2 and 37.5 percent for the veins. A definite increase in redness of the retina also was noted, with both veins and arteries taking on this color. This indicated that despite a reduction of blood flow associated with the constriction of the vessels, there was an increased supply of oxygen to the tissues. These vessel changes were suggested by these authors to provide at least part of the explanation for increases in angioscotomata size with hypoxia and decreases in angioscotomata size with hyperoxia (see Chapter 4: "Fields of peripheral and central vision").

Duguet, Dumont, and Bailliart (1947) studied the effects of hypoxia on retinal vessels and retinal arterial pressure. Fourteen men between the ages of 18 and 38, with no physical or ocular abnormalities, had their retinal arteries photographed at reduced atmospheric pressures. A decompression chamber was used to produce altitudes of 4,000, 5,000, and 6,000 meters. Photographic measures of retinal vessels were made at each of these altitudes and also at ground level. Enlargement of retinal vessels usually could be noted at 4,000 meters. Vessels increased in size as altitude increased to 6,000 meters with the increase stabilizing after 15 minutes at that altitude. The average increase was 21 percent with a range from 10 to 39 percent. Oxygen or a return to sea level caused an immediate recovery to normal vessel size.

Seven subjects had measures made of retinal diastolic blood pressure at 6,000 meters. Retinal arterial blood pressure increased in some subjects at 6,000 meters and decreased in others. All men showing increased retinal arterial pressure tolerated hypoxia well. All men showing decreased retinal arterial pressure tolerated hypoxia badly, with some collapsing. Retinal arterial pressure changes typically were correlated with changes in the general blood pressure. Although they reported ocular pressure also was measured at 6,000 meters, no data were provided or discussed with respect to ocular pressure. However, these results (typically small increases in ocular pressure) were described in Mercier and Duguet (1950) and are discussed in Chapter 13: "Intracocular pressure."

Sieker and Hickham (1953) confirmed the results of earlier investigators that normal eyes showed vessel dilation in response to hypoxia and showed constriction in response to breathing of pure oxygen. They reported a 10 percent increase in the diameter of both arteries and veins while subjects breathed 10 percent oxygen. They reported a 13.8 percent constriction of arteries and a 15 percent constriction in veins during breathing of pure oxygen. They also found this retinal vascular reactivity to pure oxygen decreased with age and was reduced sharply among hypertensives and diabetics.

Frayser and Hickam (1964) studied retinal vascular responses as a result of breathing increased CO₂ and oxygen concentrations. They found that 10 percent CO₂ in air caused an insignificant dilation of vessels. Pure oxygen produced a 12 percent constriction of arteries and a 15 percent constriction of veins. Ten percent CO₂ with 90 percent oxygen produced a 3 percent constriction of arteries and a 7 percent constriction of veins. Despite the relative constriction of vessels when CO₂ was mixed with high oxygen, retinal venous oxygen saturation was increased over the pure oxygen condition. Ten percent CO₂ in air also increased venous saturation compared to air without added CO₂. The authors suggested CO₂ may have produced dilation of vessels smaller than those which could be photographed and this may have accounted for the increased blood flow in the CO₂ condition despite the insignificant dilation of photographed vessels.

Dollery et al. (1964) used high-definition retinal photography and showed that the constriction of retinal blood vessels to pure oxygen at one and two atmospheres was related inversely to the size of the vessel. This finding held for all sizes of arteries with the constriction ranging from about 4 percent for the largest to 30 percent for the smallest for oxygen at one atmosphere. The corresponding constrictions were about 12 percent to 43 percent for oxygen at two atmospheres. The results for veins indicated only the largest showed the inverse relation between vessel size and amount of constriction. For smaller veins, constriction

percentages were fairly constant. No low-oxygen tensions or CO₂ mixtures were included, but the result suggests smaller arteries would be dilated more than large arteries for hypoxia and hypercapnia.

Saltzman et al. (1965a; 1965b) studied the retinal vascular and functional response to hyperbaric oxygenation in normal subjects and in patients with retinal vascular disease. The data apparently were collected from the experimenters themselves. Breathing of 100 percent oxygen at 3.04 atmospheres produced a decrease in size of retinal veins of 28.1 percent and a decrease in size of arteries of 19.0 percent compared to breathing air at one atmosphere. Breathing air at 3.04 atmospheres itself produced a decrease in size of retinal veins of 9.4 percent and a decrease in size of arteries of 4.6 percent. Breathing of 100 percent oxygen at one atmosphere produced a decrease in size of retinal veins of 10.7 percent and a decrease in size of arteries of 8.5 percent. Venous blood color changed to a bright arterial pink during breathing of 100 percent oxygen at 3.04 atmospheres and photographs of the fundus indicated some of the smaller vessels visible in the control picture were not visible under hyperbaric oxygenation. Hypocapnia induced by a minute of hyperventilation did not influence vessel size either while air was breathed at one atmosphere or oxygen was breathed at 3.04 atmospheres.

The researchers also measured the time that vision was retained during retinal ischaemia induced by a plunger-type ophthalmodynamometer that maintained pressure at a sufficient level to interrupt retinal blood flow until all vision was lost. Hyperbaric oxygenation prolonged the time to "blackout" from 12 seconds at 1.0 atmosphere to 58 seconds at 40 lb. gauge pressure which produced an arterial blood oxygen tension above 2,200 mm Hg. Delay of blackout was related linearly to gauge pressure for 0, 3, 12, 20 and 30 PSIG with an additional increment beyond the linear increase for 40 PSIG. These findings (which are discussed further in Chapter 8: "Persistence of vision following ischemia") and the bright red venous blood during hyperoxic exposure indicated that despite a striking vasoconstriction, hyperbaric oxygenation greatly increased the supply of oxygen to retinal tissues.

Trokel (1965) studied the effect of respiratory gases upon choroidal hemodynamics of rabbits. He found pure oxygen reduced blood flow by 32 percent, reduced blood volume by 14.2 percent, and caused a 69 percent increase in peripheral resistance. He found that 10 percent CO₂ in air increased blood flow by 61 percent, increased blood volume by 55 percent, and produced a 32 percent decrease in peripheral resistance. Trokel also found that 10 percent CO₂ and 90 percent oxygen increased blood flow by 15 percent, increased blood volume by 22 percent, and produced a 13 percent decrease in peripheral resistance. Trokel noted the similarity in choroidal hemodynamics in response to different

respiratory conditions to the dynamics of retinal blood flow established in earlier research.

Hickam and Frayser (1966) provided an analysis and review of effects of oxygen and CO_2 on retinal circulation. They reported breathing pure oxygen and hyperventilation while breathing air both produced similar reductions in retinal blood flow of about 40 percent. Breathing of a 10 percent oxygen mixture caused a 16 percent increase in blood flow. Breathing of a 7 percent CO_2 and 21 percent oxygen mixture caused a 22 percent increase in blood flow. They noted the retinal circulation behaved in many ways as does the cerebral circulation. However, the retinal circulation typically showed larger constrictions and blood flow reductions to higher-than-normal oxygen tensions and smaller dilations and increases in blood flow to increased CO_2 than was found for the cerebral circulation. A pronounced reactive hyperemia (an increase in retinal vessel diameter) followed 10 seconds of pressure on the eye sufficient to obstruct blood flow. This suggested the vessel walls were responding directly to local metabolic changes in retinal tissue. Their experiments also showed constriction of the veins to oxygen was an active process and not just a reaction to arterial constrictions. The retinal vessel reactions to these different blood gases were seen as serving the dual function of meeting metabolic requirements of the retina and also reducing fluctuations in perfusion pressure such as those associated with postural changes.

Anderson, Saltzman, and Frayser (1967) studied changes in arterial CO_2 tension and retinal vessel size with oxygen breathing. They were concerned the constrictions with pure oxygen breathing might have been a result of reduced pCO_2 instead of oxygen itself. They photographed the retinas of normal young males and found pure oxygen at three atmospheres pressure constricted arteries by 10.2 percent and veins by 16.2 percent. Measures of pCO_2 actually showed a small increase during oxygen breathing. Hyperventilation during air breathing at normal atmospheric pressure led to a significant reduction of pCO_2 (38.4 to 27.4 mm Hg) and an increase in pO_2 (95 to 106 mm Hg). This hyperventilation caused a much smaller constriction of retinal vessels than occurred for pure oxygen, but the change was not significantly different from zero. The conclusion was that hypocapnia did not produce substantial constrictions of retinal vessels.

Dollery, Bulpitt, and Kohner (1969) provided a theoretical discussion of oxygenation of the retina from the retinal and choroidal circulations at normal and increased arterial oxygen tensions. They concluded that under increased oxygen tensions the choroidal circulation could supply almost the entire retina with oxygen. In fact, they suggested the constriction of the retinal vessels with oxygen breathing is a response to the oxygen levels provided by the choroidal circulation. As will be discussed later,

empirical research indicates deep inner layers of the retina do not obtain oxygen from this choroidal source in such quantities during hyperoxia (Riva, Pournaras, and Tsacopoulos, 1986).

Frayser et al. (1971) measured changes in retinal vessel size and changes in retinal blood flow as a result of different lengths of exposure to altitude of nine Canadian Armed Forces members ranging in age from 20 to 40. A series of retinal photographs were taken 2 hours, 5 days, and 5 to 7 weeks after reaching 17,500 feet on Mount Logan in the Yukon Territory (Canada) with baseline studies carried out at an altitude of 2,600 feet. Transportation from 2,600 feet was by plane and took approximately 45 minutes. Retinal mean circulation time was estimated from densitometric analysis of sequential photographs taken following the intravenous injection of six ml of 5 percent fluorescein. Retinal arterial and retinal venous blood oxygen saturation were estimated photometrically.

Frayser et al. (1971) found arterial diameter increased 18.2 percent and venous diameter increased 20.5 percent 2 hours after reaching 17,500 feet. Arterial diameter increased 23.7 percent from baseline and venous diameter increased 27.6 percent 5 days after reaching 17,500 feet. Mean retinal circulation decreased from 4.9 seconds at base camp to 3.6 seconds after 2 hours at altitude and decreased to 3.5 seconds after 5 days at altitude. Retinal blood flow increased 89 percent 2 hours after reaching 17,500 feet. Retinal blood flow increased 128 percent 5 days after reaching 17,500 feet. Personnel who remained at altitude for 5 to 7 weeks showed similar retinal circulation times and vessel diameter changes as were observed at 5 days. Retinal blood flow, however, showed a significant decline from measurements made at 5 days at altitude to measurements made after 5 to 7 weeks at altitude. The large increase in blood flow at 2 days and at 5 days occurred despite a substantial hypocapnia ($pCO_2 = 24$ mm Hg) that they claimed on the basis of Hickam and Frayser (1966) would reduce retinal flow by approximately 40 percent in an individual at normal oxygen tension. Although no discussion of this hypocapnia occurred, it presumably resulted from an increased respiration rate at altitude.

Kobrick and Appleton (1971) assessed effects of extended hypoxia on visual performance and retinal vascular state. Eight healthy soldier volunteers were used. They ranged in age between 18 and 25 and had normal near and far acuity, normal stereopsis, and normal peripheral vision. Dark adaptation, CFF, near and far acuity (Orthorater), depth perception, and stereopsis (Orthorater) were measured at sea level and after 1, 18, 24, and 48 hours of exposure to an altitude of 15,000 feet in a decompression chamber. Retinal examinations and fundus photographs were made at sea level and after the final testing of visual and other functions at 48 hours. Fundus photographs were superimposed and it was found

enlargement of retinal vessels occurred following 48 hours of hypoxia with some changes greater than 100 percent. None of the vessels measured showed constriction. Enlargements in vessels still were present 1 hour following return to sea level although this appears to have been noted in a clinical examination and not as a result of fundus photography. No retinal hemorrhage or edema was found as a result of altitude. Changes occurred in CFF, dark adaptation, and peripheral visual response as a result of hypoxia and these are described in other sections of this report.

Wolbarsht, White, and Anderson (1973) compared the diameters of veins and arteries in the retina while breathing air at sea level and while breathing pure oxygen at 31,000 feet. No differences were expected, given that the oxygen tensions in the two situations nearly were the same, and no differences were found.

Rennie and Morrissey (1975) used fundus photography to assess retinal changes in 15 Himalayan climbers. At 19,300 feet there was observed vascular engorgement with tortuosity.¹ Arteries increased in diameter by 24 percent and veins by 23 percent over sea level measures. One-third of the climbers had retinal hemorrhages, but none of the Sherpa guides who lived at high altitude did.

Schumacher and Petajan (1975) found retinal hemorrhages in 36 percent of 39 subjects exposed to altitudes of 14,200 feet or more. Rapid ascent and strenuous exertion tended to increase hemorrhages. A direct relation existed between headache frequency at altitude and hemorrhages at altitude. A striking direct relation existed between headache severity at altitude and hemorrhages at altitude.

Shults and Swan (1975) studied retinopathy following exposure to altitude in six of eight members of an ill-fated climbing expedition who attempted to climb an Argentine peak. Two members of a four-man summit attempt died and the two survivors had incredible hallucinations that included a mountain patrol whom they believed were there to rescue their missing colleagues. Two of three members who had climbed to 17,600 feet developed retinal hemorrhages and the three members who climbed to highest altitudes (19,600 and 22,600 feet) all developed retinal hemorrhages. Dilation of retinal vessels with hypoxia combined with exercise-related reduced intraocular pressure and valsalva maneuvers associated with climbing efforts were seen as contributing to hemorrhage development. Two of the members with hemorrhages developed permanent paracentral scotomas.

¹ Tortuosity is the bending of normally "straight" vessels that reflects length increases that accompany widening in the enlarged vessel.

Wiedman (1975) studied high altitude retinal hemorrhage in four individuals and noted these hemorrhages typically do not occur in the macular area. The high arteriovenous transit time in the fovea compared to the peripheral retina was seen as preventing a hypoxic "decompensation" of vascular epithelium that may account for increased capillary permeability and peripheral retinal hemorrhages.

Clarke and Duff (1976) studied mountain sickness, retinal hemorrhages, and acclimatization on Mount Everest. They found the incidence of hemorrhages to be 4 out of 6 for new climbers, but found only 2 cases among the 14 climbers who had made previous visits to altitudes above 6,000 meters. They found only 2 cases among 75 Sherpas. They discuss what appears to be an acclimatization effect that lasts for long periods between exposures to high altitudes. It could also be that only the climbers who do not develop hemorrhages return for another climb. This could be because of the associated severe headaches (Schumacher and Petajan, 1975).

Landers (1978) demonstrated the choroidal vessels provided normal levels or greater-than-normal levels of oxygen to the inner retina when the retinal artery was obstructed if the animal breathed 100 percent oxygen at normal atmospheric pressure. Measured oxygen levels near the retina and the electroretinogram (which had been severely reduced) returned to normal with oxygen breathing.

Houston and McFadden (1979) studied long-term effects of altitude on the eye by following up the subjects who developed hemorrhages in the Mount Logan High Altitude Physiology Study (Frayser et al., 1971). After 2 years, they found perimetry and Amsler grid testing showed no abnormalities in 16 individuals whose hemorrhages were not in the premacular region. Of the five who did have premacular hemorrhages, three had a persistent scotoma which was noticeable to two and asymptomatic for the third. One subject who had cotton-wool spots after the earlier study was found to have several small scotomas which were believed to represent persistent nerve-fiber-bundle defects.

McFadden et al. (1981) studied retinopathy in 28 men and 11 women who spent varying amounts of time at an altitude of 5,360 meters prior to examination. Increased vessel tortuosity, engorgement, and disc hyperemia were found in all subjects. More than half developed retinal hemorrhages. Unlike groups that spent eight to 10 days climbing to 5,350 meters, the group flown to 5,350 meters did not display hemorrhages at initial testing, although five (41 percent) did later develop hemorrhages and this suggested some minimal period at altitude is necessary for retinal hemorrhages to develop. This probably accounts for the result that

studies of the effects of brief hypoxia in decompression chambers seldom produce retinal hemorrhage.

McFadden et al. (1981) also found exercise at altitude produced more hemorrhages than occurred during periods of non-exercise. Exercise at sea level never led to retinal hemorrhage. The explanation given was exercise at altitude increases tissue hypoxia "unlike work at sea level." Fluorescein normally does not pass the blood-retina barrier, but in eight of 20 subjects tested, fluorescein leakage was found in the area of the optic disc. Typically, there were no lasting visual disturbances associated with these retinal hemorrhages and they typically cleared up during the stay at altitude. The authors also reported a remarkable drop in blood saturation during sleep at altitude. This fits with other evidence that brain requirements for oxygen are reduced greatly during sleep, namely that the habitual smoker does not need his regular nicotine boost of cerebral blood flow during sleep and can go all night without having a cigarette (Dyer, 1986).

Sutton et al. (1980) conducted studies of the retina of four subjects who spent 24 hours decompressed to an altitude of 14,500 feet in a low-pressure chamber. Subjects also performed a maximal progressive exercise test to exhaustion on a bicycle ergometer. None of the subjects experienced any visual symptoms and the fundal examinations indicated no hemorrhages or fluorescein leakage. Studies of the visual field were not conducted, which was unfortunate, given that headaches apparently were experienced along with other symptoms of mountain sickness. The strong correlation between headaches and hemorrhages found by Schumacher and Petajan (1975) and the well-known correlation of headaches and migraine scotomata, both suggest efforts of the visual system to cope with field defects may produce headaches. This quite possibly could occur through unusual adjustments of the ocular muscles aimed at compensation for visual field loss.

Kramar et al. (1983) assessed the effects of altitude (3,050 to 4,250 meters) during a mountain climb on various ocular functions and other physiological variables in seven females ranging in age from 23 to 53. Retinal examinations showed moderate arterial and venous dilation in younger subjects while only mild dilations were observed in 35- and 40-year-old members. No changes in retinal vessels were observed in the 53-year-old. Two of the three summit climbers developed retinal hemorrhages and these were the three youngest members of the expedition.

Plewes and Farhi (1983) studied peripheral circulatory responses to acute hyperoxia in seven anesthetized dogs. Pure oxygen at atmospheric pressure was administered and blood flow at various organs was measured. Cardiac output decreased by 14 percent, renal blood flow dropped a significant 20 percent, and other intra-abdominal organs did not show changes in blood flow.

No changes were noted in skeletal muscle. Total cerebral blood flow did not change significantly, although there were significant decreases to caudate nucleus (-12 percent), cerebellum (-15 percent), mesencephalon (-20 percent), vermis (-11 percent), hippocampus (-15 percent), and retina (-27 percent). This large change for the retina undoubtedly reflects the large constriction of retinal vessels to oxygen that was found by Dollery et al. (1964) and others.

This unusual constriction of retinal vessels to hyperoxia can lead to retinopathy even as hypoxia can. Herbststein and Murchland (1994) described a visual field defect associated with a dense opaque swelling in the retinal nerve-fiber layer in a healthy 44-year-old who accompanied patients receiving treatment for multiple sclerosis in a hyperbaric chamber and who, on two occasions, inhaled oxygen from a spare mask for 1 hour at two atmospheres pressure. Ischemia from vasoconstriction was seen as the probable cause of this "cotton-wool spot." A history of migraine scotomata in this subject suggested individual differences may exist in susceptibility to vasoconstrictive retinal vascular problems during hyperbaric oxygenation.

Riva, Grunwald, and Sinclair (1983) used the technique of laser Doppler velocimetry to study the effect of pure oxygen breathing on retinal blood flow in normal human subjects. Fundus photography was used to assess changes in the diameter of retinal vessels. They found 5 minutes of breathing pure oxygen led to a 53 percent decrease in maximum centerline speed of red blood cells, vessel diameter decreased by 12 percent, and retinal blood flow decreased by about 60 percent. They calculated on the bases of these data that retinal blood volume was decreased by 45 percent as a result of breathing pure oxygen.

Grunwald et al. (1984) used the same blood-flow-measurement method and studied the effect of breathing pure oxygen on retinal blood flow in normals and in patients with background diabetic retinopathy. Normals averaged a 17 percent decrease in vessel diameter and a 63 percent decrease in blood flow. Patients showed significant differences from normals with only a 9 percent decrease in vessel diameter and a 36 percent decrease in blood flow as a result of oxygen breathing.

Riva, Pournaras, and Tsacopoulos (1986) studied regulation of local oxygen tension and blood flow in the inner retina of miniature pigs during breathing of 100 percent oxygen. Using oxygen-sensitive microelectrodes placed adjacent to arteries and laser Doppler velocimetry, they determined that PO_2 diffusing from large retinal arteries actually controlled artery constriction and limited blood flow. Their data also suggested that diffusional shunting of oxygen from retinal arteries to nearby veins could explain the increase in venous oxygen saturation during 100 percent

oxygen breathing that previously has been reported by others and pointed out this would not mean that tissue oxygen levels were elevated similarly. They found that retinal periarteriolar PO_2 always was higher than the PO_2 in the outer retina. This casts doubt on the hypothesis suggested by Dollery, Bulpitt, and Kohner (1969) that oxygen diffusing from the choroid is responsible for the constriction of the arteries during hyperoxia. The unexpectedly low levels of PO_2 in the outer retina may indicate that oxygen consumption by the photoreceptor-pigment epithelium complex increases during hyperoxia.

Kylstra et al. (1986) studied the relationship between pressure in retinal vessels and the diameter and tortuosity of the vessels. They concluded that at lower pressures, diameter changes were the better index of pressure changes. On the other hand, at higher pressures tortuosity was the better index. As described earlier, tortuosity is the bending of normally "straight" vessels that reflects increases in length of the enlarged vessel.

Conclusions and research needs

The large increases in vessel size and blood flow as a result of low oxygen levels prevent drops in visual performance until hypoxia reaches levels that the vascular changes cannot compensate. However, changes in the blood volume of the eye with these vascular changes are not insubstantial, as is discussed further in the next chapter. In regulating oxygenation of the retina and associated tissues, these vascular changes may operate to deregulate dioptric or other characteristics of the eye, simply because of the mechanical effect of large blood volume changes.

Although hyperventilation and associated hypocapnia were seen to reduce blood flow by 40 percent (Frayser et al., 1971; Hickam and Frayser, 1966), measures of vessel changes with hyperventilation typically were small (Anderson, Saltzman, and Frayser, 1967). Hypocapnia effects on vessel size and blood flow might benefit from additional research. The new laser Doppler velocimetry methods would appear to hold promise for such research.

This review typically has shown that one or another respiratory condition had been neglected in research on a visual performance such as the CFF or on a related dependent variable such as the standing potential of the eye. The only such omission noted in this review of the effects of hypoxia and related conditions on vessel size and blood flow was research on the effects of carbon monoxide. It would appear a comparison of the effects on vessel size and blood flow of comparable reductions in oxyhemoglobin as a result of hypoxic and hemic hypoxia would be important. In other words, would reduction of the availability of blood oxygen due to a COHb level of 15 percent have similar effects on the blood vessels

as an 85 percent blood oxygen saturation resulting from breathing a low oxygen mixture? If there were differences, it might indicate the important role of hemoglobin without associated oxygen (or carbon monoxide) in dilating the retinal vessels and increasing blood flow to the retina. Such differences, if found, might help account for large differences in the effects of the two types of hypoxia on visual performance that have often been found.

Chapter 13

Intraocular pressure

Simple changes in barometric pressure from increases and decreases in altitude or from exposure to decompression chambers or hyperbaric chambers might be expected to produce changes in pressure within the eye, even without any influence of the changed oxygen tensions that usually result. Regardless of the source, any substantial elevation of ocular pressures might induce visual field loss as occurs in glaucoma with dangerous consequences for aviators. The consequences of lowered ocular tension would appear to be less serious, but eyeball length or shape might change with possible effects on ocular refraction, including astigmatic changes. Several investigations of the effects of altitude, hypoxia, hyperoxia, hypocapnia, and hypercapnia on intraocular pressure (IOP) have been undertaken and the often-contradictory results are reviewed in this chapter.

Wilmer and Berens (1918) measured the IOP of 14 men in a low pressure chamber and found no correlation between the IOP and arterial blood pressure, lowered oxygen tension, or various cardiovascular changes. They promised a later detailed report which was not found and may not have appeared. The probable altitudes of decompression were 15,000 and 20,000 feet, given that these altitudes frequently were used in their other decompression experiments on visual performance.

According to Mercier and Duguet (1950), Bardenzellu (1929) found no changes in the IOP of mountain troops on winter maneuvers at 2,000 meters. According to McFarland, Evans, and Halperin (1941), Goldmann and Schubert (1933) measured the IOP of two of their subjects and found no change as a result of decompression.

On the other hand, and, again according to McFarland, Evans, and Halperin (1941), Furuya (1936a) measured the IOP of six subjects in a low pressure chamber and nearly always found increases in ocular tension at altitudes above 13,000 feet. As McFarland, Evans, and Halperin (1941) stated, "The effect was more marked in sympathicotonic than in vagotonic persons. During continued exposure at a given altitude the tension tended to recede toward its original value. Immediately after "descent" the tension dropped further, then gradually rose to its original level in about thirty minutes." According to Cooke (1970), Furuya (1936a) found the increase in ocular tension was reduced noticeably when subjects breathed oxygen during decompression.

Buscalossi (1938), according to McFarland, Evans, and Halperin (1941) and Mercier and Duguet (1950), also found an increase in ocular tension of 12 subjects exposed to low pressure in a decompression chamber at altitudes from 3,500 to 4,500 meters. These changes were found to be similar to concurrent changes in the arterial pressure. As McFarland, Evans, and Halperin (1941) stated, "It increased during the simulated ascent and then decreased toward its original value during maintenance of the low pressure for fifteen minutes. No noticeable variation occurred during "descent." The amount of elevation of the ocular tension was proportionate both to the "altitude" reached and the rate of "ascent" and was of an order of magnitude of several mm of mercury."

Pinson (1940) measured the pressure in rabbit eyes as the animals were decompressed to altitudes of 30,000 feet or more and recompressed to sea level. They used a manometer that actually was inserted into the vitreous humor. The changes that occurred typically were small reductions of the IOP during returns to sea level.

Bietti and Lo Monaco Croce (1941), according to Cooke (1970), conducted a study with 15 subjects and reported an average IOP increase of about four mm Hg when subjects were exposed to an oxygen poor breathing mixture equivalent to an 18,000 feet altitude without decompression. However, wide differences were reported in these IOP changes among their subjects.

Mercier and Duguet (1950) reported results of a study they conducted with Bailliart on seven subjects decompressed to 6,000 meters. After 15 minutes at "altitude", two showed practically no change in the IOP. The other five showed a rise of the IOP averaging about 9 mm Hg, with one of these subjects showing about a 14 mm Hg rise in the IOP. The increased tension apparently disappeared in these subjects when they returned to ground level.

Giardini and Swanljung (1951) found cats exposed to an 8.5 percent oxygen mixture showed a significantly larger breaching of the blood-aqueous barrier than cats breathing air. Fluorescein was injected intravenously and the time to its appearance in the aqueous humor was typically 2 to 3 minutes earlier in the hypoxic animal than in the normal animal. This confirmed an earlier finding by Giardini and Nizetic (1949) on guinea pigs who were subjected to a much more severe hypoxia resulting from breathing 4.16 to 5.52 percent oxygen. Increased permeability of the capillary walls of the ciliary body was hypothesized as the basis for this change in permeability of the blood-aqueous barrier with hypoxia. These increases in passage of fluorescein into the anterior chamber with hypoxia were judged by Bietti (1953) to be highly relevant to IOP changes with hypoxia. This may have been a

factor in the increased sodium concentration of the aqueous humor during hypoxia reported by Carapancea et al. (1967).

Giardini (1952) also studied the permeability of the blood-aqueous barrier to fluorescein in man as a function of hypoxia. According to his English abstract, 10 subjects were exposed to an oxygen mixture of 10 percent. Fluorescein concentration in the aqueous humor was increased significantly compared to a control test performed in air. This increased permeability was reversible even at high altitudes. This apparently meant that fluorescein leakage was reduced to prehypoxia levels upon a return to a normal atmosphere.

Newton et al. (1963) exposed men to a 30,000 feet altitude while breathing 100 percent oxygen for approximately 30 minutes, and found no changes in facility of aqueous outflow or the IOP at altitude or upon return from altitude. However, a slightly higher than sea level oxygen tension would exist when pure oxygen was breathed at 30,000 feet and hypoxia may be critical to IOP changes.

Mercier et al. (1964) measured the effects of decompression to 3,000 meters in groups of nontreated and treated patients with glaucoma. They found the IOP decreased in both groups at altitude (3.5 and 2.5 mm Hg for nontreated and treated subjects, respectively) and further decreased upon return to normal altitude (an additional 2.5 and .4 mm Hg for the two groups, respectively). Aqueous outflow rates remained constant and a reduction of aqueous humor secretion because of hypoxia was judged to be the basis for this reduction of pressure. They also noted acetazolamide appeared to enhance the hypotonic effects of hypoxia on the IOP. For one glaucomatous patient being treated with acetazolamide, the IOP was 34 mm Hg at ground level, 27 mm Hg at 3,000 meters, and 20 mm Hg an hour after returning to ground level.

Neuschuler and Palombi (1966) studied the effects of hypoxia on the IOP in 20 subjects. Subjects breathed mixtures of from 8 to 12 percent oxygen. According to their English-language abstract, they found a constant increase in the IOP. To determine the reasons for the rise, 14 of the subjects were studied tonographically. The results indicated increased production of aqueous humor, increase of its defluxion, decrease in defluxion resistance, and a decrease of scleral rigidity. It was not stated in the abstract, but apparently the increase in aqueous production overrode its increased "defluxion."

Carapancea et al. (1967) provided a discussion of changes in the concentration of sodium in the blood and aqueous humor of rabbits following a brief decompression to an equivalent of 9,000 meters. Serum sodium showed a significant decrease (352 mg percent to 311 mg percent) while sodium in the aqueous humor significantly increased (329 to 358 mg percent). This increase of sodium in the

aqueous was seen to "cause a proportional increase in the amount of aqueous humour, resulting in hypertonic retention of the aqueous humour that will bring about intraocular hypertension." No measures of the IOP were reported in this rare English-language report from these prolific Rumanian researchers.

Kaskel, Ruther, and Fink (1969) studied the relationship between the IOP and the arterial pressure and "minute volume of the homolateral carotis communis" in rabbits. Their English-language summary indicated arterial blood pressure was correlated strongly with the IOP ($r=.85$). Minute volume added to the multiple regression, but contributed only a small amount compared to arterial pressure.

Cooke (1970) found decompression of dogs to high altitudes led to sharply increased arterial pressures which were correlated with the IOPs that doubled at 45,000 feet and nearly tripled at 80,000 feet compared to sea level. This occurred during air breathing. Both arterial and ocular pressure remained low when oxygen was breathed during decompression to 45,000 feet. The IOP also increased sharply during decompression to 80,000 feet with oxygen breathing, but at this altitude even pure oxygen provides a severe hypoxic stimulus, unless there is pressurization of the gas.

Cooke (1971) carried out additional observations on dogs at near vacuum pressures and while breathing pure nitrogen. In both instances, there were sharp increases in the IOP which, as in Cooke (1970), followed sharp increases in the arterial and venous pressures.

Kaufmann, Schotte, and Holtmann (1971) studied ocular tension during controlled hyperventilation in 10 healthy young students. Alveolar and arterial oxygen and CO_2 tensions were recorded along with blood pH, blood pressure, and pulse rate. These measures occurred before, during, and after hyperventilation. Ocular tension was measured with a Schiøtz tonometer using the 5.5 g weight. Hyperventilation was carried out at a rate that maintained alveolar CO_2 at a constant level of 23.6 Torr. The IOP significantly decreased from an average of 5.6 Schiøtz units (15.6 mm Hg) during normal ventilation to 6.7 Schiøtz units (12.9 mm Hg) during hyperventilation. Significant correlations were found between the IOP and arterial oxygen ($r=-0.30$), between the IOP and arterial CO_2 ($r=+0.53$), and between the IOP and arterial pH ($r=-0.58$). No significant changes were found in blood pressure or pulse rate. The direct relationship of blood acidity to the IOP was contrary to the finding of a hypotonic effect of blood acidity by Bietti (1972) which is discussed below.

Kaufmann, Schotte, and Holtmann (1971) found every one of their 10 subjects showed a drop in the IOP during hyperventilation and an increase in the IOP following return to normal respiration.

However, large individual differences in the amount of these changes were found, ranging from less than one Schiotz unit to more than two Schiotz units. This research did not look at hypoxia, but it does show when hypoxia is accompanied by hyperventilation as it frequently is (e.g., Frayser et al., 1971), the IOP can be expected to drop. The decrease in the IOP was viewed by Kaufmann, Schotte, and Holtmann as the result of a change in ocular perfusion, presumably, due to constriction of retinal vessels.

Carapancea, Stefan, and Udrescu (1971) measured changes in the IOP of 12 hyperopic aviators before and after decompression to an altitude of 5,500 meters. Average IOP changed from 19 mm Hg at normal altitude to 21 mm Hg at 5,500 m. This change was highly significant. They also discussed that this increased IOP with altitude caused changes in ocular accommodation, especially for the far-sighted aviator.

Bietti (1972) reviewed a large body of research on the IOP, much of which was conducted by Bietti and his colleagues. This research indicated it was the blood-acidifying effect of acetazolamide that produced the reduction of ocular pressure that reliably follows administration of this drug. Calcium chloride and ascorbic acid were found to produce similar effects on blood pH (or blood alkali reserve) and IOP to the effects produced by acetazolamide.

According to Bietti et al. (1975), Benedikt, Zirm, and Harnoncourt (1974) found acetazolamide produced its hypotonizing effect even when the blood acidity was reversed by infusion of sodium bicarbonate. However, Bietti et al. (1975), found a large infusion of sodium bicarbonate induced IOP changes because of changes in the osmolarity of the blood. Thus, the fact that ocular pressure was reduced by Benedikt, Zirm, and Harnoncourt (1974), despite the elimination of blood acidosis, was not counter to Bietti's claim there is a causal relationship of blood acidosis to low ocular pressure.

Kaufmann, Kluxen, and Baumgart (1973) studied the behavior of ocular tension and rigidity during experimental extensions of the functional dead space. These respiratory manipulations produced a marked increase in arterial CO_2 from 34.5 mm Hg to 45.4 mm Hg. Blood pH shifted from 7.45 to 7.39 and arterial oxygen dropped from 105.7 mm Hg to 74.0 mm Hg. Arterial blood pressure changed from 130/70 to 145/80. Ocular tension increased from 7.0 Schiotz units (12.2 mm Hg) to 6.0 Schiotz units (14.6 mm Hg). The coefficient of rigidity changed from 0.023 to 0.015. Although oxygen tension was seen to modulate the ocular tension changes, the increased CO_2 level was viewed as the prime cause of the ocular tension increase.

This increase in the IOP found by Kaufmann, Kluxen, and Baumgart was accompanied by an increase in blood acidity. This was

contrary to the predictions of Bietti (1972) who found blood acidification from several sources all led to a reduction of the IOP. However, it may be that CO₂ and pH changes were not the basis of this IOP increase. It may have been a result of the substantial increase in arterial blood pressure that also occurred.¹ A replication of this research is needed with oxygen added to the dead space breathing mixture (or use of some other means for increasing CO₂ while holding oxygen tension constant) in order to prevent the confounds of hypoxia and the blood pressure increase.

Krupin et al. (1977) found a sharply increased IOP following topical application to the rabbit eye of nitroprusside, or azide both of which promote guanylate cyclase activity. This increased IOP was viewed as the result of increased production of aqueous humor which in turn was viewed as a result of activation of guanylate cyclase activity in the ciliary body. These results are included in this review of oxygen effects because of the potent effect of intravenous azide on the standing potential (SP) of the eye and the strong interaction of that azide-produced SP increase with oxygen in the eye (Noell, 1952). Also, there are the sharply opposite effects of acetazolamide and azide on aqueous production and on the SP, and the many parallel effects of hypoxia and acetazolamide on vision-related processes. These suggest possible parallels between effects of hyperoxia and azide on vision and its ocular bases.

Carapancea (1977) discussed changes in the IOP and in the blood of the rabbit and man at their extreme limits of hypoxia. The French-language report included an English abstract from which the following results were obtained. Sodium, calcium, and Vitamin C all were seen to increase in the aqueous humor as a result of decompression in the rabbit. The rabbit and the human showed similar biochemical changes in the blood during hypoxia and a small, but significant elevation of the IOP also was found in both species. The assumption was made that changes in the aqueous humor were similar in man as in the rabbit and these led to increased volume of the aqueous with one direct result being an increase in the IOP.

Kielar et al. (1977) studied the effects of changes in inspired CO₂ and arterial CO₂ on the IOP. Subjects were seven healthy male volunteers. In a three-phase experiment, they first breathed a gas mixture of 5.8 percent CO₂, 24.6 percent oxygen, and 69.6 percent

¹ On the other hand, it may be that increased blood acidity causes a reduction in IOP because blood acidity causes hyperventilation or is associated with the cause of hyperventilation. The subsequent hypocapnia that results from hyperventilation may be the actual stimulus for lowered IOP (see the review of Kielar et al. (1977) later in this chapter).

nitrogen for 10 minutes. This caused a rise in arterial CO_2 from 35.6 to 43.4 mm Hg with the bulk of this increase occurring at the first measurement at the third minute. Blood pH dropped slightly from 7.389 to 7.344 and the bulk of this change also occurred in the first 2 minutes. The IOP was found to show an increase of about 1.5 mm Hg at the first measurement at 3 minutes, but then it declined to initial values at the end of the 10-minute period.

In Phase 2, the gas mixture then was rebreathed by the subject for 6 minutes and this caused a further rise in arterial CO_2 to 54.4 mm Hg and a further drop in blood pH to 7.258. The IOP showed a sharp (though statistically insignificant) rise from about 16 mm Hg to 20 mm Hg with the sharpest rise occurring from the second to fifth minute of this rebreathing phase.

The subject then was allowed to breath normal air (recovery phase). Arterial CO_2 dropped sharply and blood pH rose sharply, but even after 16 minutes these had not quite returned to initial values that preceded the start of the experiment. A remarkable drop in the IOP occurred as a result of this return to normal air. At the first measurement of the IOP 2 minutes after subjects resumed breathing of normal air, the IOP had dropped from the 20 mm Hg level at the end of rebreathing (Phase 2) to less than 14 mm Hg. This was considerably below the 16 mm Hg IOP measured prior to the beginning of the experiment. The IOP remained at about this same lower-than-normal level during the 16 minutes of recovery.

In a second experiment, Kiellar et al. (1977) had subjects hyperventilate for 7 minutes while CO_2 was added to the breathing mixture in order to maintain a constant arterial CO_2 . The IOP was measured before, during, and after hyperventilation and it was found hyperventilation and recovery had almost no effect on the IOP when the blood CO_2 was held constant.

In discussion of their results, Kiellar et al. (1977) indicated that changes in inspired CO_2 appeared to be the critical factor determining the IOP changes with CO_2 decreases leading to sharp drops in the IOP and CO_2 increases leading to sharp increases in the IOP. Previous research was discussed which showed breathing of high CO_2 gas mixtures (10 percent) caused a sharp increase in ocular blood volume (e.g., Trokel, 1965). The changing CO_2 mixtures of Kiellar et al. (1977) may have had large vasodilating and vasoconstrictive effects that produced large changes in the blood volume of the eye and these in turn caused the large IOP changes by increasing the total volume of fluid within the eyeball.

Anderson and Farmer (1978) studied 10 patients undergoing repeated exposure to hyperbaric oxygen for the treatment of osteoradionecrosis and they measured the IOP following exposure to such environments. Their ages ranged from 51 to 69, with an average of 59 years. Snellen visual acuity, refractive error,

applanation intraocular tension, and corneal curvature of the patients were measured within 3 days of the first exposure and again at the end of the treatment regimen. This regimen consisted of breathing 98 percent oxygen for 2 hours while exposed to two atmospheres of absolute pressure. Forty exposures were given with one per day except Sunday. Oxygen was delivered by means of a head tent and the external portion of the eye was exposed directly to the hyperbaric oxygen.

Anderson and Farmer (1978) found a highly significant myopic shift for these patients which averaged -1.61 diopters and these changes are discussed more fully in Chapter 16: "Accommodation, myopia, and the crystalline lens". No significant shift in corneal curvature occurred and the 0.05-diopter average change in the cornea actually indicated a flatter cornea. Intraocular pressures decreased by only 0.8 mm Hg on the average and this was not significant. However, this failure to find long-term effects of hyperbaric oxygenation on the IOP does not mean that changes in the IOP may not occur during actual exposure to hyperbaric oxygen.

Chiou, Liu, and Trzeciakowski (1980) used a newly-developed cat model to study the mechanism of antiglaucoma drugs including acetazolamide. They found acetazolamide caused more than a 40 percent reduction of aqueous humor production 1 hour after administration, with little recovery of aqueous production 2 hours later. Unlike other drugs which reduced or increased outflow of aqueous humor, acetazolamide had little effect on outflow parameters over a 3-hour period following its administration.

Mapstone (1981) studied shallowing of the anterior chamber that occurs spontaneously and as a result of administration of drugs. Pilocarpine and phenylephrine were found to decrease significantly the anterior chamber depth by an average of 0.3 mm in 42 normal eyes. Similar changes in anterior chamber depth were found for patients with open-angle glaucoma and ocular hypertension. All subjects were 55 years or older. Mapstone concluded substantial acute variation in anterior chamber depth can occur in normal and diseased eyes.

Alder and Cringle (1985) studied the effect of breathing air and oxygen on vitreal oxygen tension in cats when oxygen electrodes were moved forward and backward in the vitreous to retinal locations of veins and arteries. Their results are discussed in Chapter 14: "Intraocular oxygen." The electrode was inserted into the vitreous through the temporal sclera at a point about 5 to 6 mm posterior to the limbus. The study is mentioned in this chapter on pressure changes with hypoxia because a relative movement between the electrode and the retina almost invariably occurred when respiratory gases changed, blood pressure changed, or intraocular pressure changed. These sometimes were substantial lateral movements that actually led to puncture of the retina. These

movements of the electrode relative to the retina thus would appear to be a result of changes in eyeball shape. Although the source of these movements was unknown, Alder and Cringle (1985) suggested they may have been due to retinal circulation changes and changes in blood volume.

Conclusions and research needs

The finding by Alder and Cringle (1985) of eyeball changes following a change in respiratory gases, blood pressure, or intraocular pressure also augurs for refractive changes during hypoxia, hyperoxia, hypocapnia, and/or changes in atmospheric pressure. A mechanism for such refractive changes during hypoxia (and following administration of acetazolamide) is discussed below. Such refractive changes would be expected to alter visual acuity, absolute sensitivity, contrast sensitivity, and field size. These possible refractive changes also could account for many of the contradictory findings in the literature on hypoxic effects on visual performance. The refractive change might improve target focus for an experiment with one target distance, but degrade target focus for an experiment with another target distance. These possible hypoxic refractive changes similarly could account for the frequent large individual differences in hypoxic and hyperoxic effects on sensitivity, acuity, etc., if the refractive change degraded (or improved) target focus for a subject with a close resting focus (Leibowitz and Owens, 1978), but improved (or degraded) focus for another subject with a distant resting focus.

Lassen et al. (1987) studied the effects of acetazolamide on cerebral blood flow (CBF) and on alveolar CO₂. Immediate effects of a 1-g oral dose of the drug were to increase cerebral blood flow by 40 to 50 percent at 3 hours. After 2 days, CBF had practically returned to normal, although two 500 mg doses of acetazolamide were taken each day for 10 days. Alveolar CO₂ tension showed only a small drop immediately following the initial 1-g oral dose of the drug, but over the course of 10 days of drug administration, alveolar CO₂ gradually dropped to 70 percent of the initial value. This indicated the drug produced a substantial and prolonged hyperventilation. Although their study was conducted at sea level, Lassen et al. (1987) discussed the probable benefits of such hyperventilation for boosting critical oxygen levels at altitude and thereby countering altitude sickness.

If the immediate boosts in CBF found by Lassen et al. (1987) have retinal counterparts,² the increased ocular blood volume would be expected to increase the IOP. On the other hand, acetazolamide

² This would be expected since retinal blood flow changes normally mimic CBF changes (Hickam and Frayser, 1966).

also reduces production of aqueous humor (e.g., Chiou, Liu, and Trzeciakowski, 1980) and typically lowers the IOP as a result. Hypoxia also increases ocular blood flow and volume (e.g., Hickam and Frayser, 1966) and hypoxia also may diminish aqueous production (Mercier et al., 1964). Thus a pair of conditions with potentially opposite effects on the IOP probably would exist following the taking of the drug acetazolamide and also would probably exist during hypoxia. These opposite effects may explain the many contradictory results in research on the effects of hypoxia on IOP. In some experiments increased blood volume may dominate and in other experiments the reduced aqueous flow may dominate.

The simultaneous increased vitreous pressure from dilated retinal vessels and diminished aqueous pressure from reduced aqueous volume probably would lead to a shallowing of the anterior chamber because of a forward movement of the lens/iris system (Mapstone, 1981). This probably would increase the lens-retina distance and produce an increased myopia and this may account for the small, but significant myopic shifts Ohlbaum (1969) found during hypoxia. Myopia, in turn, diminishes the extent of visual fields (Greve and Furuno, 1980) and transient myopic shifts could underlie both of the parallel effects of acetazolamide and altitude on peripheral visual fields found by Kobrick (1970).

Only ocular pressure shifts that would be expected to induce anterior chamber shallowing have been discussed. However, hyperventilation is a frequent consequence of hypoxia (e.g., Frayser et al., 1971; Livingston, 1944a; Ernest and Krill, 1971) and if hyperventilation-induced hypocapnia caused a retinal vessel constriction and reduced retinal blood flow as was discussed by Hickam and Frayser (1966), and if this reduced vitreous pressure, an opposite change could occur (if aqueous production remained largely unchanged or increased). Presumably, there would be an increase in anterior chamber depth and the lens/iris system would be moved closer to the retina, resulting in an increased hyperopia. If a reduced vitreous pressure existed, the ciliary activity associated with accommodation for near objects might have an increased effect on the cross-sectional area of the eyeball where the ciliary is attached and possibly eyeball length as well. Admittedly, this is largely speculation, but it appears enough "jigsaw puzzle pieces" are present to make research highly worthwhile that is aimed at identifying these possible changes in ocular pressure, ocular structure, ocular dimensions, and ocular refraction as a function of hypoxia and hypoxia-related respiratory conditions such as hypocapnia.

Since light levels influence oxygen consumption in the retina (e.g., Linsenmeier, 1986), and since local metabolic needs of the retina appear to control vessel changes (Hickam and Frayser, 1966), hypoxic vasodilation of the retinal vasculature would be expected to be greater in darkness. Blood volume increases and their

possible effects such as shallowing of the anterior chamber and refraction changes also might be expected to be greater in conditions of low retinal illumination than in conditions of high retinal illumination.

Chapter 14

Intraocular oxygen

Oxygen electrodes inserted into the eyes of animals allow measurement of oxygen tensions in ocular structures and fluids. These have provided data on oxygen distribution under hypoxic and hyperoxic respiratory conditions. Oxygen consumption in the eye also has been assessed with this methodology and one of the most interesting findings discussed below is that oxygen levels in and near the retina typically are lower during darkness than in light, indicating higher oxygen consumption when retinal illumination is low than high.

Krause and Goren (1956) studied the effects of hypoxia and hyperoxia upon the oxygen tension in the vitreous humor of the cat. Vitreous oxygen tension nearly was linearly related to atmospheric oxygen tension for atmospheric oxygen tensions from 114 to about 400 mm Hg (corresponding vitreous oxygen tensions were 29 to 125 mm Hg). Higher atmospheric oxygen tensions (to 745 mm Hg) produced smaller increases in the vitreous oxygen tension.

Jacobi and Driest (1966) measured oxygen levels in the anterior chamber and vitreous body of the living rabbit eye. The German-language article was not translated fully, but a range of oxygen tensions from 23 to 43 mm Hg were reported for the anterior chamber. In the central vitreous, oxygen levels of only two to five mm Hg were measured. Oxygen tensions measured in the vitreous at the peripheral retina increased to levels of 7 to 16 mm Hg and rose to 17 to 33 mm Hg at the "papillennah."

Kwan, Niinikoski, and Hunt (1972) moved small oxygen electrodes through rabbit eyes and recorded oxygen tensions within the cornea, aqueous humor, and anterior lens. Oxygen tension dropped sharply as the cornea was penetrated and the epithelium traversed. Oxygen tension continued to drop in the stroma, then rose sharply in the endothelium to a relatively high level in the aqueous humor that showed no changes across the anterior chamber. Oxygen tension then dropped sharply as the lens was penetrated and reached lowest levels in the anterior lens which was the most distant point into the eye that was measured. Anterior chamber levels averaged 72 mm Hg and this was somewhat higher than earlier research had shown or predicted.

Stefansson, Wolbarsht, and Landers (1983b) followed up a number of studies that had shown higher in vitro oxygen consumption in retinas in darkness than in light with an in vivo study of oxygen

consumption in rhesus monkeys in light and in darkness. An intraocular oxygen microelectrode was used to measure oxygen levels near the retina. Oxygen tensions dropped sharply in darkness and increased sharply in light, reflecting higher oxygen consumption in darkness than in light.

Alder and Cringle (1985) studied the effect of breathing air and oxygen on vitreal oxygen tension in cats when oxygen electrodes were moved forward and backward in the vitreous to retinal locations near veins and arteries. For veins there was little gradient between electrode locations close to the retina and more distant locations. However, a steep gradient existed for arteries with oxygen currents doubling as the electrode moved from 0.2 mm away from the artery to a point in near contact with the artery. The lack of difference between oxygen levels in the vitreous away from the retina and in the vitreous near veins held both when air was breathed and when oxygen was breathed. As would be expected, these equivalent vein and central vitreous values were substantially higher with oxygen breathing than with air breathing. They corresponded closely to the oxygen levels measured near arteries during air breathing. This apparently reflected that oxygen in solution in the plasma was providing most of the oxygen in the vitreous and that the hemoglobin in the veins remained nearly fully saturated with oxygen.

During pure oxygen breathing, Alder and Cringle (1985) found oxygen levels near arteries were elevated to levels several times levels of oxygen measured at these same locations during air breathing. These levels corresponded closely to the level of oxygen tension measured in the femoral artery. Much variability was found for electrodes at retinal locations intermediate to veins and arteries, but in at least one instance, the oxygen tension was substantially lower than at veins or further back from the retina in the vitreous.

As mentioned in the previous chapter, Alder and Cringle (1985) found movement of electrodes occurred when respiratory gases changed, blood pressure changed, or intraocular pressure changed. These sometimes were substantial lateral movements of the electrode that led to puncture of the retina. The source of these movements was unknown, but was suggested as being due to retinal circulation changes and changes in blood volume. These movements appear to be the result of changes in eyeball shape and suggest refractive changes also may occur during hypoxia, hyperoxia, or large changes in atmospheric pressure.

Alder et al. (1986) studied the vitreal oxygen tension gradients in the isolated perfused cat eye using methodology similar to that of Alder and Cringle (1985). Oxygen gradients were steep when the electrode was positioned near retinal arteries. However, when the electrode was more than one mm away from the

However, when the electrode was more than one mm away from the retina these gradients were very shallow. The results indicated the isolated perfused eye behaves similarly to the in vitro eye with respect to oxygen distribution and function.

Linsenmeier (1986) studied the effects of light and darkness on oxygen distribution and consumption in the cat retina by assessing oxygen tension at different levels of the retina in darkness and under different light conditions. Double-barreled oxygen microelectrodes were inserted into the optically intact right eye of anesthetized adult cats through a 15-gauge hypodermic needle inserted about 10 mm posterior to the limbus. One barrel measured oxygen tension polarographically and the other measured voltage. Animals were kept in a dark cage with light stimuli introduced via a fiber optic bundle to a mirror above the cat's eye. Levels of illumination up to one log above rod saturation were used.

Oxygen tension increased sharply as the electrode was positioned to increased depths of the outer half of the retina. No increase in oxygen tension was observed for the inner half of the retina or as the electrode was moved within the choroid. Oxygen tension in the outer half of the retina was substantially higher for light-adapted than for dark-adapted eyes and was proportional to light intensity up to saturation of the rods. Supra-saturating light levels prolonged the increase in oxygen tension beyond the duration of the light stimulus, although they did not increase the oxygen tension. Observations of oxygen tension in the inner retina indicated a decrease of oxygen tension during light adaptation in about half of the cases. Unlike outer retina responses, these inner retinal responses to light stimuli were slow. The results indicate light sharply reduces the requirement of the retina for oxygen (by about one-half) and that the dark-adapted retina is in a relatively oxygen-deprived state, making it highly sensitive to the changes in arterial oxygen tension produced by hypoxia.

Isenberg, Fink, and Shoemaker (1984) described a conjunctival oxygen monitor that can be used to indirectly monitor the carotid artery oxygen levels of patients. This has many advantages over current sensors that respond to oxygen levels of the skin. Although the correlations between these measures of oxygen tension from the conjunctiva and direct measures of arterial oxygen tension were not perfect (0.66 to 0.98 for different subjects), this noninvasive technique greatly reduces the need for invasive measures of arterial tension and could have many uses in research on oxygen and vision.

Conclusions and research needs

The somewhat surprising finding that an increase in retinal illumination reduces the retinal requirement for oxygen is probably

the dominant result of the research reviewed in this chapter. The increased requirement for oxygen of the dark-adapted retina undoubtedly explains the findings that changes in visual acuity with hypoxia (McFarland and Halperin, 1940) and changes in contrast sensitivity with hypoxia (McFarland, Halperin, and Niven, 1944) were much more likely to occur and were larger in conditions of low retinal illumination.

No research was found in which oxygen gradients were measured under conditions of hyperbaric oxygenation. Given the huge changes that hyperbaric oxygenation produced in persistence of vision following pressure ischemia (e.g., Carlisle, Lanphier, and Rahn, 1964), one would expect oxygen tensions throughout the vitreous would show dramatic increases under hyperbaric oxygenation even as they showed large increases with oxygen breathing at one atmosphere (Alder and Cringle, 1985).

Chapter 15

The pupil

With a normal range of from less than two mm to more than eight mm in diameter (Lowenstein and Loewenfeld, 1969), the pupil of the eye can alter the amount of light entering the eye by a factor of forty and pupil changes can have a large influence on absolute and differential visual sensitivity independent of retinal, photochemical, or other factors. If hypoxia or hyperoxia increased or decreased pupil size, these changes would produce an associated increase or decrease in visual sensitivity.

An increase of pupil size not only allows more light to enter the eye, it increases the spherical and chromatic aberration of the eye, and it has been shown recently that cycloplegia produces a small but significant decrement in contrast sensitivity under normal ambient conditions and a somewhat greater reduction in contrast sensitivity under glare conditions (Bachman and Behar, 1987). Thus, during moderate and high levels of illumination when the amount of light entering the eye is relatively high, increases in pupil size with hypoxia or hyperoxia would be expected to decrease visual acuity, contrast sensitivity, stereopsis, and other visual performances requiring contour discrimination and resolution. On the other hand, if decreases in pupil size were to result from hypoxia or hyperoxia, this would be expected to enhance these visual performances when retinal illumination is high.

Hypoxia and the pupil: Animal studies

Ury and Gellhorn (1939) found rabbits subjected to severe hypoxia (six to eight percent oxygen for 20 minutes) showed an increase in the threshold for the pupillary reflex dilation produced by painful stimulation of the sciatic nerve. However, they did not report any changes in pupillary size as a result of hypoxia.

Gellhorn and Levin (1945) studied cats and found a large dilation of the pupil above 20,000 feet and a further dilation as altitude increased to the point where animals were about to collapse. Using dogs, Hoorens (1948) reported that carbon-monoxide hypoxia, hypoxic hypoxia, and asphyxia all produced a marked dilation of the pupil. Hoorens believed this was due partly to a central neurogenic mechanism and partly to a purely peripheral one.

Kapp and Paulson (1966) studied pupillary changes induced by circulatory arrest in cats with one eye having the right cervical sympathetic nerve severed and the other pupil normal. Both pupils showed dilation when the aorta was occluded and both constricted upon restoration of blood flow. The denervated pupil started at a larger size but after 2 to 4 minutes, the two pupils dilated together. When both sympathetic and parasympathetic innervation of the same pupil were removed, dilation did not occur with circulatory arrest, but dilation did occur afterward when circulation was restored.

On the other hand, Jordanov and Ruben (1967) studied rabbits and human patients and found little or no dilation of the pupils until death, even when blood-oxygen saturations were extremely low. They made the point that current beliefs and documentation that dilation of the pupil was a reliable clinical sign of hypoxia needed to be revised.

Jordanov and Ruben (1968) studied the size of the pupil in rabbits at various oxygen partial pressures. Arterial oxygen was reduced by breathing pure nitrogen, by incomplete clamping of the tracheal canula, or by complete clamping of the tracheal canula. They found no increase in pupil size as hypoxia increased. In fact, they were more likely to find contraction with decreasing partial pressures of oxygen and to find dilation only occurring following death of the animals. They criticized current medical acceptance of pupil dilation as a symptom of hypoxia. These are the same authors as Jordanov and Ruben (1967).

Sohmer, Freeman, and Malachi (1986) looked at cortical potentials evoked by visual, auditory, vestibular, and somatosensory stimuli in as severe a hypoxia as could be maintained in cats without causing the animals to collapse. For some reason, there was a decrement in auditory evoked potentials at oxygen tensions (27 mm Hg; O_2 sat. 24 percent) that left visual, vestibular, and somatosensory potentials unchanged. With similar oxygen saturation, but even lower hypoxia ($pO_2=21.2$ mm Hg; 24.5 percent O_2 sat.), the visual evoked potential (VEP) actually was augmented instead of depressed as expected. The study is described in this chapter because this augmentation of VEPs was believed to have occurred because of a pupil dilation that was observed at these severe hypoxic levels which would augment the retinal stimulation.

Hypoxia and the pupil: Human studies

As discussed in Chapter 1: "Absolute sensitivity and dark adaptation," a number of studies have found significant decrements in absolute sensitivity as a result of low levels of hypoxia (e.g., McFarland and Evans, 1939). Through use of precise measurement procedures and trained subjects, these studies have identified

hypoxic decrements in sensitivity which are as small as a tenth of a log unit of illumination. However, such a 26 percent increase in target brightness (in actual units) required for target detection conceivably could be produced by a 12 percent reduction in the diameter of the pupil and this is less than a one-mm constriction of even the widest pupil. Some of the research on absolute sensitivity and hypoxia has avoided this possible confound of hypoxia-induced pupil changes by use of artificial pupils or use of a Maxwellian view which limits the "pencil" of light rays entering the eye to a diameter smaller than the pupil.

Other researchers working in the area of absolute sensitivity have directly observed the pupil or photographed it. Ernest and Krill (1971) observed the pupil or photographed it with infrared light in their research on absolute sensitivity and hypoxia. They reported hypoxia did not alter pupil size. According to McFarland and Forbes (1940), Bunge (1936) also measured the pupil during severe hypoxia and found minimal changes in pupil size that did not influence their sensitivity data. McFarland and Forbes (1940) did not discuss at what points in the adaptation cycle the pupil was measured or how it was measured by Bunge.

Other researchers used artificial pupils for only portions of their testing (Gellhorn, 1936a; McFarland and Forbes, 1940; Wald et al., 1942). They typically indicated that results did not differ between the two conditions, with the exception that more target luminance was needed to allow target detection with the artificial pupil.

On the other hand, Wald et al. (1942) illustrated some dramatic changes in absolute sensitivity at the onset of changes in oxygen tension (both decrements and increments) and these data illustrated in figures of the report occurred in testing conditions without an artificial pupil. One of the subjects who was tested without the artificial pupil showed an unusual increase in absolute sensitivity of nearly 0.4 log units when low oxygen was turned on and this persisted with only a small decline for the more than 10 minutes of low-oxygen breathing. With a return to normal air, this subject's threshold "overshot" to a value more than 0.2 log units above its baseline level during normal air breathing and finally returned to normal after about 5 minutes. Another subject when tested without an artificial pupil showed the more typical .3 log unit drop in sensitivity with low oxygen tension, but then showed a dramatic improvement in sensitivity over baseline (normal air breathing) levels when normal air breathing was resumed after hypoxia. This striking increase of sensitivity of more than half a log unit lasted for only a minute or two and was followed by a gradual return of sensitivity to baseline levels over 6 or 7 more minutes.

Unfortunately, Wald et al. (1942) did not discuss the possible pupil-change contributions to these unusual results, except to call

attention to the fact the displayed results occurred in conditions without artificial pupils. They regarded these unusual sensitivity shifts to be the result of respiration changes such as hyperventilation. However, even if this were the case, hyperventilation (and associated hypocapnia) may have caused these effects via changes in pupil size. It is remarkable, but despite the relative ease of measuring pupil size, and despite the ease of manipulating the independent variable of hyperventilation, no research was located that related hyperventilation to pupil size.

Furuya (1936b) may have provided the first study aimed directly at observing the effects of hypoxia on pupil size. According to the German abstract, Furuya used six subjects ranging in age from 18-30. He found hypoxia increased the size of the pupil for decompressions over 5,000 meters. The pupil continued to dilate as "altitude" increased above 5,000 meters. The pupil tended to return to its original size when subjects remained at the altitude for some period. Upon return to the original pressure, the pupil recovered quickly. Breathing oxygen during decompression prevented or moderated pupil changes.

Newsome (1971) studied the behavior of the pupil in complete darkness following 2 minutes of exposure to a bright stimulus field, such as the field typically used to produce light adaptation in studies of dark adaptation. Newsome found the pupil initially dilated at offset of the bright field, but then constricted almost to the small size it took while viewing the "bleaching" stimulus field. The pupil remained at considerably less than full dark-adapted size for nearly 20 minutes and appeared to be responding to the positive afterimage of the bleaching stimulus field. Given these dramatic changes in pupil size found by Newsome during the first 20 minutes of dark adaptation, it almost is inconceivable there were not large pupil fluctuations in other studies of dark adaptation such as the study of McFarland and Forbes (1940), since entoptic phenomena were present which actually interfered with target viewing (McFarland, Halperin, and Niven, 1944). It also is difficult to believe that these large fluctuations in retinal area did not produce major differences in sensitivity to dark adaptation targets and did not cause major changes in dark adaptation curves from the curves produced with artificial pupils.

Newsome (1971) also found Craik blindness induced while subjects were viewing the positive afterimage of the bleaching field eliminated the positive afterimage and the pupil constriction. This was the result of finger pressure on the eyeball (Craik, 1900, 1906) and leads to a relatively neutral perception of brightness, without any blackening of the visual field. The Newsome (1971) finding that Craik blindness prevented bright afterimages from being seen and also prevented their constriction of the pupil suggests that Craik blindness also will cause the pupil to dilate when it occurs during conditions of illumination that are

brighter than this "grey." Conversely, Craik blindness should cause the pupil to constrict when it occurs during conditions of illumination that are darker than this "grey." The large dilation of the pupil that has been reported just prior to unconsciousness in hypoxia (Gellhorn and Levin, 1945) and hyperoxia (Young, 1967) may in fact reflect total or near total diminution of retinal output because of "black out" from the general ischemia. No research on such probable effects of Craik blindness on the pupil was found.

According to Mercier and Duguet (1950), Züst (1940) found a reliable and rapid constriction of the pupil as a result of hypoxia in a study of 20 subjects conducted in a decompression chamber and also at Jungfrau Pass. Pupil behavior was studied in darkness and with surround luminances of 15 and 85 lux. A change from 400 to 3,000 meters caused the area of the pupil to decrease by 10 percent, 14 percent, and 15 percent at the three increasing levels of ambient illumination. The corresponding figures for 6,500 meters were 15, 32, and 24 percent. Large individual differences were found ranging from zero to 27 percent for the dark-adapted pupil. Return of the subjects to 400 meters produced dilation of the pupil, but generally not to original levels. Following the hypoxia-induced constriction of the pupil, they found increased sensitivity of the pupil to reflex changes under constant illumination.

According to Mercier and Duguet (1950), McFarland, Holway, and Hurvich (1942) studied the pupil using infrared photography in four subjects while breathing 17, 14, 12, and 10 percent oxygen. An initial substantial contraction first was observed at the onset of low-oxygen breathing which was followed by a gradual return to the initial value as exposure continued. Marked differences in this hypoxic response were found in their four observers, however.

Mercier and Duguet (1950) concluded from the studies of Züst and McFarland, Holway, and Hurvich that pupil constriction was a reliable correlate of moderate hypoxia (up to 7,000 meters). They noted numerous psychic and humoral manifestations accompanying hypoxia would tend to dilate the pupil and the constriction observed must reflect a true hypoxia effect to counter all of these dilations. They suspected the constriction was due to hypoxic disinhibition of a central "iridoconstrictor center."

Fuelling (1961) reported the pupil constricts during hypoxia, but provided no reference to the research that demonstrated this in his aviation medicine review of hypoxia effects. Given the above results of Züst (1940) and McFarland, Holway, and Hurvich (1942), one suspects the U.S. Air Force translation of the 1947 Physiopathologie Oculaire de l'aviateur (Mercier and Duguet, 1950) may have been the secondary source that led to Fuelling's hypoxic constriction conclusion.

Other studies have indicated dilation of the pupil with hypoxia. According to Bietti (1953), Bietti and Scano reported hypoxia increased the size of the pupil and also increased the speed of contraction and dilation to "adequate" stimulation.¹ They also found anisocoria (different-sized pupils in the two eyes) and a reduction of the amount and duration of pupillary contraction to light stimuli. Bietti and Scano also reported that with very low illumination and in severe hypoxia the pupil may become nonexcitable and may escape the well-known effects of an acoustic collateral stimulation (psychic restitution effect of Loewenstein). Bietti (1953) presented data showing severe hypoxia (20,150 and 24,800 feet) produced substantial differences in the pupil size of the two eyes (anisocoria), although these data originally may have come from the research of Bietti and Scano.

In a study of hypoxia effects on the central visual field (size of the angioscotomata), Evans and McFarland (1938) measured pupil changes and found small (typically one mm), but reliable increases for three of four subjects when the altitude was 17,000 feet or more.²

Mathew et al. (1985) examined a number of autonomic nervous system measures following a sojourn to 3,500 meters and found a 12 percent increase in pupil diameter on the third day following arrival at 3,500 meters. Repeated measures indicated this dilation declined almost to the sea level value as these young volunteers spent 3 weeks at altitude. This decline from day 3 onward suggests that if measures upon arrival at altitude had been made prior to the third day, they might have shown larger dilations than 12 percent. Interestingly, upon return to sea level, the pupil again showed an increase in size and took 2 weeks to return to initial sea level values.

Perhaps the most unusual report about hypoxia effects on the pupil was that of Duguet and Mercier (1951) who reported the pupil tended to dilate in light and constrict in darkness under hypoxia. According to Beside (1957), Duguet and Mercier found 55.5 percent of their subjects showed a contraction with darkness, 27.7 percent showed a dilation, and 16.8 percent showed no pupillary

¹ The "1948" Bietti and Scano report cited by Bietti (1953) was not found, apparently because of an incorrect reference.

² It is remarkable that McFarland and Evans (1939) a year later claimed that hypoxia-related "variations in pupil size were too small to be detected with a pupillometer" when referring to this same study of Evans and McFarland (1938).

reaction. In light, 50 percent showed a dilation, 18.8 percent a showed a contraction, and 31.2 percent showed no reaction.

Hyperoxia and the pupil

Behnke, Forbes, and Motley (1935) reported pupils were observed to be moderately dilated over the first 3 hours of oxygen breathing at a pressure of three atmospheres. Anisocoria was noted in one subject after 3 hours exposure with the right pupil dilated more than the left and the left temporal field showing a substantial contraction suggesting a left temporal hemianopsia. During the fourth hour in two of four experiments, there was a wide dilation of the pupils, but the pupils still reacted to light and accommodation. Dilation was a signal of impending collapse along with an abrupt rise of blood pressure, increased pulse rate, and facial pallor. According to the authors, all were symptoms that suggested hyperoxic stimulation of the sympathetic nervous system.

Kent (1966) measured pupil changes with an infrared pupilometer in his research on oxygen breathing effects upon night vision thresholds. "The range of variation in mean pupil diameter was no more than 0.2 mm for any subject measured during air-oxygen experiments at one atmosphere." Pupil measurements were not made during Kent's hyperbaric experiments.

Like Behnke, Forbes, and Motley (1935), Young (1967) reported dilation of the pupil preceded convulsions produced by long-term exposure to a hyperbaric atmosphere that was 86.6 percent oxygen. Pupil dilation was "measured" by observation of an attendant and was not noted as an early symptom of oxygen toxicity. Major symptoms of oxygen toxicity (severe nausea, incoordination, etc.) were not seen before subjects were at an oxygen depth of 25.9 FSW and pupil dilation itself was not seen until an oxygen depth of 33.7 FSW.

Conclusions and research needs

The paradoxical pupil responses to light during hypoxia of Duquet and Mercier (1951) and the conflicting reports of constrictions, minimal changes and dilations by other researchers, all indicate hypoxia effects on pupil size are complex and, in some instances, probably are mediated by anxiety or other factors. Since no studies were found which appear to have resolved this complexity, pupil changes with hypoxia appear to be ripe for additional research. Given that hyperventilation-mediated pupil changes may have been a factor in unusual sensitivity changes reported by Wald et al. (1942), hypocapnia effects on the pupil also should be investigated. The high probability of hypocapnic pupil changes also augurs for pupil changes if research were

conducted on the effects of hypercapnia. Possible effects of carbon monoxide (hemic hypoxia) on the pupil also need to be identified in humans.

Some of the contradictory results may reflect pupil changes associated with hypoxic changes in convergence and accommodation. Ohlbaum (1969) found a small but significant increase in myopia following hypoxia and an associated reduction of the AC/A ratio. Several studies of lateral phoria have noted increased esophoria when measured at a distance (e.g., Adler, 1945; Neely, 1951). The near vision pupil reaction (Lowenstein and Lowenfeld, 1969) would predict any hypoxic increases in accommodation and/or convergence would be accompanied by a constriction of the pupil and any hypoxic outward shifts in accommodation and/or convergence would be accompanied by a dilation of the pupil.

Mapstone (1981) described the influence of the pupil on anterior chamber shallowing following administration of pilocarpine. The iris operates to reduce this forward movement of the lens and it was claimed that midsized pupils would exert the maximum force against forward lens movements. No discussion of the effects of this forward pressure of the lens on pupil size was provided, but presumably this interaction of lens and pupil is not totally one sided. If forward lens movement occurs it may produce a change in pupil size and this would most likely be pupil dilation. It was discussed in Chapter 13: "Intraocular pressure," that there was a strong possibility that reduced aqueous flow combined with increased ocular blood volume would lead to a similar shallowing of the anterior chamber during hypoxia as that produced by pilocarpine. Some of the contradictory and unexpected pupil shifts with hypoxia may result from the forward lens movement that causes shallowing of the anterior chamber.

Another possible hypoxic mediator of pupil size would be entoptic phenomena that are generated by hypoxia. As discussed earlier, Newsome (1971), showed entoptic phenomena have a strong influence on pupil size. Since oxygen administration following hypoxia produces a substantial "red-veil" entoptic phenomenon (Rose, 1950b; Wald et al., 1942), it is possible pupil constriction will accompany this entoptic phenomenon, even as pupil constriction was associated with positive afterimages of the bleaching stimulus during dark adaptation for Newsome.

Chapter 16

Accommodation, myopia, and the crystalline lens

The bulk of research in this area has dealt with changes in the near point of accommodation as a result of reduced oxygen tensions and this includes changes in the onset of fatigue for repeatedly accommodating to a close target. A small amount of research has looked at effects of greater-than-normal oxygen tension on this ocular system and the changes in refraction appear to be related to cataract formation during hyperbaric oxygenation. This research is discussed following the research on hypoxia changes.

Hypoxia and accommodation, myopia, and the lens

Early balloonists may have been the first to note that hypoxia influenced ocular accommodation (McFarland, 1932; Mercier and Duguet, 1950). At high altitudes without oxygen they became aware of an inability to focus on the fine graduations of the mercury column of their barometers, their watches, and other near objects. On the other hand, vision for distant objects remained unchanged. Aviators in World War I reported similar experiences such as being unable to find the way home because they could not read their maps, although they were able to see the ground (McFarland, 1932).

Wilmer and Berens (1918) studied the effects of hypoxia on ability to focus at close distances. For some subjects they used a rebreathing apparatus that continuously reduced oxygen tensions over a period of about 20 minutes to levels that frequently led to unconsciousness. They also tested some subjects in a low-pressure chamber at altitudes of 15,000, 20,000, and even above 20,000 feet. The rebreathing apparatus was used with 148 qualified service personnel who had the near point measured subjectively every minute using a Prince rule. Of these men, 44.6 percent showed a receding of the near point, 18 percent had a closer near point, 23 percent showed no change in near point with hypoxia, and "fluctuating changes in accommodation" were found in 14.4 percent. Similar percentages were obtained for 17 men tested in the low-pressure chamber. Personnel who could not meet vision standards for aviators were also tested and a higher percentage showed a receding near point (64 percent) when breathing oxygen at low tensions.

Wilmer and Berens (1918) looked at one possible cause of the large individual differences in changes in the near point. They tested whether or not stress might predict differences and compared near point changes for subjects who exhibited strong cardiovascular

reactions to hypoxic stress with near point changes for subjects who did not show such cardiovascular reaction. They found nearly identical proportions of men showing decreased, increased, no change, and fluctuation of accommodation power as were found among those subjects who did not exhibit such strong cardiovascular reactions.

Wilmer and Berens also looked at recovery of the near point following either a return to sea level or inhalation of oxygen at 20,000 feet. Both conditions led to a return of the near point of accommodation to the value measured at sea level. This recovery was rapid for some and slow for others, although no discussion of these individual differences in recovery rate was provided.

Furuya (1937b) was reported by McFarland, Evans, and Halperin (1941) also to have found a decrease in the range of accommodation (reduced near point) which began soon after reaching 16,400 feet. Continued exposure at this altitude led to further reduction in the range of accommodation. Furuya also found recovery of accommodative power was slow. Sixty minutes of exposure at this altitude led to decrements in the range of accommodation that required 40 minutes for recovery at normal oxygen tensions.

McFarland and Edwards (1937) measured the near points of persons on trans-Pacific flights at altitudes of 8,000 to 12,000 feet. They found the near point only receded a small amount (less than one cm) and was "therefore quite insignificant."

Evans and McFarland (1938) in their research on the effects of hypoxia on size of the angioscptomata repeatedly measured acuity and refraction during the testing. They used four healthy subjects highly trained in experiments on oxygen deprivation. Acuity was measured with a Snellen chart illuminated by 5 ft-c and acuity remained unaffected with low-oxygen mixtures equivalent to 8,000, 17,000, and even 20,500 feet. However, two of the four subjects required large increases in minus correction to maintain acuity at the lowest oxygen tensions. For subject L.R. the sea level correction for maximum acuity was minus one diopter. After 7 minutes of breathing a mixture with 9.2 percent oxygen, he required a correction of minus four diopters. Subject R.McF. went from a correction of plus five diopters while breathing a mixture of 12.36 percent oxygen to minus three diopters when breathing 9.23 percent oxygen. The other two subjects did not show refractive shifts as a function of hypoxia.

Nicholls and Minnes (1943), according to Mercier and Duguet (1950), found the near point to move outward for eight subjects (typically less than three cm) and to remain unchanged for another seven subjects. The altitude in the decompression chamber was not specified by Mercier and Duguet.

Livingston (1944b) measured the near point of accommodation and found it decreased from about 12 cm at sea level to 15 cm at 15,000 feet and to about 16 cm at 17,000 feet (altitudes were simulated in a decompression chamber). However, Livingston noted identification of "the point at which print becomes blurred is most difficult to define when the mind is losing its capacity to discriminate. Often it has been impossible to take reliable records at simulated altitudes over 17,000 feet when the exposure time is 30 minutes." Unlike for accommodation, Livingston (1944b) found it possible to measure visual acuity, convergence, and "desire for binocular vision" (Bishop-Harman test) up to 19,000 feet.

Mercier and Duguet (1950) measured changes in the near point in eight subjects going from sea level to 6,000 meters. They found recession of the near point from one to five cm with an average of three cm. Oxygen at 6,000 meters brought the near point back almost to normal. They found less recession of the near point (or perhaps generally closer near points) when the subject adjusted the distance of the print than when the experimenter did. They concluded that this greater accommodative power when the subject adjusted the print distance complicated interpretation of their results and prevented the development of general conclusions about hypoxia effects on accommodative power.

Ohlbaum (1969) assessed the effects of hypoxia on accommodation and also on convergence, phorias, and stereopsis in 19 men aged ranging from 20 to 39. Fifteen were aviation crew members and four were instructors in aviation physiology. All had 20/20 vision with correction, if needed, and none had any marked ocular muscle imbalance. All had previously been exposed to hypoxia in an altitude chamber up to and including the point of hypoxic collapse. Four test altitudes of 0, 7,000, 15,000, and 18,000 feet were chosen. Accommodation and convergence were tested by means of a Prince Rule. Accommodation was tested monocularly. Subjects were placed behind the phoropter (wearing spectacles, if needed) and a Snellen chart at 15 feet (in the chamber) was used for a subjective spherical refraction. Subjects entered the chambers in groups of three or four and testing of each took about 10 minutes. Oxygen masks were worn until 10 minutes prior to testing.

The range of accommodation was significantly reduced as altitude increased. Ohlbaum used a performance index which was the percentage of the subjects sea level near point although it was not discussed whether this was diopters or distance. At 7,000 feet, the near point receded by an average of 6 percent, at 15,000 by 13 percent, and at 18,000 feet by 16 percent. Three-quarters of his subjects demonstrated a "measurable drop" in accommodative power by 18,000 feet. However, as with Wilmer and Berens (1918) this left a substantial proportion who did not show hypoxic recession of the near point.

Despite finding the near point to recede for most of the subjects, Ohlbaum (1969) found a myopic shift in refraction as a result of hypoxia. This myopic shift was small, averaging 0.12 diopters at 18,000 feet, but it was highly significant. Myopic shifts averaging 0.07 diopters at 7,000 feet and 0.08 diopters at 15,000 feet also were found, but these were not found to be significant. One can only speculate about the reason for the refractive shift, but one possibility is lengthening of the lens-retina distance due to a simultaneous increase in retinal blood volume and reduction in aqueous volume (see Chapter 13: "Intraocular pressure"). As mentioned, this myopic shift was occurring at the same time Ohlbaum was finding a significant decrement in accommodative power. It would be expected that subjects showing the largest increase in myopia would have shown the least recession of the near point. However, this was not discussed by Ohlbaum.

Carapancea (1971) provided a brief English abstract that indicated disturbances of visual accommodation at high altitudes occurred as a result of increased intraocular pressure following hypoxic decompression. These problems were directly related to the degree and duration of hypoxia. The problem appeared to be confined to hyperopic aviators used in research by Carapancea and his associates (it may be that Rumanian aviators were selected for hyperopia). These accommodation "disturbances" apparently were significant shifts of the near point closer to the subject with this shift being 1.2 cm with decompression to 5,000 meters without oxygen, and with the shift ranging from 1.4 cm to 3 cm for decompression to altitudes from 12,000 to 18,000 meters with oxygen (Carapancea, Stefan, and Udrescu, 1973). This 3-cm shift represented a shift of the average near point from 10 to 15 diopters.

Wolbarsht, White, and Anderson (1973) measured the near point of accommodation under various oxygen tensions and altitudes. With 20 percent oxygen at 9,500 feet, they reported an insignificant change in near point for the average of five subjects of only -0.06 diopters. However, they appear to have accidentally reported the average for a condition with 40 percent oxygen breathed at 14,000 feet instead of the correct one in their Table III. All five subjects showed a decrease in range of accommodation and a recalculation of the average change from individual data presented in Table IV indicates that the change was -0.59 diopters for all subjects and -0.44 diopters if a subject who may have changed his criterion for laser speckle motion is excluded.¹ Both averages would appear to indicate a significant decrement in the range of

¹ Like Livingston (1944b), Wolbarsht, White, and Anderson (1973) reported that it became difficult under the hypoxic condition to concentrate on the fine details of the target.

accommodation and subsequent communications with Wolbarsht indicate that this was the case. Pure oxygen breathed at 31,500 feet also may have led to a decrement of accommodation range with an average change of -0.42 diopters, but only three of the five subjects showed a decrement. Near zero average changes in near point were noted in oxygen tensions which were breathed at 7,250 and 14,000 feet. In these cases, the oxygen tension at altitude was equal to the sea level oxygen tension.

Mountain climbing expeditions also have produced data on hypoxia-based accommodation difficulties. Clarke and Duff (1976) reported two Mount Everest expedition members (one emmetrope and one myope) "noted quite independently" problems with their accommodation when they returned to 4,000 meters at the end of the expedition. It was not specified, but the accommodation problem probably was a recession of the near point. The accommodation problem recovered after several days.

Kramar et al. (1983) did not find a change in near point for three young climbers on an expedition of females that climbed to an altitude of 5,500 meters. On the other hand, a 43-year woman did show a moderate increase in both near point of accommodation and also the end point of accommodation.² However, the most unusual result was found for a 53-year old member who was a "nonclimber" and who did not go above 5,000 meters. She showed a large receding of the convergence near point (31 percent) between sea level and 3,050 meters. The near point stabilized during further climbing and remained constant during a 2-week stay at 5,000 meters. Surprisingly, on her return to 4,250 meters and later back to sea level, she showed a dramatic improvement in both accommodation and convergence with her near point about six cm closer than the near point measured at sea level before the climb. The improvements lasted for several days, during which time she was able to read without her reading glasses. Unfortunately, there was no discussion of her far point, but one suspects that she probably became somewhat myopic.

This increase in "accommodation" probably was not the result of any ciliary-based alteration of the lens, given that the woman was 53 years old and accommodation loss with age is one of the most reliable physiological changes with age that exists. The myopia suggests some change in the dimensions of the eye resulted from the altitude change, either a total lengthening of the eyeball or perhaps a forward movement of the lens as a result of shallowing of the anterior chamber (Mapstone, 1981). A possible hypoxic mechanism for this was mentioned above and was discussed in some

² It is not clear whether this increase in the end point is a more distant or closer end point. A dioptric increase in the end-point distance would be a closer end point.

detail in Chapter 13: "Intraocular pressure." Alternatively, some new "accommodation" process developed as a result of the exposure to altitude. One can only speculate, but ciliary tension on a rigid presbyopic lens might lead to a lengthening of the eyeball if hypoxia or altitude has reduced intraocular pressure.

Hypoxia and fatigue of accommodation.

Wilmer and Berens (1918) measured fatigue of accommodation as well as range of accommodation. They used a modified Howe ophthalmic ergograph which required focussing on a target moving toward the subject and reporting to the tester when it was closer than the near point (when the target first blurred). The target then was moved away from the subject to its original position and then it repeated the forward movement requiring increased focus. At sea level, three minutes of these rapidly-repeated accommodative efforts showed little effect on the near point. A decline in the near point was noted at an altitude of 15,000 feet and a very marked and rapid fatigue of accommodation was noted at 20,000 feet. The authors presented data for one subject collected at sea level, at 22,000 feet, and during recovery in normal air 1.3 minutes after exposure to 22,000 feet. This illustrated the physically-shortened near excursion of the target at altitude at which the subject already reported blurring. It also showed that recovery of fatigued accommodation does not immediately occur at the end of hypoxia. This series of accommodative efforts during the recovery period also indicated substantial fluctuations in the near point of about 1-minute duration. However, no discussion of these interesting sinusoidal fluctuations or the extent to which they typified other subjects' responses was provided by Wilmer and Berens.

McFarland (1937b) used the same apparatus as Wilmer and Berens (1918) to study accommodation fatigue at different altitudes in research carried out in the Andes mountains. For each subject (and, although it is not clear, probably at the beginning of each test at altitude), the near point was determined and the target then was moved away from the subject by a distance which McFarland indicated to be 20 mm, but given the picture of the device, which must have been 20 cm. The target moved forward and subjects noted when their accommodation to the target failed and blur set in. Subjects then returned the device to its starting point by moving a handle. The approaching accommodation stimulus was presented at a rate of 30 to 36 approaches per minute for a period of 10 minutes or until substantial fatigue set in. Fatigue was defined as failure of the target to reach the initial near point prior to target blur. Only a small amount of fatigue occurred at sea level testing with 256 trials (256 forward movements of the target) occurring before fatigue set in. At 9,200 feet, a small amount of fatigue was noted. This increased progressively through 12,020 and

15,440 to 17,500 feet, where fatigue first was noted after only 38 trials. At this altitude, subjects were able to continue accommodating to any target distance within 20 cm of the initial near point for an average of only 5 minutes. In addition, a 10-cm forward movement of the target from its starting point led to blur after only an average of about 100 trials.

In his English summary, Giardini (1949) reported results on fatigue of accommodation that were highly similar to the results of McFarland (1937b). Eight subjects breathed low-oxygen mixtures corresponding to 3,900, 4,900, and 5,900 meters. A modified Howe Ergograph was used. Only a slight fatigue or no fatigue was noted when breathing normal air. Fatigue of accommodation already was noted at the 3,900 meter altitude and this became more marked with longer stays and higher altitudes.

Hyperoxia and accommodation, myopia, and the lens

The effects of hypoxia on accommodation near point and accommodation fatigue appear to be largely short-term changes, although recovery after hypoxia appears to be relatively slow compared to, for example, recovery of absolute or differential sensitivity. Short-term effects of hyperoxia, and more specifically, hyperbaric oxygenation on accommodation near point and accommodation fatigue probably exist, but no report was found describing such research.

At least three studies have shown there are cumulative effects on refraction of hyperbaric oxygenation. These have produced striking increases in myopia in patients undergoing long-term exposure for treatment of various diseases that typically are unrelated to any visual problem.

Scullica and Bisantis (1968) studied changes induced by hyperoxia on the lens epithelium. Immediate and delayed effects of a 1-hour exposure to normal and hyperbaric hyperoxia were measured. Unfortunately, the English summary of this Italian-language article did not provide any discussion of the results.

Anderson and Farmer (1978) appear to have been the first to describe a myopic shift following repeated exposure to hyperbaric oxygen. They studied 10 patients undergoing repeated hyperoxic exposure for the treatment of osteoradionecrosis. Their ages ranged from 51 to 69, with an average of 59 years. Snellen visual acuity, refractive error, applanation intraocular tension, and corneal curvature of the patients were measured within 3 days of the first exposure and again at the end of the treatment regimen. This regimen consisted of breathing 98 percent oxygen for 2 hours while exposed to two atmospheres of absolute pressure. Forty exposures were given with one per day except Sunday. Oxygen was

delivered by means of a head tent and the external portion of the eye was exposed directly to the hyperbaric oxygen.

Anderson and Farmer (1978) found a highly significant myopic shift for these patients which averaged -1.61 diopters. No significant shift in corneal curvature occurred and the 0.05-diopter average change in the cornea actually indicated a flatter cornea. Intraocular pressures decreased by only 0.8 mm Hg on the average and this was not significant. Following hyperbaric oxygen treatment, the refraction gradually changed back toward pretreatment levels but still averaged -0.23 diopters at the last examination which occurred 12.5 weeks (on the average) after the end of hyperbaric-oxygen treatments. Three of these patients were given another 40 days of treatment and two of them showed similar increases to those found previously.

The absence of miosis and the persistence of the myopia indicated accommodative spasm probably was not the basis of the myopic change. Unfortunately, measures were not made of axial length, anterior chamber depth, or lens thickness/curvature. Attendants in this treatment process who were in the chamber breathed air instead of oxygen. They did not show these effects or, at least, there was no report of blurred vision as reliably occurred for patients. This implied it was not pressure per se that produced the myopia, but the hyperbaric oxygen.

Lyne (1978) studied refractive changes in a series of 26 patients (aged 36-80) undergoing hyperbaric oxygen therapy for more than a month with the treatment typically for ischemic ulcers. Patients typically received chamber treatment daily (some more frequently) with this consisting of 30 minutes while pressure was raised to 2.5 atmospheres, 1 hour at 2.5 atmospheres, and another 30 minutes while the pressure was reduced to atmospheric levels. Several measures were made at the start of treatment and every month afterward until the refractive state had been stable for at least 3 months. These measures were refraction with and without cycloplegia, keratometry, corneal thickness estimation, anterior chamber depth, applanation tonometry, and fundus examination. The Farnsworth-Munsell 100-hue color test was given and axial length (ultrasonography) was measured at the beginning and end of the hyperbaric treatment for some of the patients.

Lyne (1978) found that 13 of the 26 patients examined showed a significant change in refraction toward myopia. One diabetic patient became six diopters more myopic in only 20 weeks. Typically, the observed change was about 0.5 diopter per month. Changes in the two eyes always were comparable, differing at most by 0.5 diopter. The younger patients showed less tendency to this refractive change than older patients and this age difference was not related to treatment length. There was no significant change in keratometry, anterior chamber depth, corneal thickness, or axial

length. The intraocular pressure was unchanged and there was no alternation in color vision or central fields. No fundus changes were observed."

No patient without lens opacities at the outset of treatment developed opacities. Those patients with opacities at the outset of treatment did not show any increase in opacities (but see the contrasting results below from Palmquist and his associates). Increased refraction of the lens was concluded to be the cause of this myopic increase and this was not related to any accommodative spasm since the myopia was not altered by cycloplegia. There was some indication increased curvature of the surfaces of the nucleus of the lens was occurring. Since the refractive index of the nucleus differs from that of the lens cortex, this could account for the increased lens power. In all cases, termination of hyperbaric oxygen led to a rapid initial decrease in lens power, followed by a slower decrease, with this total decrease apparently to pretreatment refraction levels. Apparently, axial-length measures were for only a subset of patients and this number was not given. The text of the report indicated that all four of the diabetic patients in the sample showed the myopic shift, whereas the table giving changes indicated only three of these four changed.

Palmquist, Philipson, and Barr (1984) studied refractive and lens changes in 25 generally older patients (mean age=65.5, SD=15.9) who were being treated with 100 percent oxygen at 2 to 2.5 times the normal atmospheric pressure for persistent leg ulcers. A control group consisted of other patients on a waiting list. Visual acuity was assessed and biomicroscopic lens examination occurred after each 100 hyperbaric oxygen treatments. The treatment consisted of 1 hour of exposure to hyperbaric oxygen and typically occurred twice daily, 7 days a week.

A myopic shift appeared for 24 of 25 patients. This was at least one diopter and both eyes were affected equally. The average maximum change for all patients was 3.0 diopters with the maximum occurring between 100 and 300 hours. Vision testing occurred too infrequently to pin down the early time course of these effects of hyperbaric oxygen on the lens. Myopia typically began to reverse after 300 hours of therapy. Myopic changes persisted for at least 6 months after termination of oxygen therapy. No myopic shifts of one diopter or more were observed in the reference group. Nuclear cataracts developed in seven of the 15 patients who had clear lens nuclei before treatment. No nuclear cataracts developed among the 12 patients in the reference group who had clear nuclei. There was a confound of hyperbaric oxygenation with Vitamin E which was administered to all patients.

Palmquist, Fagerholm, and Philipson (1986) provided additional information about the nuclear vacuoles that resulted from

hyperbaric oxygen treatments. Nuclear vacuoles were found in 11 out of 25 patients treated with hyperbaric oxygen compared to 19 out of 100 preoperatively examined senile nuclear cataracts. Under slit-lamp photography and quantitative microradiography, the vacuoles appeared as dark rounded areas with a lower dry mass content (approximately 0.30 g X cm^{-3}) than the surroundings (approximately 0.50 g X cm^{-3}). The opacities (vacuoles) in the human lens nucleus were found to be similar to opacities found in the lens cortex. This was true of lenses with nuclear cataract, whether they were of senile type or induced by hyperbaric oxygen. In cataracts induced by hyperbaric oxygen, the vacuoles were reversible to some extent. There was no discussion of whether or how these vacuoles were related to the myopia produced by hyperbaric oxygenation.

Conclusions and research needs

One reason research on respiratory effects on accommodation is important is that changes in accommodation with hypoxia often would influence other visual performances. Whether a target is in proper focus or not will be critical for contour resolution and even for maximum concentration of light in absolute sensitivity studies if the targets are small. Whenever some subjects show an improvement in visual performance with hypoxia and others show a decrement, it suggests a change in refraction, such as the increase in myopia reported by Ohlbaum (1969), made the target sharper for some and made the target more blurred for the others. This could happen if the resting point of accommodation³ were farther than a target for subjects with a distant resting point and nearer than a target for subjects with a close resting accommodation point. Any treatment that caused a shift of the resting state of accommodation (as might be expected for hypoxia) would increase target focus for one of these groups, but reduce target focus for the other.

No studies were located that investigated the effects of hypoxia and hyperoxia on the resting point of accommodation (Leibowitz and Owens, 1978). The same absence of research on the resting point of accommodation was noted for smoking (Dyer, 1986). There is a need for research on respiratory effects on the accommodation resting point. Possible effects of hypoxia, hypocapnia, hyperoxia, hypercapnia, carbon monoxide, and smoking might shed a great deal of light on the general and idiosyncratic factors determining the accommodation resting state. The results also might have practical value, since they might allow prediction

³ The resting point of accommodation or "dark focus" refers to the distance adopted by accommodation and convergence in the absence of visual stimulation (Leibowitz and Owens, 1978).

of target detection failures associated with night and empty field myopia during hypoxic conditions.⁴ One might expect these myopias would be increased by hypoxia, given the Ohlbaum (1969) finding of increased myopia in conditions of normal illumination with "full" visual fields. On the other hand, if hyperoxia, hypocapnia, or another respiratory variable were to push the resting focus outward and actually reduce night and empty field myopia, appropriate respiratory mixtures or respiratory patterns might enable aviation personnel to improve their detection of aircraft or other targets at optical infinity. The moving laser-speckle phenomenon used by Wolbarsht, White, and Anderson (1973) to measure the distance at which the eyes were focussed would have many advantages for measuring resting focus in such research.

Individual differences in hypoxic effects on accommodation also would appear to be a prime area of research. The Wilmer and Berens (1918) research indicated while most subjects showed a recession of the near point, 18 percent of the 148 "normals" actually showed a closer near point during hypoxia. Ohlbaum (1969) had a significant minority that did not show a recession of the near point. The Kramar et al. (1983) findings also indicated large individual differences in accommodation (and convergence) during actual ascents to high altitudes.

The strong role of hyperventilation differences in other individual differences associated with hypoxia such as sensitivity (Wald et al., 1942) and standing potential changes (Fenn et al., 1949), suggests hyperventilation differences among subjects may produce the large individual differences in accommodation. Duguet and Mercier (1951) found pupil constriction and pupil dilation with hypoxia also varied greatly among different subjects. The near reflex of the pupil strongly suggests these large individual differences in accommodative and pupillary responses to hypoxia might be linked. Individual differences in hyperventilation (or some other factor) may influence directly one or the other visual system while indirectly influencing the other. Alternatively, both systems could be influenced directly by hypocapnia or hypoxia.

Wilmer and Berens (1918) showed there was wide variation in time for recovery of the near point following a return to normal air. Furuya (1937b), according to McFarland, Evans and Halperin (1941), indicated it took 40 minutes in normal air for the near point to recover from the effects of 1 hour at 16,400 feet. These

⁴ As is discussed in the final chapter, night myopia may be caused by "night hypoxia," i.e., a relative hypoxia produced by the greater requirement for oxygen in darkness that was shown by Steffanson, Wolbarsht, and Landers (1983) and Linsenmeier (1986).

long-term effects on accommodation may indicate some general shift in autonomic nervous system function. On the other hand, pure oxygen at normal atmospheric pressure or even hyperbaric oxygenation (but see below) might greatly speed this slow recovery from hypoxia. Research investigating recovery from hypoxia-induced recession of the near point also would appear to be of considerable theoretical and practical value.

No studies were found which looked at the effects of hyperoxia on the accommodation near point or on fatigue of accommodation. Reduced ocular blood volume as a result of hyperoxic retinal vasoconstriction perhaps could alter the dioptric characteristics of the eye and the far point of accommodation would be of interest as well as the near point. One might expect fatigue onset would be slower during hyperoxia than at sea level, given the additional oxygen available to the ciliary muscle (and the near-reflex-linked extraocular muscles). Research on these questions may have both practical and theoretical value. However, given the potential problems for the eye associated with hyperbaric oxygenation which were discussed above (and see Chapter 20: "Oxygen toxicity"), such research on hyperoxia should be limited initially to breathing pure oxygen at a single atmosphere's pressure. Given positive results or given other reasons for assessing these accommodation functions during hyperbaric oxygenation, it would be best to limit subjects to patients who must undergo the hyperbaric oxygen exposure for clinical reasons.

Chapter 17

Convergence and heterophoria

Wilmer and Berens (1918) included measures of phoria and convergence in their extensive decompression chamber and rebreathing apparatus studies of hypoxia and visual performance. In a group of 25 men with normal ocular function, both maximum abduction (turning of eyes outward) and maximum adduction (turning of eyes inward) showed a decrease as oxygen tension decreased and the same was true for sursumvergence (vertical divergence of the two eyes).

The near point of convergence was tested in 147 men with normal eyes on the rebreathing apparatus. Of this total, 50.3 percent showed a decrease in convergence power, 17.6 percent showed an increase in power of convergence, 11.5 percent showed "fluctuation," and 20.6 percent showed no change in convergence power. Similar percentages were obtained in 72 subjects showing an increase in pulse rate and a maintenance in pulse pressure, indicating the finding was not related to a heightened cardiovascular reaction.

Fatigue of convergence was measured by repeated convergence movements on Howe's ophthalmic ergograph. Fatigue of convergence was marked at 15,000 feet and above and similar results for accommodation were discussed in the last chapter. All of these decrements in oculomotor functions with hypoxia were restored quickly by breathing air or oxygen.

Nicholls (1950b) described the results of a study conducted by the U. S. War Department (1919) which appears to have been highly similar to the work of Wilmer and Berens (1918) on convergence and heterophoria. "In all the subnormal subjects examined, particularly in those with convergence insufficiency, alone or combined with divergence (exophoria), there was a marked loss in the power of adduction and diplopia often occurred between 10,000 and 15,000 ft. Men with over one degree of hyperphoria, particularly when it was combined with exophoria, showed a rapid reduction in muscle strength, which often resulted in diplopia, the work thus demonstrated that exophoria and hyperphoria are more objectionable than esophoria."

Nicholls (1950b) reviewed a pair of early studies that indicated heterophoria tends to become heterotropia under conditions of hypoxia. Mercier and Duguet (1950) reported that von Tavel (1943) described a pilot who flew at 6,300 meters without oxygen and

experienced images of two airplanes when only one was in front of him. He did not know which was real and was sure he had lost his mind. His "mind" became normal when he flew down to 6,000 meters. The ocular balance of this pilot at sea level was not described.

McFarland (1937a) looked at the effects of rapid ascents by airplane and train in the Andes on a number of functions including deviations from orthophoria. Six subjects were compared at sea level and at Morococha (14,890 feet). As McFarland stated, "The phoria test showed completely significant deviations for the group with the 5 degree prisms at a distance of 40 cm and fairly significant deviations for the 3 degree prisms at 6 meters." Phoria measured at 40 cm at sea level was 1.2 prism diopters and at 14,890 feet it was 4.2 prism diopters. Phoria measured at 6 meters at sea level was 0.08 prism diopters and at 14,890 feet phoria was 1.2 prism diopters. Unfortunately, it is not clear whether these were esophoric changes or exophoric changes since McFarland probably averaged both esophoric and exophoric shifts as he did in a similar study (McFarland, 1937b).

McFarland (1937b) studied phoria and convergence fatigue in another of his studies of psychological and physiological functioning at high altitude in the Andes. Phoria was measured at 40 cm and at 6 meters. Changes in phoria with altitude were minimal when phoria was measured at a distance of 6 meters, but phoria changes measured at 40 cm increased from 1.5 prism diopters at sea level to 2.8 prism diopters at 9,200 feet, to 3.3 prism diopters at 15,440 feet, to 4.5 diopters at 17,500 feet, and to 6.7 prism diopters at 20,140 feet. These changes were highly significant at the two higher elevations. Unfortunately, these means were calculated without regard to whether the change was esophoric or exophoric. Seven of the subjects were reported to be exophoric and three esophoric (apparently at the 40-cm measurement distance) and this strongly suggests the significant changes were exophoric and this, in turn, suggests a convergence insufficiency for the near measurements. Unfortunately, the convergence near point was not measured. According to Nicholls (1950b), Pol (1938) confirmed these findings of McFarland related to hypoxia and heterophoria.

Fatigue of convergence and accommodation also were tested by McFarland (1937b) with the Berens-Howe ocular ergograph. Subjects focussed on a stimulus that moved from a point 20 mm away from the near point to the near point (determined for each subject). When the near point of convergence was reached (diplopia), the stimulus was moved back to its starting point. Forward strokes of the target occurred at a rate of 30 to 36 per minute. For convergence/accommodation fatigue measurements at sea level, most subjects could converge from the near point plus 20 mm to the near point (and back) for the full 10 minutes. This time declined in proportion to altitude until at 17,500 feet it was only 5.6 minutes for convergence and 5.0 minutes for accommodation.

According to Nicholls (1937b), Velhagen (1937) found hypoxia increased esophoria for distance. He examined 16 men in a decompression chamber at altitudes up to 18,000 feet. Three minutes at that altitude produced a marked increase in convergence "in those with primary esophoria for distance." There was an "increased convergence insufficiency" for those subjects with a "primary exophoria for near." Diplopia did not occur as a result of hypoxia for any subjects. Administration of oxygen or return to normal atmospheric pressure led to return of normal ocular muscle balance.

Scobee (1944) studied the effects of moderate hypoxia and exhaustion on vertical and lateral phorias in 10 subjects. Phorias were determined at 13 inches by a Maddox rod. The first measurements occurred at ground level and were repeated after 30 minutes at 18,000 feet in a decompression chamber without oxygen. Seven subjects showed exophoric shifts and three esophoric shifts, but the average phoria change was nearly zero. Measurements of phoria were not made at 20 feet because of restricted room in the chamber. Vertical phorias also were virtually unchanged, although five men showed less vertical phoria during hypoxia. Exercise to exhaustion on a treadmill also did not cause any systematic phoria changes when phoria was measured immediately after exercise at both far and near in 14 subjects.

Livingston (1944b) measured the near point of convergence at various levels of decompression in a chamber. The convergence near point receded 4.5 cm upon change from 15,000 to 17,000 feet and receded another 2 cm going from 17,000 to 19,000 feet. This smaller change at 19,000 feet could reflect some stimulus to convergence associated with severe hypoxia.

Livingston (1944b) also found when subjects measured depth perception by adjusting a center post to be at the same distance as two fixed posts on either side of it, their performance under hypoxia differed from sea level in that the center post was located closer than the surrounding posts. This was seen as loss of power to "maintain binocular concentration," due apparently to difficulty in converging at the distance of the posts under hypoxia, although this required only a "small degree of convergence."

Adler (1945) studied the effect of hypoxia on phorias measured at far and near and the effect of hypoxia on the range of fusion. Subjects were eight "normal subjects." Maddox-Rod phoria measurements were made at 33 cm and at "far." Fusion-range measurements were made with an "Orthoptoscope." All measures were made at sea level and at 16,000 and 18,000 feet in a decompression chamber. Esophoric shifts appeared during Maddox-Rod measurements at distance for seven of eight subjects. Consistent with this finding was a reduction of exophoria for near measurements, although this exophoria reduction at near was somewhat less reliable than the

esophoric shift at distance. Orthoptic testing indicated closer fusion break points and recovery points as hypoxia increased and less distant abduction break and recovery points. These results were contrary to results of Wilmer and Berens (1918), Livingston (1944b), and others who have found the convergence near point to recede during hypoxia. All of Adler's results pointed to an increased tone of convergence or reduced divergence tone during hypoxia.

According to Bietti (1953), Bietti and Giardini (1949a) found a deficiency of the convergence in near vision, as well as a slight vertical heterophoria as a result of hypoxia. According to Bietti (1953), Bietti and Giardini (1949b) found the amplitudes of convergence and divergence were reduced in severe hypoxia. In their own English summary, Bietti and Giardini (1949b) reported 10 orthophoric subjects breathed mixtures of from 8.5 to 10 percent oxygen. Fusional amplitude was measured by placing prisms before the right eye until a nonfusible diplopia occurred. The fusional amplitude in adduction was diminished perceptibly. After 5 minutes at the simulated altitude of about 7,000 meters, an average diminution in amplitude of 5.1 prism diopters occurred. After 10 minutes this decreased to 6.4 prism diopters. After 15 minutes this decreased to 7.4 prism diopters, but fusional amplitude in adduction did not decrease further at 20 minutes. The fusional amplitude in abduction was reduced moderately by about two prism diopters. For both adduction and abduction, fusional amplitude returned to normal shortly after resumption of air breathing.

Rose (1949) studied the effect of altitude and adaptation to altitude on night vision and ocular muscle balance. Measures were made on nine subjects of phoria, abduction, and adduction at near sea level and then repeatedly during nearly 2 weeks at 10,000 feet. Phoria measurements were made at six meters with a Maddox rod. Subsequent to the stay at elevation, additional measures were made in a decompression chamber and in normal air at near sea level.

Initial phoria measures at altitude showed an esophoric shift of 0.7 prism diopters.¹ Following this, a gradual increase in exophoria occurred over the next week leading to a measurement that was 2.5 prism diopters different from the first test at altitude. Low pressure chamber measures made a month or more after the stay at 10,000 feet showed a 2.2 prism diopter increase in esophoria compared to a measure made at ground level (761 feet) immediately prior to decompression. Adduction power showed a striking increase of nine diopters over the stay at 10,000 feet, with four prism diopters of this occurring at the first testing and five more on

¹ This was according to Table 5 and Figure 7. Table 6 indicated 0.3 prism diopters but this appears to be an incorrect sum of -0.5 and +0.2.

the next test 2 days later. Abduction power increased on the first day of testing by three prism diopters then declined slightly over the remaining tests.

Mercier and Duguet (1950) tested phorias at distance of seven subjects in a decompression chamber at 16,400 feet. Six of the subjects had sea level phorias ranging from 9 prism diopters of esophoria to 6 prism diopters of exophoria, while the seventh had 15 prism diopters of alternating esotropia. Although the latter's tropia underwent a temporary reduction to 10 prism diopters, all 6 of the binocular subjects showed a change of from 1 to 10 prism diopters in the esophoric direction. Breathing oxygen at "altitude" restored the former state of ocular balance. Two subjects with hyperphoria showed no changes in the hyperphoria during hypoxia.

Neely (1951; 1955) assessed the effects of hypoxia (20,000 feet in a decompression chamber while breathing air) on phorias, accommodation, convergence, adduction, and abduction. Subjects were 10 men with an esophoria measured at 6 meters that was greater than 6 prism diopters, 10 men with an exophoria measured at 33 cm that was greater than 6 prism diopters, and 5 men with normal phorias. Subjects were first tested at ground level then decompressed at a rate of 3,000 feet per minute to an altitude of 20,000 feet. Subjects remained at 20,000 feet for 3 to 5 minutes before being tested again.

All but one esophoric subject showed an increase of esophoria with the average increase being 3.8 prism diopters. The single esophoric subject who had a one prism diopter decrease in esophoria "was a well-trained athlete of some distinction." All exophoric subjects showed a decrease in exophoria with the average decrease being 4.5 prism diopters. Measures were made "on the way up" as well as at final altitude for some subjects and the esophoric shift was noted in many as early as 10,000 feet. Accommodation "deteriorated" in 15 cases, improved in 2 cases, and was unchanged in 3 cases. Convergence improved in 2 cases, deteriorated in 7 cases, and was unchanged for 10 cases. Adduction improved in 1 case, deteriorated in 6 cases, and was unchanged for 10 cases. Abduction improved in no case, deteriorated in 7 cases, and was unchanged for 10 cases. Manifest convergent squint occurred in one subject and this prevented measures of convergence and adduction. In two cases no readings were possible for abduction.

One problem with the research is that a few more minutes than the 3 to 5 spent at 20,000 feet probably would have been required for stable reduced levels of oxygen saturation. Measurements were made quickly to prevent "undue stress to the patients" and examiners. However, this stressful setting itself may have contributed to the increased esophoria and reduced exophoria and stress effects probably were confounded with hypoxia effects.

Ten Doesschate (1955) measured lateral and vertical phoria during decompression to 20,000 feet for a period of 15 minutes. Subjects were 20 men with phorias at ground level ranging from 3 prism diopters of esophoria to 2.5 prism diopters of exophoria. Lateral and vertical phoria measurements were made in a low pressure chamber at ground level, at 20,000 feet immediately after an ascent while breathing pure oxygen, at 20,000 feet after 15 minutes without oxygen, and at 20,000 feet after 20 minutes of breathing pure oxygen. It was not clear at what distance phoria was measured in the chamber.

Sixteen of 20 subjects became more esophoric under hypoxia with the range of these esophoric shifts being 0.5 to 7 prism diopters and with the average for these 16 subjects being 2.4 prism diopters. One of the subjects did not have a phoria change and two showed a 0.5 prism diopter decrease in esophoria. Minimal changes in vertical phoria during hypoxia were found with both increases and decreases noted.

Kobrick (1968) measured lateral phoria and vertical phoria at sea level and again after 24 hours of exposure to an altitude of 12,800 feet in his study of the effects of exposure to 12,800 feet (with and without administration of the drug acetazolamide) on visual performance. Hypoxia did not produce any changes in lateral phoria and vertical phoria (or changes in any of the other variables). The 24-hour adaptation period probably was a factor in these negative results, along with the relatively mild level of hypoxia.

Ohlbaum (1969) assessed the effects of hypoxia on accommodation, convergence, phorias, and stereopsis. Subjects were 19 men, ranging from 20 to 39. Fifteen were aviation crew members and four were instructors in aviation physiology. All had 20/20 vision, with correction if needed, and none had any marked muscle imbalance. All previously had been exposed to hypoxia in an altitude chamber up to and including the point of hypoxic collapse. Four test altitudes of 0, 7,000, 15,000 and 18,000 feet were chosen. Subjects entered the chambers in groups of three or four and testing of each took about 10 minutes. Oxygen masks were worn until 10 minutes prior to testing.

Accommodation and convergence were tested by means of a Prince Rule. Distant phoria measurement (horizontal and vertical) used dissociation and Risley prisms with the target being a single letter at 15 feet. The same procedures with a single letter at 16 inches on a reduced chart were used for measurement of near lateral phoria. "Plus acceptance" was measured by presenting the subject with a grid consisting of three fine vertical and three fine horizontal lines. Jackson crossed cylinders were placed vertically in the phoropter and plus lenses were added binocularly until the

vertical and horizontal lines were equally clear. The amount of plus lens added to the distant refraction was recorded as the plus acceptance at near.

A small but significant decrease in the AC/A ratio was found that appeared to accelerate going from 15,000 to 18,000 feet, even as the increase in myopia accelerated from 15,000 to 18,000 feet. The AC/A ratio at sea level averaged 4.05, this ratio averaged 3.62 at 7,000, averaged 3.44 at 15,000, and averaged 3.2 at 18,000 feet. As discussed in the last chapter, the range of accommodation was reduced significantly as altitude increased. The range of convergence showed a similar trend under hypoxia as the range of accommodation, but this result was much less reliable. No significant hypoxic changes were found for near and far lateral phorias, vertical phoria, or plus acceptance at near.

The absence of an increase in esophoria found by Ohlbaum was in marked contrast to the results of Velhagen (1937), Adler (1945), Mercier and Duguet (1950), Neely (1951; 1955), and ten Doesschate (1955) which were described above. Ohlbaum's subjects were highly familiar with decompression and this may have been a major factor in his negative results for phoria. If stress or anxiety were a factor in the esophoric shifts found in earlier research, effects would be expected early in decompression or breathing of low oxygen tensions before adaptation and relaxation occurred. Typically esophoric shifts were noted within a very few minutes. In one instance, esophoria that was measured early in hypoxia was replaced by exophoria in later measurements at altitude (Rose, 1949).

Amos (1976) studied the effect of a 50 percent nitrous oxide/50 percent oxygen mixture on the lateral heterophoria. The particular mixture was selected because it produced a desired analgesic effect. Three minutes of breathing this mixture caused a large 4.65 prism diopter average shift toward esophoria in the 10 subjects when phorias were measured at 40 cm. Phoria measures at six meters showed 1.05 prism diopters of increased esophoria, but this was not significant. Distance refraction changed by an average of -0.237 diopters and the AC/A ratio changed from 5.94:1 to 4.35:1. These AC/A ratio changes were similar to those found by Ohlbaum (1969) during hypoxia. It was not clear whether it was the nitrous oxide or high oxygen that produced the changes in phoria, refraction, and AC/A ratio. Respiration changes associated with the analgesic reduction in anxiety also could have been a factor.

Kramar et al. (1983) examined the effects of altitude on the ocular functions of seven 23-53-year-old females during ascent of a 6,798 meter peak. The only consistent change was a decrease in convergence amplitude (a recession of the near point of convergence) as altitude increased. The accommodation amplitude did not decrease as much as convergence amplitude, but this may have reflected hypoxic influences increasing the refractive power of the

eye, as was discussed in the previous chapter. Significant, but inconsistent changes in phoria occurred for three of the seven subjects.

Conclusions and research needs

Typically, there was an increase of esophoria associated with hypoxia, but this result was not found in all of the studies. The reasons for this divergence of research results are not well understood. Anxiety in the testing situation may have been a factor and Ohlbaum's negative results may have reflected the absence or the low levels of anxiety as a result of the extensive previous experience his subjects had with hypoxia up to collapse. The fact that the esophoria typically is found early in the hypoxic situation also would support an anxiety or stress factor in the esophoric shifts. Such anxiety effects on phoria might very well be mediated by hyperventilation which frequently accompanies anxiety.

Differences in hyperventilation associated with hypoxia may account for some of the differences found between various investigators on changes in phoria and some of the huge individual differences in the effects of hypoxia on phorias. Studies looking at the resting point of convergence and at individual differences in hypoxic effects on convergence also are needed.

Although several studies investigated the effects of breathing pure oxygen on recovery of convergence and phoria changes with hypoxia, no studies were found which looked at the effects of increased oxygen tensions on convergence and phoria without preceding hypoxia. Nor were any studies found which looked specifically at the effects of hypocapnia or hypercapnia on phoria. Carbon monoxide-induced hypoxia also apparently has not been studied as it affects phoria and convergence. Research in each of these areas would appear to have both theoretical and practical benefits.

Chapter 18

Reading and other eye movements

The effects of hypoxia on coordinated eye movements have received only a small amount of attention over the years, although this research goes back to the 1930s. In perhaps the earliest of these studies, Gellhorn and Spiesman (1935) induced caloric nystagmus while subjects breathed mixtures high in CO₂ and low in oxygen, and also after hyperventilation which would produce low CO₂ levels. They found breathing a CO₂-air mixture decreased the number of nystagmoid movements and hyperventilation increased the number of nystagmoid movements. Oxygen lack reduced the number of nystagmoid movements, but had a much smaller effect than hypercapnia and hypocapnia on nystagmus. Only when hypoxia was prolonged for 20 minutes or more did significant decrements typically occur. Since hyperventilation is a fairly reliable correlate of hypoxia (e.g., Ernest and Krill, 1971), hyperventilation may have been operating to counter hypoxic effects.

McFarland, Knehr, and Berens (1937a) studied the effects of hypoxia on the highly-practiced response of reading in 10 healthy college students 19-34 years of age. These subjects read paragraph material at a distance of 33 cm after breathing either air, 12.5 percent oxygen, 10.5 percent oxygen, or (four subjects) 5 percent CO₂ (in air) in a portable oxygen chamber. CO₂ levels in the chamber never exceeded 0.7 percent. Eye movements were measured by photographing reflections from each cornea on moving film.

They found the time required to read a line of print and the number of fixations per line increased with increasing hypoxia. Accuracy of adjustment of eye movements decreased during hypoxia. Some acclimatization was noted by the end of 1 hour for these subjects for the 12.5 percent oxygen condition, but no such acclimatization was noted with 10.5 percent oxygen. The subjects breathing elevated CO₂ in air did not show differences from their performance in air without CO₂. However, the increased respiration rate produced by the CO₂ apparently caused head movements that caused some problems for eye movement recording.

McFarland, Knehr, and Berens (1937a) found large individual differences in the effects of hypoxia on reading. No measures of oxygen saturation (or CO₂ levels) of the blood were made which might have helped to account for the large individual differences. The individual differences also may have reflected differences in resting level of accommodation and convergence which made fixation

at the 33 cm viewing distance of increased difficulty during hypoxia for those with more distant resting fixation points. On the other hand, despite the close reading distance, subjects typically diverged their eyes when they fixated. This divergence became less during hypoxia, but it is not clear whether this reflected less accurate binocular superimposition of images or whether there was a general divergence of the eyes under hypoxia that led to a smaller divergence requirement.

McFarland, Knehr, and Berens (1937b) conducted a similar investigation on 12 patients who had refractive errors, muscle imbalances, and heterotropias. Eye movements were photographed in air and at a single "altitude" ranging from 10,000 to 18,000 feet, depending on the patient's physical condition. The average altitude was 15,000 feet (11.5 percent oxygen). As for the normal subjects in the earlier study, the number of fixations increased and reading time increased during hypoxia.

According to Newberry, Johnson, and Smiley (1965), Grüttner (1944) found a severe oxygen lack (without hyperventilation) caused a decreased frequency of "post autokinetic nystagmus." No details of methodology or elaboration of these results was provided in this secondary source.

According to Bietti (1953) and Mercier and Duguet (1950), Bietti and Scano (1946) studied reading in 14 subjects who were tested while breathing low oxygen mixtures that simulated altitudes of 5,800 to 8,000 meters. They found changes in reading with hypoxia were similar to the findings of McFarland, Knehr, and Berens (1937a). Reading was slowed by an average of 61 percent with individuals showing changes that ranged from 11 to 218 percent. The slowing apparently occurred in two phases. First, there was an increase in number and duration of fixations as a result of interference with perceptual and mental processes. Second, there was a slowing of the eye movements analogous to the symptoms associated with fatigue of the eyes. This second phase was viewed as the result of "an aggravated oxygen deficiency." In addition to these slower movements of the eyes and increased fixations, there was a more frequent swinging back to groups of figures previously viewed.

Wiesinger (1948), according to Bietti (1953), found a slight protrusion of the eye during hypoxia which was attributed to sympathetic hyperexcitability. Subjects were tested during an expedition to the mountain Jungfrauoch at an elevation of 3,457 meters.

Many, perhaps most, subjects show a tendency to hyperventilate during hypoxia (e.g., Ernest and Krill, 1971), and it may be significant that Fenn et al. (1949), who used electrooculography to assess the effects of hypoxia and acapnia on the standing

potential, found hypocapnia following hyperventilation caused the lateral eye movements used to generate these potentials to be slowed and to become erratic. Although hypoxia also was studied in their research, they made no mention of hypoxia disrupting eye movements, only the hyperventilation.

Newberry, Johnson, and Smiley (1965) studied the effects of hypoxic hypoxia on nystagmus induced by angular acceleration. In one trial, hypoxia was produced by decompressing the subject to an altitude of 20,000 feet. In another trial, hypoxia was produced by having the subject breathe a 10 percent oxygen/90 percent nitrogen mixture. Trials in air at ground level both preceded and followed the trials under hypoxic conditions.

Breathing 10 percent oxygen at ground level produced a 61 percent increase in the slow phase angular velocity compared to breathing air at ground level, but this was not a significant increase. However, much larger and highly significant effects occurred in the decompression condition for all dependent variables. There was nearly a 100 percent increase in total angular deviation, maximum angular velocity, and total duration of nystagmus compared to breathing air at ground level. These changes were not viewed as being the result of the hypoxia or the pressure change, but as a result of the subjects' anxiety. The decompression condition was viewed by subjects as much more dangerous than other conditions, despite reassurances about its safety, and despite actual demonstrations of its safety. This unrelieved anxiety was seen to be the basis for the increase in nystagmus and not hypoxia or the pressure change itself. Although respiration changes were not measured, the authors believed hyperventilation caused by the anxiety mediated these effects on nystagmus.

Scano, Mazza, and Caporale (1966) studied the influence of mild hypoxia on visual perception during postrotatory optical nystagmus. They found hypoxia or pretest rotation alone did not increase significantly perceptual errors over those with neither hypoxia or pretest rotation. However hypoxia combined with pretest rotation did significantly reduce performance.

Pierson (1967) examined mild hypoxia effects and effects of 100 percent oxygen on visual sensitivity and on performance on a reading test (U.S. Air Force hypoxia demonstration chart). The subjects were 10 males with 20/20 uncorrected vision with an average age of 28.3 (SD=4.8). They were tested at ground level (1,300), 8,000, and 9,300 feet. Ground level testing was followed by "altitude" testing which again was followed by ground level testing. Chamber air and pure oxygen were counterbalanced across the first two sessions. There were no effects of altitude or 100 percent oxygen on the reading test or on the visual sensitivity test (sensitivity results were discussed earlier). Pierson

indicated although the reading test was insensitive to the mild hypoxia of 8,000 and 9,300 feet, it provided "a dramatic demonstration of the effects of hypoxia at 18,000 feet in altitude indoctrinations."

Alder and Cringle (1985) studied the effects of breathing air and oxygen on vitreal oxygen tension in cats when oxygen electrodes were moved forward and backward in the vitreous to retinal locations of veins and arteries. In almost all instances, movement of electrodes occurred when respiratory gases changed, blood pressure changed, or intraocular pressure changed. These sometimes were substantial lateral movements that led to puncture of the retina. The source of these movements was unknown, but it was suggested as being due to retinal circulation changes and changes in blood volume. These appear to be changes in eyeball shape which produced movement of the side of the eyeball (where the electrode entered) relative to the retina. Such changes in eye shape augur for refractive changes of the eye during hypoxia, hyperoxia, or changes in atmospheric pressure. Such refractive changes would be expected to degrade or to enhance acuity, sensitivity, field size, etc., and these refractive changes could account for many of the contradictory findings in this literature and also could account for large individual differences in effects of hypoxia, if the refractive change improved target focus for one subject but degraded target focus for another (see Chapter 13: "Intraocular pressure").

Conclusions and research needs

The research has typically shown that eye movements are influenced by hypoxia, although the results of Gellhorn and Spiesman (1935) and of Newberry, Johnson, and Smiley (1965) on nystagmus indicate the hypocapnia that often accompanies hypoxia may be a major factor in some of these "hypoxic" changes. No research was found which looked specifically at the effects of carbon monoxide hypoxia (hemic hypoxia) on eye movements. This also was true for respiratory conditions producing hyperoxia, although research was found on the effects of hypercapnia.

The dynamic visual scenes encountered in fast moving military aircraft frequently must require rapid tracking of stimuli in the visual field. It would be important to learn whether or not these pursuit movements, general visual search movements, and optokinetic nystagmus¹ are altered by low-oxygen hypoxia, hemic (COHb) hypoxia,

¹ Any turning of the head or eyes of an aviator or any turning of the aircraft would produce the lateral movement of contours in a single direction that typifies the revolving-drum contours used to generate optokinetic nystagmus.

hyperoxia, and, perhaps of most importance, hyperventilation and its resultant hypocapnia. Hypocapnia is stressed because the Newberry, Johnson, and Smiley (1965) finding of anxiety-produced hyperventilation surely has its combat-anxiety counterpart.

Chapter 19

The cornea

The effects of hypoxia on the cornea received little attention from vision researchers prior to introduction of contact lenses. As will be discussed in this chapter, placing a contact lens over the cornea sharply reduces the oxygen available to the cornea and this can lead to swelling (edema) of the cornea and to formation of epithelial microcysts. Just closing the eyes reduces oxygen available to the cornea by two-thirds. When contact lenses are worn during sleep or under lids closed for reasons other than sleep, this combination of hypoxia-producing conditions leads to corneal hypoxia and frequent corneal swelling even with extended-wear lenses (Efron and Carney, 1981).

Not all research on hypoxia and the cornea has been related to contact lens problems. Zwahlen and Grandjean (1948) looked at the effects of altitude on the sensitivity of the cornea to stimulation. Subjects spent 10 days at an altitude of 3,450 meters. Sensitivity of the cornea was found to increase at altitude.

Leonardi (1951) reported in his English summary the sensitivity of the cornea increased for 19 out of 30 subjects when oxygen mixtures were breathed corresponding to simulated altitudes of 4,000 to 7,000 meters. Subjects breathing mixtures with the lowest oxygen levels were most likely to experience increased sensitivity. The summary did not indicate whether the eyes were exposed to the low oxygen mixture. As will be discussed later, sensitivity of the cornea decreased following extended exposure of the cornea to much lower oxygen tensions than these (Millodot and O'Leary, 1980).

Smelser (1952) typically is credited with being the first to observe that hypoxia produced by contact-lens wear led to problems such as the appearance of halos. He found exposing the eye to pure nitrogen for 4 hours led all four of his subjects to report the appearance of bright halos. Two of the subjects saw these at 3 hours. The halos may have been present even earlier for all subjects, but condensate on the inner surface of the goggles made clear vision impossible. The angular size of these halos was identical to the halos that had previously been viewed as a result of wearing contact lenses. A CO₂-nitrogen mixture produced basically the same results as an all nitrogen mixture. To test whether CO₂ would produce halos, a mixture of 15 percent CO₂ and air was circulated around the cornea. No halos appeared during a 4-hour period.

Fatt and Bieber (1968) provided a theoretical discussion of the steady distribution of oxygen and carbon dioxide in the in vivo cornea with both an open and a closed eyelid. The model was based on system parameters for diffusion, solubility, consumption, and production of the two gases determined from previous research. With the eyes open, sharp gradients for oxygen and CO₂ were postulated to exist across the cornea. Oxygen tension was high at the epithelium where it entered the cornea and declined to a value of 55 mm Hg at the endothelium where it left the cornea. CO₂ was high at the endothelium and declined to near zero at the epithelium where it left the eye. With closed lids, CO₂ tension was predicted to show little variation across the cornea, although it was estimated to be somewhat higher within the cornea (where it was produced) than at both corneal surfaces where it passed from the cornea. Oxygen tension was calculated to be sharply lower at midcornea with closed lids, but rose to approximately equal tensions at both corneal surfaces.

Polse and Mandell (1970) exposed the surface of the goggled eye to pure nitrogen and to low oxygen mixtures of 1.0 percent, 1.5 percent, and 2.5 percent oxygen. They monitored corneal thickness to determine the hypoxic threshold for corneal swelling (edema).¹ Pure nitrogen produced a rapid thickening of the cornea and this thickening accelerated over a period of 90 minutes. Oxygen tensions of 1.0 and 1.5 percent produced a thickening of the cornea that was linearly related to exposure time. For the 2.5 percent, oxygen mixture (oxygen pressure equal to 19.0 mm Hg), there was no evidence of corneal thickening over 4 hours of exposure. Results were the same with dry and humidified gases. They concluded if oxygen is "below a critical range of 11 to 19 mm Hg, the cornea will hydrate and swell."

Kwan, Niinikoski, and Hunt (1972) moved small oxygen electrodes through rabbit eyes and recorded oxygen tensions within the cornea, aqueous humor, and anterior lens. Oxygen tension dropped sharply as the cornea was penetrated and the epithelium traversed. Oxygen tension continued to drop in the stroma, then rose sharply in the endothelium to a relatively high level in the aqueous humor that showed no changes across the anterior chamber. Oxygen tension then dropped sharply as the lens was penetrated and reached lowest levels in the anterior lens which was the most distant point into the eye that was measured. Anterior chamber levels averaged 72 mm Hg and this was somewhat higher than earlier research had shown or predicted. The sharp rise of oxygen in the endothelium would appear to counter predictions made by Fatt and Bieber (1968) of a

¹ Control experiments in air had shown no diurnal variation in cornea thickness.

linear drop in oxygen tension from epithelium to aqueous humor and for a negligible endothelium effect on corneal oxygen tension.

Polse, Sarver, and Harris (1975) studied corneal edema and vertical striae accompanying the wearing of hydrogel lenses. They found corneal swelling increased linearly over the first several hours of wearing time and the average increase in corneal thickness for seven subjects was about six percent after 8 hours. Vertical lines were observed (striae) after swelling by about one-half of the subjects. Corneal swelling diminished and striae disappeared when the lenses were removed. Although the striae were correlated with corneal swelling, striae sometimes did not appear concurrently with swelling and in other instances striae remained after the swelling declined. Hydrogel lenses appeared to be a factor in the striae since, according to the authors, swelling following hard lens wearing was not accompanied by striae.

Polse and Mandell (1976) conducted additional research on the etiology of corneal striae accompanying hydrogel lens wear. Contrary to the conclusions of Polse, Sarver, and Harris (1975), Polse and Mandell found exposure of the goggled eye to pure nitrogen caused swelling and striae without any need to wear a hydrogel lens. Striae appeared when corneas had swollen by about five percent and this took less than 2 hours. Exposure of the cornea to air diminished swelling and the striae disappeared when the thickness returned to the critical five percent level. The authors also investigated the effect of exposing an eye wearing a gel lens to oxygen. After about 4 hours of wearing the lens in normal air, swelling had increased and striae were present. The gas goggles then were put on and 80 percent oxygen was circulated within the goggles. Swelling decreased sharply and the striae disappeared. The goggles were then removed and, following another 3 hours, the swelling and striae returned.

Hess and Garner (1977) studied the effect of corneal edema on visual acuity. Observations were made on the single eye of one subject. Age, refractive status, and other information about the subject were not provided. The goggled eye was exposed to 100 percent nitrogen for a period of 3.5 hours. Corneal shape and thickness measures were made as well as measures of acuity for Snellen test letters, Landolt Cs, and sine wave gratings. The viewing distance was 57 cm. for sine wave gratings with spatial frequencies of 0.3 to 3 cycles per degree. The viewing distance was 570 cm for the higher spatial frequencies of 5 to 100 cycles per degree.

Corneal thickness remained constant for 1 hour then increased linearly for the next 2 hours with a small increase from hour three to hour four. Corneal thickness increased by six percent over the period of anoxia. A significant loss of acuity occurred for Landolt Cs (6/3.8 to 6/7.2) and for higher-frequency sine wave

gratings. However, the confound of viewing distance with its different accommodation requirement may partially explain the change in contrast sensitivity for the higher-frequency sine wave gratings that occurred with edema.

Decker, Polse, and Fatt (1978) manipulated the center thickness and oxygen transmissibility of soft contact lenses and determined the amount of corneal swelling for these lenses over an 8-hour period. On the basis of these data and results from previous research, they calculated the minimum oxygen tensions under the lens necessary to maintain normal corneal hydration (prevent swelling) was 10 mm Hg.

Polse (1979) demonstrated the flow of tears under hydrogel contact lenses contributed only a very small portion of the oxygen received by the cornea. Typically, this was only a little over one mm Hg for each of the three lenses tested. Diffusion of oxygen through the lenses provided a much greater amount of oxygen. This varied from 7.1 mm Hg for the AOssoft lens through 25.8 mm Hg for the HydroCurv II lens.

Efron and Carney (1979) placed polarographic oxygen electrodes on the corneal surface beneath closed lids and determined the level of oxygen to be 7.7 percent (56.7 mm Hg). This corresponded closely to earlier measurements by Fatt and Bieber (1968). Efron and Carney (1981) made further measurements of oxygen tension in human eyes beneath contact lenses under open and closed eyelids. They compared daily wear and extended wear lenses. Oxygen tension beneath the daily wear lens (Hydron) was 2.2 percent with an open eyelid. With a closed eyelid this dropped to zero. For one extended wear lens (Permalens) the comparable oxygen atmosphere figures were 6.5 and 2.4 percent. For the other extended wear lens (Gelflex 75) the comparable figures were 6.9 and 1.4 percent. Since Mandell and Farrell (1980) found an oxygen atmosphere of about three percent was necessary to prevent corneal swelling (see below), there was some question whether the "extended wear" lenses were truly suitable for extended wear.

Wagner, Polse, and Mandell (1980) studied tear pumping and corneal edema with soft contact lenses. They varied the base curve of lenses to see if this would promote tear flow under the lens and increase oxygen which would prevent corneal swelling. Their results indicated changing the base curve from 7.8 to 9.0 mm had no appreciable effect on tear replenishment or corneal swelling.

Millodot and O'Leary (1980) studied the effect of oxygen deprivation on corneal sensitivity. They exposed goggled eyes to low oxygen mixtures (2.1 percent and 3.15 percent) for extended periods and periodically measured corneal sensitivity using the Cochet-Bonnet esthesiometer. Corneal touch thresholds increased by well over 100 percent in 8 hours for 2.1 percent oxygen. A similar

effect was found with 3.15 percent oxygen although it took about another hour before initial decrements in sensitivity set in. These reductions in corneal sensitivity occurred with oxygen atmospheres that are sufficient to prevent corneal swelling. Corneal sensitivity to touch thus may have clinical significance as an indicator of less severe corneal hypoxia that may have consequences for vision or ocular pathology, even though it is not severe enough to cause corneal edema.

Wilson and Fatt (1980) investigated the thickness of the corneal epithelium during anoxia in rabbits. They found the swelling of the cornea was due almost totally to swelling of the stroma and not swelling of the epithelium. Although they recognized epithelial swelling can occur in some instances, they concluded it was not a factor in hypoxic corneal edema in rabbits nor (probably) in human corneal swelling as a result of hypoxia. They noted changes in the epithelium do occur with hypoxia with these changes leading to halos, glare, and visual acuity loss. They did not believe these were due necessarily to epithelial edema, however.

Mandell and Farrell (1980) conducted another study of corneal swelling at low atmospheric oxygen pressures. Goggled eyes were exposed to pure nitrogen and to low oxygen mixtures of 0.95 percent, 2.34 percent, and 2.77 percent. Pachometry measures were made through the goggles. Corneal swelling was regressed against the oxygen percentage and, as a result, a zero swelling oxygen percentage of 3.2 percent was determined.

Larke, Parrish, and Wigham (1981) studied apparent human corneal oxygen uptake rate using a micro-oxygen sensor applied to the unanesthetized eye for approximately 40 seconds. They found wide variation among 68 subjects. They did not find any diurnal variation occurred.

Lambert and Klyce (1981) studied the origins of Sattler's veil (increased glare and halos surrounding bright lights) in isolated rabbit corneas. Optical techniques indicated hypoxia produced a polygonal mesh of light scattering, outlining cells in the intermediate and basal epithelium. Optical transformation of this mesh produced a halo of the same dimensions observed in Sattler's veil. Prolonged hypoxia also produced an increase in stromal light scattering. However, no consistent changes in epithelial thickness as a result of hypoxia were observed.

Klyce (1981) used rabbit corneas to investigate the mechanisms underlying hypoxic corneal edema. He determined epithelial hypoxia increased production of epithelial lactate and increased its release to the stroma. This stromal lactate accumulation produces an osmotic imbalance that leads to hydration and edema.

Wilson and Stevenson (1981) found a technique where subjects judged the brightness of halos provided a much more reliable measure of recovery from hypoxic stress than was provided by traditional pachometry measures of corneal thickness. Their results indicated corneal swelling was an insensitive indicator of the hypoxic and osmotic changes in the epithelium that lead to halo formation.

Weissman and Fatt (1982) studied corneal hydration dynamics under conditions of external hypoxia. Hypoxic changes in metabolic pump rate at either or both corneal surfaces were viewed as the mechanism underlying corneal swelling. They argued the slowed metabolic pump at the endothelial side of the cornea must be producing the bulk of the effect, even though the epithelial pump is closer to the hypoxic stimulus.

Weissman, Fatt, and Horn (1982) studied the effects of breathing pure oxygen on corneal edema. They induced corneal swelling by having one subject wear a gas impermeable contact lens for 150 minutes. Corneal swelling reached values of over eight percent. Another subject had his goggled eye exposed to pure nitrogen for a similar period and an even larger swelling occurred. Sharp reductions in swelling occurred for both subjects when they breathed pure oxygen at normal atmospheric pressure, even though no removal of the external source of corneal hypoxia occurred. Resumption of air breathing led to a resumption of the corneal swelling for both subjects.

Sarver, Polse, and Baggett (1983) studied individual difference in the corneal edema response to hypoxia. Three hours of open eyed wear of a low-oxygen-transmission lens led to cornea thickness changes ranging from 3.7 percent to 12.2 percent in 30 subjects. The average change was 6.4 percent. The edema response to the experimental lens was correlated highly with the edema response to a conventional lens ($r=.79$). Subjects with higher swelling were more apt to report vertical corneal striae. The Schirmer tear test and measures of tear film breakup did not predict these large individual differences in corneal swelling.

Stefansson, Wolbarsht, and Landers (1983a) investigated effects of a corneal contact lens on oxygen tensions in the aqueous humor in cats. They found the hypoxic effect of placing the lens on the eye led to increased flow of oxygen from the aqueous to meet the metabolic needs of the cornea. Large decrements in aqueous oxygen tension occurred of 20 mm Hg or more. Removal of the contact lens led to nearly complete recovery of aqueous oxygen tension. This suggests individual differences in aqueous humor production and/or flow may account for the large individual differences in corneal swelling associated with contact lens wear.

O'Neal, Polse, and Sarver (1984) measured corneal response to rigid and hydrogel lenses during eye closure. They determined an oxygen tension of 40 mm Hg was necessary to prevent hypoxic corneal edema in the eyes-closed situation. This was substantially higher than the thresholds determined by Polse and Mandell (1970) and Mandell and Farrell (1980) which were determined by exposing goggled eyes to low-oxygen mixtures. They suggested the difference may result from increased metabolic activity of the cornea during contact lens wear and eye closure.

Castren (1984) investigated the effects of decompression to 4,000 meters on the eyes of seven subjects who wore soft contact lenses. All subjects reported at least mild symptoms after 3 hours of decompression. Most subjects reported strong symptoms after 4 hours of decompression. Symptoms apparently were visual disturbances, tearing, dryness, "injection," and smarting of the eyes. Eye examinations showed corneal erosions in 4 eyes and opacities of corneal stroma in 10 eyes.

Holden, Sweeney, and Sanderson (1984) provided further data on the minimum precorneal oxygen tension required to avoid corneal edema. Goggled eyes were exposed to air and low-oxygen mixtures of 1.0, 2.5, 4.9, 7.5, 10.1, and 21.4 percent for 8 hours. As would be expected, swelling was related inversely to the percentage of oxygen. From the average data for eight subjects, the minimum percentage of oxygen required to prevent swelling of the cornea was determined to be 10.1 percent. This corresponds to an oxygen tension of 74 mm Hg which was two to six times the tensions identified in earlier research (Polse and Mandell, 1970; Mandell and Farrell, 1980; O'Neal, Polse, and Sarver, 1984). Large individual variation in swelling was found among the eight subjects with changes in corneal thickness ranging from 2.1 to 7.4 percent for the 1.0 percent oxygen mixture. No explanation of these individual differences was attempted, but they appeared to coincide with clinical observations of wide individual differences in corneal swelling following wearing of contact lenses.

Polse and O'Neal (1985) provided oxygen requirements for extended wear contact lenses. In order to prevent corneal swelling beyond the 4.2 percent that occurs in the closed eye without a lens, they indicated the minimum lens oxygen transmissibility was approximately 75×10^{-9} cm ml O_2 /sec ml mm Hg. An oxygen tension of 40 mm Hg under the contact lens for the closed eye condition was required to prevent more than this 4.2 percent swelling.

Brennan and Girvin (1985) examined the performance of 17 aircrew members wearing soft contact lenses under conditions of hypoxia, rapid decompression, pressure breathing, vibration, acceleration, heat, cold, and while wearing an aircrew respirator. Hypoxia involved spending 2 hours in a decompression chamber at an altitude of 12,000 feet while breathing air and 2 hours at an

elevation of 27,000 feet while breathing oxygen. The eyes were exposed to air during oxygen breathing at 27,000 feet.

According to the authors, hypoxia did not produce any important decrements in Snellen acuity or contrast sensitivity, although two subjects showed decreased acuity in one eye at 12,000 feet and one subject showed a reduction of acuity in both eyes at 27,000 feet. Exposure to 12,000 feet produced "instances of minimal increases in flare and corneal oedema, but these are also considered to be without significance to aircrew." Rapid decompression produced minor decrements in acuity in two of eight subjects, but the visual acuity of all subjects was considered to be satisfactory. Slit lamp examinations revealed no bubble formation or change in transparency of the lenses or the cornea. Pressure breathing also led to no significant change in visual acuity and lenses maintained a stable position.

Only expected decrements in visual performance occurred as a result of vibration and acceleration. Contact lens movements during acceleration occurred for some subjects, but they did not interfere with vision. Heat and cold testing produced no significant changes. The respirator did not affect acuity or contrast sensitivity, but flare did increase a small amount after it was worn for 120 minutes. The authors concluded soft contact lenses are acceptable for use by aircrews. The results contrast with those of Castren (1984) who reported numerous problems associated with contact lens wear during prolonged mild hypoxia. The contrasting results may reflect different expectations of the investigators.

O'Neal and Polse (1985) investigated mechanisms controlling corneal hydration. Hypoxia was used to induce corneal swelling and recovery was studied under various conditions of eye closure and humidity. It was concluded both the endothelial pump and evaporation contributed to removal of excess fluid from the swollen cornea. With eyes open, evaporation accounted for 80 percent of this change. O'Neal and Polse (1986) used a similar methodology and compared younger (average age = 26.7 years) and older subjects (average age = 65.7 years) on recovery from hypoxia-induced corneal swelling. Data indicated slower recovery for the older subjects in both the eyes open condition (3.0 vs. 2.5 hours) and the eyes-closed condition (3.5 vs. 4.0 hours). A decrease in endothelial pump function of 10 percent was estimated for the older group compared to the younger subjects tested in O'Neal and Polse (1985).

Kenyon, Polse, and Sieger (1986) studied the influence of wearing schedule of extended wear contact lenses on complications associated with such extended wear over a 9-month period. Lenses were removed either every 4, 7, 14, or 28 days for different groups. Epithelial microcysts were the most common complication of extended wear and were experienced by all participants, regardless

of lens removal intervals. On the other hand, daily wear subjects did not develop the microcysts and this indicated the probable hypoxic origin of the microcysts.

Weissman (1986) provided a summary of critical corneal oxygen values that are required to minimize hypoxic corneal swelling for open eye and closed eye conditions. A critical precorneal oxygen tension of 30 mm Hg was identified for daily wear lenses. This required a lens oxygen transmissibility of 13×10^{-9} cm ml O₂/sec ml mm Hg. Projections of these figures to the extended wear condition also were provided.

Conclusions and research needs

Corneal swelling is a reliable consequence of low oxygen tensions. Entoptic striae are another consequence if the swelling reaches fairly high levels, although these striae do not appear to provide a major detriment to visual performance. Epithelial microcysts appear to be another consequence of hypoxia associated with contact lens wear when the hypoxia exists for several days. Given the revisions that have occurred over two decades of research, the last word is probably not in on the minimum oxygen requirement that will prevent corneal edema and other problems.

Large individual differences in corneal swelling associated with contact lens wear have been found in a number of studies (e.g., Holden, Sweeney, and Sanderson, 1984). Stefansson, Wolbarsht, and Landers (1983a) showed the aqueous humor supplies an abnormal amount of oxygen to the hypoxic cornea compared to the normal cornea. This suggests individual differences in aqueous humor production and/or flow may account for individual differences in corneal swelling associated with contact lens wear. One might predict aerobically fit individuals would have higher than normal aqueous oxygen levels. Smokers with their COHb-reduced blood oxygen saturations may have lower-than-normal aqueous oxygen levels. Research on the large individual differences in corneal edema would appear worthwhile, since they might suggest prophylaxes that would reduce or prevent the problem.

Chapter 20

Oxygen toxicity

In perhaps the first study indicating the potential toxic effects of high oxygen tensions on the human visual system, Behnke, Forbes, and Motley (1935) studied circulatory and visual effects of oxygen at three atmospheres pressure in four "healthy young men." Subjects breathed pure oxygen via a mask or helmet in a large pressure chamber at a pressure of three atmospheres for a period of at least 3.5 hours and up to 4 hours. Measurements included visual acuity and area of the visual field. Over the first 3 hours of oxygen breathing at three atmospheres pressure, pupils were dilated and visual acuity decreased by up to 25 percent. During the fourth hour, contraction of the visual fields began. Contractions ranged for different subjects from one-half the initial area to as much as the 10-degree circle of the perimeter chart. Recovery following exposure to air took 50 minutes in one extreme contraction. In one session, the field contraction suggested left temporal hemianopsia and the right pupil was dilated to a greater degree than the left. Central vision for form and color was impaired, but not seriously until the period of impending collapse. Visual acuity was reduced as much as 60 percent or even temporarily lost at impending collapse. Color acuity also typically was lost at impending collapse. Two examinations of retinal vessels indicated no retinal ischemia or constriction of vessels although subsequent research using photographic techniques has found constriction with hyperbaric oxygen (e.g., Anderson, Saltzman, and Frayser, 1967). A feeling of alertness and stimulation accompanied recovery. Breathing oxygen under pressure increased blood pressure, heart rate, and pupil size and this indicated a stimulation of the autonomic nervous system.

Comroe et al. (1945) found 23 percent of their subjects who breathed near 100 percent oxygen for 24 hours experienced irritation of the conjunctiva. However, 10 percent of a control group breathing air through the mask also experienced this condition and it partly may have reflected the mask which conducted inspired air directly over the eyes.

Noell (1962) showed pure oxygen at normal pressure, but especially at elevated pressures, had devastating effects on the rabbit retina. Rod cells were destroyed as a result of a few hours of hyperbaric oxygen and a day of pure oxygen. The electroretinogram declined gradually to zero as this process occurred. Exposure to air at any point in this process typically led only to incomplete recovery. Fortunately, a number of studies

discussed in this chapter indicate human eyes are much less susceptible than rabbit eyes to hyperoxia.

Beehler et al. (1963) exposed 10 dogs to 90 to 100 percent oxygen at normal atmospheric pressure for an average of 72 hours. All dogs died at the time of removal from the chamber or shortly thereafter from pulmonary complications. Five of the animals showed gross eye lesions which included bilateral retinal detachments, conjunctival edema, corneal haze, and anterior-chamber hemorrhage. These findings were confirmed by histology and a heavy lymphatic infiltrate was noted just under the squamous epithelium in sections from the conjunctiva with edema. Daily examination occurred for another group of six dogs exposed to the same oxygen levels, and this examination provided the dogs with a 1- to 2-hour period of room air breathing. Five of these animals showed significant eye changes, including the three who survived. These were bilateral retinal detachments, conjunctival edema, hypotony, and dilated fixed pupils. The detachments noted did not seem to be associated with the tapetum which is present in the superior half of the dog's retina, between the retina and the choroid. The authors were unsure whether the findings would generalize to human eyes, but the possibility of human eye damage as a result of extended hyperoxia was emphasized.

Like Noell (1962), Bridges (1966) also assessed electroretinographic changes of rabbits during hyperoxia (pure oxygen administered at pressures of 2.5, 3, 4, 5, 6, and 7 atmospheres). ERG b-waves and a-waves were abolished following exposure to three atmospheres of pure oxygen and following exposure to all pressures above three atmospheres. An atmosphere 2.5 times normal greatly reduced the a-wave, but did not abolish it at 5 hours of exposure. However, this hyperoxic condition did abolish the b-wave at about 3.5 hours.

Bridges (1966) found abolishment of the a-wave occurred in less than 2 hours and the b-wave was abolished in less than an hour with a pressure of seven atmospheres. The a-wave always survived longer than the b-wave with the ratio of a-wave to b-wave survival times increasing with the atmospheric pressure. Paradoxically, early exposure to hyperoxia increased the magnitude of both these waves over those obtained at atmospheric pressure. These peak responses were reached rapidly with seven atmospheres pressure and more slowly for lower pressures. Peak response latencies were similar for the two waves. The author noted the electroretinographic changes were similar to those resulting from poisoning the respiratory metabolic pathway.

Rosenberg, Shibata, and Maclean (1966), found inhalation of oxygen at three atmospheres produced constriction of the visual fields in two of seven human subjects. Little discussion of these defects occurred, but the field reductions were accompanied by

lights that "appeared too bright" and a distortion in the appearance of objects. Vision returned in both cases to normal 40 minutes after the experiment. Hypocapnia occurred in five of the six subjects for whom blood samples were obtained. Arterial CO₂ tension began to decrease during the first 5 minutes of oxygen breathing and continued until it reached 35 mm Hg after about 90 minutes and remained at that level for the 3 hours of exposure to hyperbaric oxygenation. Convulsions were not experienced as a result of the 3-hour exposure.

Margolis and Brown (1966) assessed the effects on the dog eye of exposure for up to more than 4 hours to 100 percent oxygen at a pressure of three atmospheres. Approximately a dozen dogs were exposed for 240 minutes or more and another 85 dogs exposed for shorter periods. Individual dogs were placed without restraint in a 1-m³ chamber and exposed to 100 percent oxygen at 30 lb/in² gauge pressure, equivalent to approximately three atmospheres of absolute pressure. Animals were observed for 6 to 23 days for the presence of neurologic impairment, then killed to study their nervous systems.

The only change attributable to oxygen toxicity was a characteristic retinal lesion consisting of a segmental degeneration of axons in the nerve-fiber layer of the retina in the region encompassing and surrounding the optic-nerve head. The lesion was not present in two dogs exposed for 210 and 225 minutes nor in 83 dogs exposed for shorter periods of hyperbaric oxygenation ranging from 45 to 120 minutes. Increased vascular resistance appears to be a factor in the production of this lesion, since adding two percent CO₂ to the hyperbaric oxygen mixture shifted the locus of toxic action from the eye to the CNS with increased production of convulsive responses.

Nichols and Lambertsen (1969) provided a review of the effects of high oxygen pressures on the eye that included discussion of unpublished data indicating retinal detachment in dogs exposed to pure oxygen at one atmosphere for up to 50 hours. They also included an extensive discussion of retrolental fibroplasia, the pathologic effect of hyperoxygenation that occurs in premature infants exposed to high oxygen levels.

Nichols, Lambertsen, and Clark (1969) reported a case of transient unilateral loss of vision associated with oxygen at high pressure. The subject had a history of retrobulbar neuritis and this apparently was a factor in the near total loss of vision in one eye following 4 hours of breathing pure oxygen at two atmospheres pressure. Another possible factor was an acute effect of oxygen on enzymes or nutrient flow that interfered with function of neuronal elements. The authors warned of the importance of screening for possible visual problems prior to selecting patients for hyperbaric oxygen treatment of nonocular problems.

Nichols et al. (1972) reported 4 to 8 hours of exposure to oxygen at three atmospheres pressure produced flattening of the corneal endothelium and pyknosis and nuclear loss in lens epithelium of guinea pigs. Retinal swelling was noted, but animals died or were sacrificed before the several days that probably would have been required to observe any destruction of visual cells as Noell (1962) noted in rabbits.

Schocket et al. (1972) found exposure to hyperbaric oxygen induced cataracts in mice. Groups of mice were exposed to hyperbaric oxygen at three atmospheres, pure oxygen at one atmosphere of pressure, and air. Exposures were twice weekly for 2 to 3 hours over a 2-week period. Of 50 surviving mice from the 100 receiving hyperbaric oxygen exposures, 26 developed cataracts by 8 months following exposure. This compared to 5 of 38 for the pure oxygen group and 1 of 47 for the air group. Vacuolization was found in the lens cortex of the rats receiving hyperbaric and pure oxygen, but not in the air group. The group receiving hyperbaric oxygen also had degeneration of the lens epithelium and lens fiber disorganization.

Beehler, Kobayashi, and Murakami (1972) reported the case of a man who was maintained on a respirator with 80 percent oxygen for 150 days and who became blind in both eyes at that time. When placed on a lower oxygen schedule, a slight increase in sight occurred for one eye, but the defect largely was irreversible. Retinal circulatory arrest as a result of oxygen-induced constriction of the retinal artery was seen as the cause of this blindness.

Kinney, McKay, and Gordon (1977) used fluorescein angiography in an exploratory study of oxygen toxicity in three adult squirrel monkeys who spent 50, 75, and 117 hours, respectively, in a nearly pure oxygen environment. The animal exposed for 50 hours showed no leakages or choroidal hemorrhages of the choroid blood vessels of either eye nor were any other problems seen. The animal with 75 hours of exposure showed subretinal leakages in both eyes. However, this condition corrected itself in normal air and angiograms taken 5 and 8 days after exposure were completely normal. The monkey with 117 hours of exposure did not show leakages in either eye, but evidence of leakage was found in the angiograms during testing 3, 6, 16, and 19 days after exposure. This animal showed "bilateral disciform macular elevations which contained yellowish subretinal exudates." On the other hand, histopathologic examination on the 20th day following exposure indicated no abnormalities of the eyes related to the hyperoxic exposure. These authors referred to their oxygen exposure as hyperbaric oxygen, however, the pure oxygen apparently always was breathed at normal ground level pressure.

Ray and Hawgood (1977) investigated the effects of hyperbaric oxygenation at up to seven atmospheres pressure on the ERG and the visual-evoked-response (VER) of the rat. Both a- and b-waves declined after about 1 hour of exposure and this was followed by a sharp rise in both which was interpreted as the result of a probable loss of the negative feedback elements that normally inhibit retinal responses. Effects of hyperoxia on respiration also were studied and sharp declines in respiratory rate and blood pressure typically preceded any drops in the ERG. Respiratory failure was seen as the mediator of the ERG and VER changes that occurred in hyperoxia and these changes were not seen as resulting from a direct influence of oxygen on the visual system as has been claimed for hyperoxia effects on the ERG of the rabbit (e.g., Noell, 1962).

Plewes and Farhi (1983) studied peripheral circulatory responses to acute hyperoxia in seven anesthetized dogs. Pure oxygen at atmospheric pressure was administered and blood flow at various organs was measured. Cardiac output decreased by 14 percent. Renal blood flow dropped a significant 20 percent. Other intra-abdominal organs did not show changes in blood flow. No changes were noted in skeletal muscle. Total cerebral blood flow did not change significantly, although there were significant decreases to caudate nucleus (-12 percent), cerebellum (-15 percent), mesencephalon (-20 percent), vermis (-11 percent), hippocampus (-15 percent), and retina (-27 percent). This large change for the retina shows the unusual constriction of retinal vessels to oxygen that was noted by Dollery et al. (1964) and others and which may lead to ocular lesions normally associated with hypoxia.

Palmquist, Philipson, and Barr (1984) studied refractive changes and lens changes in 25 generally older (mean age = 65.5, SD = 15.9) patients being treated with 100 percent oxygen at 2 to 2.5 times the normal atmospheric pressure for persistent leg ulcers. A control group consisted of other patients on the waiting list for hypobaric treatment. Visual acuity was assessed and biomicroscopic lens examination occurred after each 100 hyperbaric oxygen treatments. The treatment consisted of 1 hour of exposure to hyperbaric oxygen and typically occurred twice daily, 7 days a week. A myopic shift showed of at least 1 diopter was found in 24 of 25 patients with both eyes equally affected and this was discussed earlier in this report. Nuclear cataracts developed in 7 of the 15 patients who had clear lens nuclei before treatment. No nuclear cataracts developed among the 12 patients in the reference group who had clear nuclei.

Palmquist, Fagerholm, and Philipson (1986) provided additional information about the nuclear vacuoles that resulted from hyperbaric oxygen treatments. They pointed out the erroneous belief that opacities of the lens nucleus always were congenital

defects. Their investigations disclosed relatively transparent vacuoles in the nucleus of similar appearance as cortical vacuoles. Nuclear vacuoles were found in 11 out of 25 patients treated with hyperbaric oxygen. These vacuoles induced by hyperbaric oxygen were reversible to some extent. Slit-lamp photography and quantitative microradiography showed the vacuoles appeared as dark rounded areas with a lower dry mass content (approximately 0.30 g X cm^{-3}) than the surroundings (approximately 0.50 g X cm^{-3}). There was no discussion of how these vacuoles were related to the myopia produced by hyperbaric oxygenation, but presumably they were, and this gradually increasing myopia may be an indicator of the toxic effects of hyperbaric oxygen on the lens.

Bitterman, Melamed, and Perlman (1986) looked at the effects of hyperbaric oxygen on CNS function in rats. Although they did not look at the effects of hyperbaric oxygen on the eye, they found a strong relationship between the onset of EEG activity associated with seizures and the ambient illumination. Somewhat reduced (but still hyperbaric) oxygen pressures that did not induce the EEG seizure activity in light, did induce seizure activity in darkness. Every oxygen pressure that produced seizure activity led to the activity sooner in darkness than in light. Higher light levels increased the latency of these "convulsions," with the relationship strongest at the highest ambient levels. Rats who previously suffered severe retinal damage as a result of a 24-hour exposure to a very bright light showed a similar latency of convulsions in light as was found for rats with normal vision in darkness.

CO_2 increases the size of retinal and brain blood vessels and also increases the probability of convulsions during hyperbaric oxygenation. Light reduces the requirements of the retina for oxygen and reduced retinal illumination increases oxygen requirements. The dark conditions probably stimulated oxygen consumption in these rats' retinas and may have led to a reduction of retinal vasoconstriction or even to vasodilation. It is possible this relative or actual vasodilation of the retina somehow carried over to the brain and this caused the increased probability of convulsions during darkness in rats found by Bitterman, Melamed, and Perlman (1986).

Conclusions and research needs

The toxic effects of oxygen at high tensions take a number of forms and affect several ocular systems. Humans are far less susceptible than rabbits which become blind with exposure to pure oxygen at normal atmospheric pressure for relatively brief periods. Ironically, some of the toxic effects of hyperbaric oxygenation appear to be almost identical to the toxic effects of severe hypoxia. The reason for this appears to be the constriction of retinal vessels in response to the high-oxygen tensions is so

severe that retinal tissue becomes deprived of oxygen, despite the high levels of oxygen that go into solution in the plasma of the blood. The insidious development of myopia with repeated hyperbaric oxygenation that recently has been reported appears to reflect development of small cataracts and this cataract problem may be much more serious than the refractive change.

Dozens of different studies have looked at the effects of hyperbaric oxygenation on visual or ocular processes with human subjects over the years. Almost always these humans appear to have tolerated the hyperbaric oxygenation without problems, although convulsions and collapse were common in early research that explored the effects of extended exposures. However, the recent findings of Palmquist and his colleagues suggest the incidence of cataracts may have increased for these men and women who experienced hyperbaric oxygenation, either as experimental subjects or as patients.

The cataracts and ischemic changes (including blindness) in humans, and even the results of research on animals that showed retinal degeneration (rabbits) and detachment (dogs) all indicate research on the effects of hyperbaric oxygenation on vision or ocular systems may involve risks to human subjects. These risks must be weighed carefully in the decision to proceed. A history of retrobulbar neuritis appeared to be a factor in blindness that developed in one hyperbaric oxygen patient and this suggests that subjects selected for hyperbaric oxygenation research should be as free of ocular pathology as possible.

One solution to the research problem may be to use patients who are undergoing treatment with hyperbaric oxygenation. Although hyperbaric oxygenation has been described by Gabb and Robin (1987) as "a therapy in search of a disease," patients undoubtedly will continue to be selected for this treatment, despite the disturbing lack of results showing its effectiveness. Such patients typically have little to do while they are being oxygenated and they may be available and willing to report on their flicker and fusion thresholds or some other theoretically important dependent variable while they are in the chamber.

Given the potential dangers to the eye and vision of hyperbaric oxygenation, additional research on changes in vision or ocular structures of patients undergoing hyperbaric oxygenation would appear to be of immense value. The long-term consequences of developing lens-nucleus vacuoles such as those described by Palmquist and his associates would appear to be of particular importance. Hopefully, full-blown cataracts are not the outcome.

Chapter 21

Summary and integration of needed research

There are a number of general areas of vision and ocular function that need research on hypoxia and related respiratory effects. There also are a number of visual performances that have been largely or totally ignored in research on the effects of hyperoxia, hypocapnia, hypercapnia, and/or hemic (CO) hypoxia. The bulk of this chapter will discuss these general research needs and research gaps. The initial section in this chapter deals with four critical experiments which were identified as providing key information to confirm or disconfirm theoretical predictions about the effects of hypoxia and related respiratory conditions on the eye and vision. These critical experiments also would provide important methodological information that would bear directly on research methods used to tackle other research questions.

Critical experiments related to hypoxia effects on vision

One critical experiment would be a replication with appropriate controls of the Berger et al. (1943) critical experiment on the effects of hypoxia on resolution and fusion of a pair of adjacent bright dots where the clear prediction is for an improvement in resolution with hypoxia compared to performance in normal air or higher-than-normal oxygen tensions.¹ One of four subjects in the Berger et al. study showed the predicted improvement and this result apparently showed the important similarity between hypoxia decrements in visual sensitivity and decrements in visual performance associated with reduced luminance. However, the researchers failed to accept the significance of this "majority of one."

The research also is important because it should help identify the factors associated with hypoxia that, for three of four subjects, reduced visual resolution more than the hypoxic decrease in effective luminance increased resolution. They used a large

¹ Resolution of separate bright dots is improved for lower compared to higher luminance levels of the dots. This prediction of improved resolution during hypoxia was derived from the hypothesis that hypoxia effects on vision are comparable to effects of reductions in target luminance. This hypothesis provided an excellent explanation of contrast sensitivity and acuity decrements with hypoxia.

three-mm artificial pupil and pupil dilations with hypoxia (and increased spherical aberration) are one possible explanation of the decrement in resolution of dot separation. An artificial pupil or Maxwellian view smaller than the pupil used in the Berger et al. research should control for these. Refractive changes in the eye with hypoxia are an even more likely basis for the hypoxic decrements in resolution, since a three-mm pupil would not greatly reduce the depth of field. Frequent correction of refraction changes during hypoxic testing might solve this problem. Another solution would be to use a Badal optometer and present the resolution targets at several different optical distances. This would prevent the small, but possibly, significant changes in retinal image size that would be associated with spherical correction in the spectacle plane.

The second critical experiment would be designed to identify whether or not hypoxia decrements in the CFF are related directly to stimulus size in the same way that increments caused by hyperventilation in the CFF were related directly to stimulus size (Granger and Ikeda, 1961). If so, it would help identify the bases of hypoxic changes even as Granger and Ikeda shed light on retinal-integration bases of hypocapnic improvements in CFF. This experiment also would serve the important methodological function of providing information about the CFF target size that maximizes hypoxia effects and this would be useful for increasing sensitivity of experiments used to identify individual differences in effects of hypoxia on the CFF, interactions of hypoxia with luminance levels of CFF stimuli, etc. The unusually large effects of CO on CFF found by Seppanen, Hakkinen, and Tenkku (1977) may have been related to their unusually large CFF stimulus.

The third critical experiment is related closely to the second experiment on the interaction of size of the CFF stimulus and hypoxia effects and easily could be combined with it. This experiment would determine if hypoxic and hypercapnic decrements in the CFF would be comparable to the decrements in the CFF produced by a decrease in target luminance. It was found contrast sensitivity changes during hypoxia and acuity changes during hypoxia mimicked the changes produced by reducing target luminance. However, such shifts of CFF data on the luminance axis could not account for the hyperventilation increments in the CFF in the Granger and Ikeda research. Instead, Granger and Ikeda found hyperventilation improved CFF by a constant amount for all luminance levels, including low luminance levels where CFF was related directly to luminance, higher levels of CFF target luminance that caused a leveling off of the CFF, and highest luminance levels that actually led to a drop in the CFF. If hypoxic (and hypercapnic) decrements in CFF paralleled the hyperventilation increments, with the drops in CFF at high luminance levels similar to drops in CFF

at lower target luminance levels, this would indicate an important basic difference between hypoxic decrements in absolute sensitivity and hypoxic decrements in flicker sensitivity.

The fourth critical experiment relates to the finding that metabolic requirements of the retina determine vasodilation (Hickam and Frayser, 1966) and to the finding that darkness increases metabolic requirements of the retina (Stefansson, Wolbarsht, and Landers, 1983b; Linsenmeier, 1986). As a result, retinal vasodilation, retinal blood flow, retinal blood volume, and intraocular pressure (IOP) would be expected to be greater in darkness than in light. Research using retinal photography during moderate hypoxia should show more retinal vasodilation in darkness than in light. If measures of other circulation-related variables such as blood flow, blood volume, and IOP were included in this research, these measures also would be expected to show increases in the dark. The expected finding is that for a given low oxygen tension, hypoxia is "greater" with lower than with higher retinal illumination. If results met these expectations, it would imply retinal illumination must be taken into consideration in specifying the effective level of hypoxia in research and in operations involving low oxygen tensions. Extensive research with multiple levels of retinal illumination and multiple hypoxia levels could quantify the contribution of illumination to degree of hypoxia.

If an effective hypoxia existed during air breathing in a dark environment (because of the increased oxygen requirements in darkness), retinal vasodilation and increased blood volume would be expected as a means to compensate for this "night hypoxia." As will be discussed in the next section, these blood volume increases would produce IOP increases that might cause anterior chamber shallowing (Mapstone, 1981) because of a forward displacement of the lens. Refraction of the eye would be expected to increase as a result of the increased distance from the lens to the retina. This might provide the explanation of night myopia. A replication of this fourth experiment with normal air instead of moderate hypoxia, with the inclusion of ultrasound measures of lens-retina and lens-cornea distances, and with concurrent measures of refraction (in the other eye) might put an end to speculation about this phenomenon. Further support for this hypoxia explanation of night myopia would be derived if night myopia were reduced or absent during breathing of higher than normal oxygen concentrations.

Research on hypoxic eye changes that influence vision

This section discusses probable pressure-related ocular changes caused by hypoxia or by associated respiratory conditions such as hypocapnia. These changes would be expected to produce significant changes in performance on a range of visual activities and tasks. Some of these hypotheses already have been mentioned in Chapter 12:

"Ocular vessels and blood flow," in Chapter 13: "Intraocular pressure," and in other chapters which dealt with the pupil, accommodation/refraction, and phoria. This section will attempt a fuller integration of these ideas and identify initial experiments to assess these hypotheses.

This needed research would cover at least the following efforts:

1. Concurrent measures of vitreous pressure and aqueous pressure during hypoxia, hypocapnia, hyperoxia, and hypercapnia.
2. Anterior chamber depth and hypoxia, hypocapnia, hyperoxia, and hypercapnia.
3. Axial length and lens-to-retina distances as a function of hypoxia, hypocapnia, hyperoxia, and hypercapnia.
4. Changes in refraction in presbyopic and normal eyes as a function of hypoxia, hypocapnia, hyperoxia, and hypercapnia.
5. Accommodation and hypoxia, hypocapnia, hyperoxia, and hypercapnia.
6. Pupil size and hypoxia, hypocapnia, hyperoxia, and hypercapnia.
7. Pupil changes associated with anterior chamber shallowing.
8. Retinal disparity as a function of hypocapnia, hypoxia, hyperoxia, and hypercapnia.
9. Lateral phoria at far and near as a function of hypoxia, hypocapnia, hyperoxia, and hypercapnia.
10. AC/A ratio changes with hypoxia, hypocapnia, hyperoxia, and hypercapnia.

However, measurement of the shifts in location of the lens as a result of greater pressures on one side of the lens than the other may be the key to understanding and predicting most of the ocular changes in the above list. If these changed dioptric conditions during hypoxia and other respiratory conditions were well understood, it should be possible to make strong predictions about the

refraction changes, phoria changes, retinal disparity changes, AC/A changes, etc.

The key role of refractive state and pupil size on vision make the identification of the probable hypoxic changes in refraction and/or the pupil critical for understanding effects of hypoxia on vision. As was discussed earlier, no area of research may have provided more contradictory results than the research on the effects of hypoxia on the pupil, with some studies showing dilation, some showing constriction, and some showing no changes. Contradictory results also were found in research on hypoxia and the refractive state of the eye, although much less research exists on ocular refraction than for the pupil. Ohlbaum's (1969) well planned and carefully conducted research raised as many questions as it answered, since he found a significant increase in myopia and a significant recession of the near point in the same subjects. Phoria changes with hypoxia are another area where there is a large diversity of results, although increased esophoria and convergence tone with hypoxia has been the dominant finding.

Thanks to the near reflex of the pupil, pupil changes with hypoxia could be an indirect result of hypoxic changes in accommodation and/or vergence. The anterior chamber shallowing discussed by Mapstone (1981) may be another mechanism for indirect hypoxic changes in pupil size. The forward displacement of the lens against the iris might push the pupil to a larger diameter. Presumably, anterior chamber "deepening" also would exist and this reduced lens pressure on the iris might constrict the pupil. Of course, if lens displacements causing anterior chamber shallowing or deepening occur during hypoxia this also would produce changes in refraction since the lens would be farther from the retina during shallowing and closer to the retina during deepening. Given the Mapstone finding of "spontaneous" and drug induced lens-iris displacement and anterior chamber shallowing, it is possible both refractive changes and pupil changes during hypoxia are indirect results of hypoxia-induced changes in pressure within the eye that cause these lens-iris displacements.

Shallowing of the anterior chamber due to forward displacement of the lens/iris system would be expected if there were increased pressure of the vitreous against the lens and/or decreased pressure of the aqueous on the lens. As was seen in the chapter on the IOP, many contradictory results have been found from research looking at the effects of hypoxia on IOP. Some studies found increased IOP, some found decreased IOP, and some found no changes in IOP. The parallels with the many contradictions in results from hypoxia-pupil research are striking and if IOP-caused anterior shallowing/deepening influences the pupil, this may be no coincidence. As was pointed out in that chapter, increased blood volume in the retina increases the pressure of the vitreous and decreased aqueous production reduces aqueous pressure. What is more, both increased

retinal blood volume and decreased aqueous production have been identified as consequences of hypoxia.²

The diverse results in research on the effects of hypoxia on the IOP may reflect a greater contribution of aqueous tension reduction for studies showing lower IOP with hypoxia and a greater contribution of blood volume increases in studies showing higher IOP with hypoxia. A research method is needed that allows simultaneous monitoring of effects of hypoxia on retinal blood volume (or vitreous pressure) and aqueous production (or aqueous pressure). Since lens shifts and anterior chamber shallowing are predicted to result from these pressure changes (and may be the most critical pressure changes for vision), simultaneous ultrasonic measurement of axial length of the eye, lens position within the eye, and anterior chamber depth might serve this purpose and these would have the advantage of being suitable for use with human subjects.

This needed research on the probable effects of hypoxia on IOP changes that cause changes in ocular structures/processes that, in turn, cause visual changes, further is complicated by the typical confound of hypocapnia with hypoxia. This hypocapnia results from hyperventilation which occurs in many and probably most instances where low oxygen tensions are breathed (e.g., Frayser et al., 1971; Livingston, 1944a; Ernest and Krill, 1971). There are probable direct and/or indirect influences of hypocapnia on the pupil, accommodation, vergence movements, anterior chamber shallowing, which are opposite in direction to the changes on these systems produced by hypoxia. Both hypoxia and hypocapnia would be expected to influence these different ocular functions and structures, due to their well established effects on the retinal circulation.³ Opposite effects would be expected since hypoxia would tend to increase ocular blood volume and hypocapnia would tend to reduce ocular blood volume. The contradictory findings on the effects of hypoxia on the IOP may reflect hypocapnic effects dominating hypoxic effects in some studies and hypoxic effects dominating hypocapnic effects in other studies. This factor could be operat

² The drug acetazolamide also probably produces increased pressure in the back of the eye and definitely reduces pressure in the front of the eye and this may explain why this drug has produced many effects on vision and the eye that are similar to the effects of hypoxia.

³ However, hypocapnic retinal vasoconstriction and reduction of blood flow and blood volume were not as well documented in the literature as hypoxic retinal vasodilation and increased blood flow and blood volume.

ing to produce contradictory effects in addition to, or instead of, the different relative contributions of blood volume changes and aqueous production that were discussed earlier.

Since hypoxia and hypocapnia are often confounded during exposure to low oxygen tensions, the failure to find consistent increases or decreases in IOP, refraction, pupil size, etc., across studies is not surprising. As a starting point, research on these expected hypoxic increases in the IOP (and the ramifications of these IOP increases) should occur without associated hypocapnia and research on expected hypocapnic decreases on IOP (and the ramifications of these IOP decreases) should occur without changes from normal oxygen levels. By controlling respiration and/or adding CO₂ to breathing mixtures, it would be possible to study effects of hypoxia without hypocapnia. By using slightly lower than normal oxygen levels in breathing mixtures during hyperventilation, it would be possible to study effects of hypocapnia without the elevated oxygen tensions that normally accompany hyperventilation in air.⁴ Frequent measurements of blood and alveolar levels of oxygen and CO₂ are critical in this research.

The determination of hypoxia and hypocapnia effects on these diverse ocular structures and functions will be no small task, but it appears to be crucial to any basic understanding of the effects of hypoxia on vision. It would appear changes in ocular pressure that cause forward and backward displacement of the lens (and anterior chamber changes) would have the most influence on vision and, for this reason, investigation of the existence and magnitude of such hypoxic/hypocapnic lens displacements should receive initial research emphasis.

If this shallowing of the anterior chamber and any "deepening" of the anterior chamber counterpart are produced by these respiratory conditions, the forward lens displacements would boost refraction directly because of the greater distance from the lens to the retina and the backward lens displacements would increase farsightedness. Such nonciliary influences on refraction would be expected to alter the AC/A ratio, lateral phorias at far and near, and retinal disparity,⁵ because of the smaller-than-normal or

⁴ Elevated oxygen would be expected to have a vasoconstrictive effect of its own.

⁵ Retinal disparities in one direction would be expected for stimuli closer than the fixation rest position and retinal disparities in the opposite direction would be expected for stimuli farther away from the subject than his fixation rest position. Any change in retinal disparity with hypoxia would indicate a shift in the fixation rest position and/or the change in normal accommodation-convergence relationships.

greater-than-normal accommodation effort required to focus targets. One research study already has shown the AC/A ratio to decline with hypoxia (Ohlbaum, 1969). Phoria research typically has shown esophoric shifts, but the results have been mixed. However, it must be remembered there typically has been a confound of hypoxia and hypocapnia in these studies.

Since different effects on retinal disparity, the AC/A ratio, and phorias would be predicted if the lens moved forward than if it moved backward, it would be an efficient research strategy to identify the nonciliary-mediated hypoxic or hypocapnic refraction changes that occur with hypoxia and hypocapnia first (perhaps through ultrasound measurement of changes in eyeball length and lens location), predict the effects on the retinal disparity, phoria, and the AC/A ratio, and then collect the retinal disparity, phoria, and AC/A ratio data and see if they confirm predictions. Inclusion of some presbyopic subjects in this research on lens displacements and their consequences for ocular refraction would appear to have much value, since there would be no contamination of refraction measures by lens shape changes as a result of normal ocular accommodation.

Forward and backward lens displacements also could explain some pupil changes if pushing the iris forward with the lens dilates the pupil and backward lens displacement constricts the pupil. However, the reduced stimulus to accommodation resulting from a forward displacement of the lens (increased refraction) itself would lead to a relatively dilated pupil and the increased stimulus to accommodation from a backward displacement of the lens (reduced refraction) would lead to a relatively constricted pupil. If research shows that anterior chamber shallowing occurs with hypoxia (and hypercapnia which also would increase blood volume) and if research shows anterior chamber deepening occurs with hypocapnia (and hyperoxia which also would decrease blood volume), then concurrent measurement of pupil changes could identify whether the alterations in pupil size discussed above actually occur.

Refraction changes produced by whole lens displacements would be expected to strongly influence vision when the refractive changes prevented accurate focus on targets and such refractive changes probably would dwarf any effects of pupil size on visual performance. However, if the target were within the new range of ocular accommodation and could be maintained in sharp focus, pupil changes associated with the accommodation or produced by the whole lens displacements of the iris could become a more important factor than the refraction changes on visual sensitivity or visual acuity.

The "pure" hypoxic and "pure" hypocapnic effects on IOP and the effects of the IOP changes on refraction, the pupil, vergence movements, anterior chamber depth, etc., need to be determined at mild, moderate, and severe hypoxias and hypocapnias. Following

this, it would be critical to look at some combined effects of hypoxia and hypocapnia which are representative of the combinations that occur in hypoxia when hypocapnia is not controlled. Hypoxia and hypocapnia effects would be expected to cancel each other in at least some combinations, due to their opposite effects on retinal blood volume. Their effects on aqueous production are understood less well, however, and this could produce some surprising findings on IOP, anterior shallowing/deepening, lens displacement, refraction, etc.

In summary, a tentative initial schedule of research on what appears to be an important mechanism by which hypoxia influences vision through its direct influence on blood volume and through effects of the resultant pressure changes on the lens, iris, and the eyeball itself. Should ultrasound measurements of the dimensions of the eyeball and its components (or other measurement technology) confirm these respiratory effects on ocular structures occur, this would open the door to prediction and assessment of the quantitative and qualitative effects of these changes on visual performance.

Causes of dimming, brightening, and red veils

The subjective dimming of the visual world during exposure to low oxygen tensions, the brightening that follows a return to air or higher oxygen tensions, and the entoptic red veils that accompany a return to air and oxygen breathing following hypoxia all may mark significant ocular or neural events. One possibility is large blood volume and associated IOP changes are occurring as a result of the change in respiratory gasses. The dimming and brightening may reflect differences in the amount of light transmitted through the dilated and constricted vascular network, respectively. The red veils may be pressure phosphenes associated with mechanical changes in the retina because of large blood volume and pressure changes. Research is needed which measures at least ocular pressure, but which also might include measures of axial length, lens location, pupil size, and other variables, while respiratory gases are changed suddenly and while subjects provide concurrent reports of these visual and entoptic phenomena. If these visual and entoptic phenomena do indeed mark significant circulatory changes or other events, they can become important dependent variables in subsequent research on hypoxia and vision and the eye.

Response and decision effects in CFF research

There is need for an extension to the critical flicker/fusion frequency domain of the Ernest and Krill (1971) research showing sharply increased scalloping of sensitivity thresholds for ascending and descending trials during hypoxia compared to during air

breathing. Not only hypoxia, but hypocapnia, hyperoxia, hypercapnia, and carbon monoxide could be included in this research that would accurately establish effects of the respiratory condition on the CFF through elimination of the influence of hypoxic changes in decision or response processes. However, this research also would quantify response delays for different respiratory conditions and allow judging of the amount of confounding of these delays (or speed-ups) with actual respiratory effects as this confounding has occurred in the results of previous research that used all ascending or all descending trials to establish the CFF threshold. Rate of change in the flash-rate also could be varied in this research to identify the rate that effectively would eliminate the confounded response-decrement effects.

Respiratory effects on the resting state of accommodation

Obviously, if the forward/backward displacements of the lens occur as a result of hypoxia, hypocapnia, and other respiratory conditions, there would be a shift in the resting position of accommodation. However, this would not preclude changes in accommodation mediated by changes in tonus of the ciliary. The tricky thing is to find a methodology that would allow separation of whole lens displacements and lens shape changes. If ultrasound measurements could cope with small lens thickness changes as well as lens location changes, both influences on refraction could be measured in the same research. Carbon monoxide and smoking effects also need to be examined in this research since they might highly increase night and empty-field myopias with serious consequences for military performance.

Neglected variables in research on hyperbaric oxygenation

No studies were found which looked at CFF changes with hyperbaric oxygenation, despite the relative ease with which such a study could be conducted and the availability of patients who could provide the data as an incidental task during their treatment for medical problems. Given what appear to be basic differences in the effects of respiratory conditions on flicker sensitivity and absolute/differential sensitivity, hyperbaric oxygenation may produce improvements in the CFF, even though it does not increase these other types of sensitivity. Such a result could help elucidate basic flicker perception mechanisms.

No one appears to have followed up the Behnke, Forbes, and Motley (1935) finding of an immediate decrement in visual acuity with hyperbaric oxygenation. Several studies have found oxygen at one atmosphere does not produce decrements in acuity and the poorly documented decrement with hyperbaric oxygenation found by Behnke, Forbes, and Motley may have been a spurious result. Study of

visual acuity and/or contrast sensitivity under hyperbaric oxygenation would appear to be worthwhile, especially if subjects would be subjected to the potentially toxic environment for other medical reasons and the acuity study would not increase or modify this exposure. If decrements in performance were found, investigation of their bases should follow.

No studies were found which looked at the effects of hyperbaric oxygenation on the standing potential in man or animals. This would appear to be an important area for future research. It is true pure oxygen at a single atmosphere had negligible effects on the SP (Drummond and Rebuck, 1981), but persistence of vision following retinal ischemia also showed little difference between air breathing and pure oxygen breathing at one atmosphere. On the other hand, dramatic increases in persistence of vision occurred for pressures above one atmosphere. The Kozousek (1967) finding of enhanced positive and negative ERG potentials with hyperbaric oxygenation also may augur for substantial SP changes with hyperbaric oxygenation.

No studies were found which looked at the effects of hyperbaric oxygenation on the VEP. Pure oxygen at one atmosphere did not produce changes in the VEP (Smith and Strawbridge, 1974), but, as discussed above, hyperbaric oxygenation sometimes is qualitatively different in its effects than oxygen at concentrations from 21 to 100 percent at sea level.

Although several studies investigated the effects of breathing pure oxygen on recovery of hypoxic changes in accommodation and convergence nearpoints, accommodation and convergence fatigue, and phoria, no studies were found which looked at the effects of increased oxygen tensions on accommodation, convergence, and phoria without preceding hypoxia. Research in each of these areas would appear to have both theoretical and practical benefits.

No research was found that measured oxygen gradients in the eyes of animals under conditions of hyperbaric oxygenation. Given the huge changes hyperbaric oxygenation produced in persistence of vision following pressure ischemia (e.g., Carlisle, Lanphier, and Rahn, 1964), one would expect oxygen tensions throughout the vitreous would show dramatic increases under hyperbaric oxygenation even as they showed large increases with oxygen breathing at one atmosphere (Alder and Cringle, 1985).

Some research has shown what appears to be increased ability to make color discriminations during hyperbaric oxygenation. These may deserve replication and extension. The vivid sequence of colors that occur in viewing an afterimage of a bright white stimulus also might show variation during hyperbaric oxygenation compared to normal air. Matching of entoptic colors generated with

Benham's top with spectral colors also might be found to differ during hyperbaric oxygenation than during breathing of air.

Research on hypocapnia, hypercapnia, and carbon monoxide

Research on the effects of carbon monoxide on vessel size and blood flow was not found. It would appear a comparison of the effects on vessel size and blood flow of comparable reductions in oxyhemoglobin as a result of hypoxic and carbon-monoxide hypoxia would be important. It is expected this research would indicate the important role of hemoglobin without associated oxygen (or carbon monoxide) in retinal vasodilation and increases of blood flow to the retina. Such differences, if found, might help account for large differences in the effects of the two types of hypoxia on visual performance that often have been found.

Effects of carbon monoxide, hypocapnia, and hypercapnia on color vision, also appear to have been neglected. Identification of any significant specific color defects that may exist for these conditions would be important, since the information could be used to develop "Ishihara" signs warning of the dangerous respiratory condition that could only be read during the presence of the defect.

Needed research on the effects of acetazolamide

Acetazolamide increases cerebral blood flow (Lassen et al., 1987) and probably increases retinal blood flow. Acetazolamide also sharply reduces aqueous production and anterior chamber pressure. As was discussed earlier in this chapter and in previous chapters, this is parallel to effects of hypoxia for retinal blood flow and, according to Mercier et al. (1964), parallel to hypoxia effects on aqueous production. This is the pair of conditions that would be expected to lead to anterior chamber shallowing (Mapstone, 1981). Acetazolamide also induces hyperventilation (Lassen et al., 1987) and this also is frequently true of hypoxia. Since acetazolamide may provide a model for hypoxic effects, it is not surprising that it has similar effects on visual and ocular processes as hypoxia. It would be of interest to know whether it produces decrements in the CFF and absolute sensitivity like it produced decrements in visual field size (Kobrick, 1970). No CFF research with acetazolamide was found and the single study of the drug's effect on visual sensitivity was poorly controlled (Miller, 1956).

Hypocapnia and contrast sensitivity

Hypocapnia improved absolute sensitivity and sensitivity to flicker (e.g., Alpern and Hendley, 1952). There were no comparable

improvements found for hypocapnia in contrast sensitivity or acuity. If the hypocapnic improvements in sensitivity that led to increased absolute sensitivity and higher CFF somehow were countered by dioptric or pupillary changes that increased target blur, one would expect improved contrast sensitivity during hypocapnia for very coarse gratings where focus largely is irrelevant and decreased sensitivity for fine gratings where focus is important. Even fine acuity might be improved (above "normocapnia" levels) during hypocapnia if close attention were paid to refractive state and targets were presented at optimal focus either through spectacle correction or through positioning of the target at the focal plane (perhaps with a Badal optometer). Research on hypocapnia and contrast sensitivity is important because it may help identify the bases for hypocapnic increases in absolute and flicker sensitivity.

Individual differences in hypoxic effects on vision

Large individual differences in performance were found in virtually every study of the effects of hypoxia on human visual performance reviewed in this report. Large individual differences existed even when blood oxygen saturations were equated (Ernest and Krill, 1971). Individual differences in hypocapnia during hypoxia were somewhat more apt to predict individual performance than individual differences in blood oxygen saturation (e.g., Wald et al., 1942). One thrust of research on individual differences should be to identify the bases of these individual differences. However, until a better understanding exists of the ocular and neural bases for visual performance changes during hypoxia, no complete picture of individual differences is possible.

Some subjects almost have been immune to hypoxic stimuli that cause large changes in others. It is important to determine whether individuals who show large decrements on one class of visual performance such as absolute sensitivity also show large decrements on other classes of visual performance such as CFF. It also would be important to determine whether or not they also show more recession of the accommodation near point, more fatigue of accommodation, and more slowing of reading eye movements. Identification of high and low performers during hypoxia (if they exist) would have important implications for selecting military personnel for work at altitudes.

If as is expected, there are hypoxia-tolerant individuals, it is important to identify whether other easily-measured variables are related to hypoxia tolerance, since these would assist in selection of such personnel. Correlates of hypoxia tolerance such as cardiovascular fitness particularly would be important, since they probably would indicate individuals can be trained to increase their hypoxia tolerance.

Although it is expected hypoxia-tolerant individuals exist who do well on a wide range of visual and oculomotor tasks, it also is possible that some specific visual performances such as CFF may not be correlated with most other performances for individuals with a range of hypoxia tolerance. If so, this information would be valuable for improving our understanding of the maverick visual function and its changes with hypoxia.

Individual differences were large for tolerance/susceptibility to corneal hypoxia. Any research aimed at identifying hypoxia-tolerant individuals and their cardiovascular or other characteristics or any research aimed at identifying means for increasing hypoxia tolerance, might also include measures of corneal swelling when eyes are submitted to very low oxygen tensions for several hours. Since there are advantages of contact lenses over spectacles for aviators in some situations (Brennan and Girvin, 1985), any results that allowed selection of or training of hypoxia-tolerant corneas would be important for military aviation.

Hypoxia and hypocapnia and eye movements of aviators

The dramatic effects of hyperventilation in hypoxic settings on nystagmus induced by angular acceleration found by Newberry, Johnson, and Smiley (1965) would appear to have large implications for military aviators. The dynamic visual scenes encountered in fast moving military aircraft frequently must require rapid tracking of stimuli in the visual field. Increased susceptibility to nystagmus from angular acceleration of the aircraft could interfere with this target location and identification. Optokinetic nystagmus would be induced whenever the head or eyes were not in a straight-ahead position or when the aircraft was turning. The increased angular nystagmus following hyperventilation may augur for increased optokinetic nystagmus following hyperventilation and this too would be expected to interfere with vision in moving aircraft. It seems important to learn whether or not pursuit movements, general visual search movements, and optokinetic nystagmus are altered by low-oxygen hypoxia, hemic (COHb) hypoxia, hyperoxia, and hyperventilation with its resultant hypocapnia. Even though Newberry, Johnson, and Smiley (1965) believed their increased angular nystagmus responses were not induced directly by hypoxia, but by anxiety induced hyperventilation, the results have much relevance to military aviation, since there is probably no lack of combat-anxiety-produced hyperventilation.

Other needed research

The "Conclusions and research needs" sections of the previous 20 chapters included research needs that were not selected for inclusion in this chapter. Although, these were judged to have

somewhat less theoretical or practical importance than the studies described, some of them actually may have much more relevance when viewed from another researcher's perspective.

References

- Abraham, F. A., Brill, S., Yoran, P., and Blumenthal, M. 1984. Scotopic threshold of the human retina during dynamic physical effort. Ophthalmic Research. 16:334-336.
- Abramson, E., and Heyman, T. 1944. Dark adaptation and inhalation of carbon monoxide. Acta Physiologica Scandinavica. 7:303-305.
- Adams, C. K., Dawson, W. W., Perez, J. M., Lieberman, H. R., and Tyler, T. R. 1977. Respiratory stress, visual function and moderation by chemotherapy. Fort Detrick, MD: U.S. Army Medical Research and Development Command. Contract DADA 17-71-C-1110 Final Report.
- Adler, F. H. 1945. Effect of anoxia on heterophoria and its analogy with convergent concomitant squint. Archives of Ophthalmology. 34:227-232.
- Adler, H. F., Burkhardt, W. L., Ivy, A. C., and Atkinson, A. J. 1950. Effect of various drugs on psychomotor performance at ground level and at simulated altitudes of 18,000 feet in low pressure chamber. Journal of Aviation Medicine. 21:221-236.
- Aisenberg, R. B., Rosenthal, A., Wolff, P. H., and Nadas, A. S. 1974. Hypoxemia and critical flicker frequency in congenital heart disease. American Journal of Diseases of Children. 128:335-338.
- Alder, V. A., and Constable, I. J. 1981. Effect of hypoxia on the mean firing rate of retinal ganglion cells. Investigative Ophthalmology and Visual Science. 21:450-456.
- Alder, V. A., Cringle, S. J., and Constable, I. J. 1983. The retinal oxygen profile in cats. Investigative Ophthalmology and Visual Science. 24:30-36.
- Alder, V. A., and Cringle, S. J. 1985. The effect of the retinal circulation on vitreal oxygen tension. Current Eye Research. 4:121-129.
- Alder, V. A., Niemeyer, G., Cringle, S. J., and Brown, M. J. 1986. Vitreal oxygen tension gradients in the isolated perfused cat eye. Current Eye Research. 5:249-256.

- Alpern, M., Faris, J., Eskildsen, P., and Garnett, P. 1955. Effect of hyperventilation on the human electroretinogram. Science. 121:101-102.
- Alpern, M., and Hendley, C. D. 1952. Visual functions as indices of physiological changes in the acid-base balance of the blood. American Journal of Optometry. 29:301-314.
- Amos, C. S. 1976. The effect of a nitrous oxide-oxygen mixture on the lateral heterophoria. American Journal of Optometry. 53:182-186.
- Anderson, B., and Farmer, J. C. 1978. Hyperoxic myopia. Transactions of the American Ophthalmological Society. 76:116-124.
- Anderson, B. Jr. 1968. Ocular effects of changes in oxygen and carbon dioxide tension. Transactions of the American Ophthalmological Society. 66:423-474.
- Anderson, B., Jr., Saltzman, H. A., and Frayser, R. 1967. Changes in arterial pCO_2 and retinal vessel size with oxygen breathing. Investigative Ophthalmology and Visual Science. 6:416-419.
- Arden, G. B., and Greaves, D. P. 1956. The reversible alterations of the electroretinogram of the rabbit after occlusion of the retinal circulation. Journal of Physiology. 133:266-274.
- Arden, G. B., and Kelsey, J. H. 1962. Some observations on the relationship between the standing potential of the human eye and the bleaching and regeneration of visual purple. Journal of Physiology. 161:205-226.
- Bachman, W. G., and Behar, I. 1987. The effect of cycloplegia on the visual contrast sensitivity function. Aviation, Space, and Environmental Medicine. 58:339-342.
- Baer, D. J. 1967. Hyperventilation effects on the critical flicker frequency of smokers and nonsmokers. The Journal of General Psychology. 76:201-206.
- Bagby, E. 1921. The physiological effects of oxygen deprivation. Journal of Comparative Psychology. 1:97-113.
- Bardenzellu, T. 1929. Ricerche sulla tensione oculare in occhi normali di soldati alle manovre alpine invernali. Bollettino Oculistica. 8:1281-1292.
- Bean, J. W. 1945. Effects of oxygen at increased pressure. Physiological Reviews. 25:1-147.

- Beard, R. R., and Grandstaff, N. 1970. Carbon monoxide and cerebral function. Annals of the New York Academy of Sciences. 174:385-395.
- Becker-Freysing, H. 1950. Physiological and patho-physiological effects of increased oxygen tension (Chapter V-E). In: German aviation medicine in World War II. Washington, DC: Department of the Air Force.
- Beehler, C. C. 1964. Oxygen and the eye. Aeromedical Review. 3:1-21.
- Beehler, C. C., Kobayashi, T., and Murakami, S. 1972. Blindness of an adult caused by oxygen. Journal of the American Medical Association. 219:741-742.
- Beehler, C. C., Newton, N. L., Culver, J. F., and Tredici, T. 1963. Ocular hyperoxia. Aerospace Medicine. 34:1017-1020.
- Behnke, A. R., Forbes, H. S., and Motley, E. P. 1935. Circulatory and visual effects of oxygen at 3 atmospheres pressure. American Journal of Physiology. 114:436-442.
- Benedikt, O., Zirm, M., and Harnoncourt, K. 1974. Die Beziehungen zwischen metabolischer Acidose und intraocularen Druck nach Carboanhydrasehemmung mit Acetazolamid. Albrecht von Graefes Archiv für klinische und experimentelle Ophthalmologie. 190:247-255.
- Bennett, P. B., and Cross, A. V. C. 1960. Alterations in the fusion frequency of flicker correlated with electroencephalogram changes at increased partial pressures of nitrogen. Journal of Physiology. 151:28P-29P.
- Berg, O. 1949. A study of the effect of Evipan on the flicker fusion intensity in brain injuries. Acta Psychiatrica et Neurologica. Supplementum 58:1-116.
- Berger, C., and Bøje, O. 1937. Über den Einfluss von Sauerstoffmangel auf das Auflösungsvermögen des emmetropen Auges. Skandinavian Archiv für Physiologie. 77:129-138.
- Berger, C., McFarland, R. A., Halperin, M. H., and Niven, J. I. 1943. The effects of anoxia on visual resolving power. American Journal of Psychology. 56:385-407.
- Bietti, G. 1953. Effects of experimentally decreased or increased oxygen supply in some ophthalmic diseases. Archives of Ophthalmology. 49:491-513.

- Bietti G. 1972. Recent experimental, clinical, and therapeutic research on the problems of intraocular pressure and glaucoma. American Journal of Ophthalmology. 73:475-500.
- Bietti, G. B., and Giardini, A. 1949a. Influenza dell'annossia sui movimenti oculari: II. Richerche comparative sull'azione dell'anossia e dell'alcool da soli o associati. Rivista di Medicina Aeronautica. 12:198-210.
- Bietti, G. B., and Giardini, A. 1949b. Influenza dell'annossia sui movimenti oculari: III. Azione dell'anossia sul potere di fusione delle immagini retiniche. Rivista di Medicina Aeronautica. 12:339-348.
- Bietti, G. B., and Lo Monaco Croce, T. 1941. Variazioni della pressione arteriosa retinica e omerale, del tono endo-oculare e del quadro endo-otto-scopico retinico nella anossia. Rivista di Medicina Aeronautica. 4:177-248.
- Bietti, G. B., and Scano, A. 1946. Influenza dell'annossia sui movimenti oculari: I. Azione sui movimenti dell'occhio nella lettura. Rivista di Medicina Aeronautica. 9:12-22.
- Bietti, G., Virno, M., Pecori-Giraldi J, and Pellegrino, N. 1975. Acetazolamide, metabolic acidosis, and intraocular pressure. American Journal of Ophthalmology. 80:360-369.
- Birren, J. E., Fisher, M. B., Vollmer, E., and King, B. G. 1946. Effects of anoxia on performance at several simulated altitudes. Journal of Experimental Psychology. 36:35-49.
- Bitterman, N., Melamed, Y., and Perlman, I. 1986. CNS oxygen toxicity in the rat: Role of ambient illumination. Undersea Biomedical Research. 13:19-25.
- Bogetti, B., and Molfino, A. 1965. Comportamento del senso cromatico durante iperossia in camera iperbarica. Annale di Ottalmologia e Clinica Oculistica. 91:1148-1158.
- Boles Carenini, B., and Cima, V. 1952. Studi sul comportamento del senso cromatica (equazione de Rayleigh) all'anomaloscopia di Nagel sotto alterato apporto di Ossigeno all'apparato oculare. Rivista di Medicina Aeronautica. 15:527-542.
- Brennan, D. H., and Girvin, J. K. 1985. The flight acceptability of soft contact lenses: An environmental trial. Aviation, Space, and Environmental Medicine. 56:43-48.
- Bridges, W. Z. 1966. Electroretinographic changes during hyperoxia. Archives of Ophthalmology. 75:812-817.

- Brognoli, C., and Boles Carenini, B. 1952. Sulla possibilita' di influenzare con mezzi medicamentosi le alterazioni della macchia cieca e degli angioscotomi da anossia. Rivista di Medicina Aeronautica. 15:274-286.
- Brown, J. L., Hill, J. H., and Burke, R. E. 1957. The effect of hypoxia on the human electroretinogram. American Journal of Ophthalmology. 44:57-67.
- Bunge, E. 1936. Verlauf der Dunkeladaptation bei Sauerstoffmangel. Archiv für Augenheilkunde. 110:189-197.
- Burns, J. D. 1971. Hyperbaric gas effects on critical flicker frequency in the rhesus monkey. Physiology and Behavior. 7:151-156.
- Buscalossi, A. 1938. Comportamento del tono oculare in individui normali sotto l'influenza della decompressione ambiente. Annali di Ottamologia e Clinica Oculistica. 66:292-312.
- Carapancea, M. 1971. ERG scotopic manifestation and their determinism, in experimental conditions of high altitude. Vision Research. 10:1219.
- Carapancea, M. 1977. L'hyperophtalmontonie experimentale et clinique des hautes altitudes. Archives de Ophthalmologie. 37:775-784.
- Carapancea, M., Popescu, M. P., Corneanu, M., and Busneag, C. 1967. Constant Na and inconstant K transfer from the blood to the aqueous humour in the course of experimental hypobarism: A mechanism of high altitude glaucoma. Romanian Medical Review. 21:3-13.
- Carapancea, M., Stefan, M., and Udrescu, E. 1971. Hyperophthalmotonie hypobarique de l'aviateur aux consequences visuelles a grande altitude. Revue Roumaine de Physiologie. 8:345-351.
- Carapancea, M., Stefan, M., and Udrescu, E. 1973. Indications visuelles sur les criteres fonctionnels de l'accommodation cilio-zonulo-cristallinienne hypermetropique, chez l'aviateur, aux grandes altitudes fictives. Revue Roumaine de Physiologie. 10:379-385.
- Carlisle, R., Lanphier, E. H., and Rahn, H. 1964. Hyperbaric oxygen and persistence of vision in retinal ischemia. Journal of Applied Physiology. 19:914-918.
- Castrén, J. 1984. The significance of low atmospheric pressure on the eyes with reference to soft contact lenses. Acta Ophthalmologica Supplementum. 161:123-127.

- Chase, A. M., and Hagan, W. H. 1943. The photochemical and thermal reactions of visual purple in absence of oxygen. Journal of Cellular and Comparative Physiology. 21:65-76.
- Chiou, G. C., Liu, H. K., and Trzeciakowski, J. 1980. Studies of action mechanism of antiglaucoma drugs with a newly developed cat model. Life Sciences. 27:2445-2451.
- Christensen, C. L., Gliner, J. A., Horvath, S. M., and Wagner, J. A. 1977. Effects of three kinds of hypoxia on vigilance performance. Aviation, Space, and Environmental Medicine. 48:491-496.
- Clamann, H. G. 1938. Die Dunkeladaptation des Auges bei Sauerstoffmangel. Luftfahrtmedizin. 2:223-225.
- Clarke, C., and Duff, J. 1976. Mountain sickness, retinal haemorrhages, and acclimatisation on Mount Everest in 1975. British Medical Journal. 2:495-497.
- Comroe, J. H., Dripps, R. D., Dumke, P. R., and Deming, M. 1945. Oxygen toxicity: The effect of inhalation of high concentrations of oxygen for twenty-four hours on normal men at sea level and at a simulated altitude of 18,000 ft. Journal of the American Medical Association. 128:710-717.
- Cooke, J. P. 1970. Intraocular Pressure and Retinal Responses of Dogs at 45,000 and 80,000 Feet. Aerospace Medicine. 41:283-289.
- Cooke, J. P. 1971. Effects of helium and nitrogen upon intraocular pressure during near-vacuum exposure. Journal of Applied Physiology. 30:313-318.
- Craik, K. J. W. 1940. Origin of visual after-images. Nature. 145:512.
- Cusick, P. L., Benson, O. O., and Boothby, W. M. 1940. Effect of anoxia and of high concentrations of oxygen on the retinal vessels: Preliminary report. Proceedings of the Mayo Clinic. 15:500-502.
- Decker, M., Polse, K. A., and Fatt, I. 1978. Oxygen flux into the human cornea when covered by a soft contact lens. American Journal of Optometry and Physiological Optics. 55:285-293.
- Dodt, E. 1951. Elektroretinographische Untersuchungen zur Analyse des Flimmerphänomens im menschlichen Auge. Bericht über die Zusammenkunft der Deutschen Ophthalmologischen Gesellschaft. 57:242-245.

- Dollery, C. T., Bulpitt, C. T., and Kohner, E. M. 1969. Oxygen supply to the retina from the retinal and choroidal circulations at normal and increased arterial oxygen tensions. Investigative Ophthalmology and Visual Science. 8:588-594.
- Dollery, C. T., Hill, D. W., Mailer, C. M., and Sousa Ramalho, P. 1964. High oxygen pressure and the retinal blood-vessels. Lancet. 2:291-292.
- Drummond, J. C., and Rebuck, A. S. 1981. Effect of hypoxia on the corneoretinal potential in man. Ophthalmic Research. 13:213-223.
- Duguet, J. 1947. Le comportement de la parallaxe stéréoscopique en anoxémie. La Médecine Aéronautique. 2:36-42.
- Duguet, J., Dumont, P., and Bailliart, J. P. 1947. Action de l'anoxémie et de l'inhalation d'oxygène sur la circulation rétinienne. La Médecine Aéronautique. 2:201-211.
- Duguet, J., and Mercier, A. 1951. Les modifications de l'aire pupillaire en anoxie. La Médecine Aéronautique. 7:433-436.
- Dyer, F. N. 1986. Smoking and soldier performance: A literature review. Fort Detrick, MD.: U. S. Army Medical Research and Development Command. USAARL Report No. 86-13.
- Dyer, F. N., and Allen, T. M. 1968. Effects of the apparent size of afterimages in studies of Emmert's law. Proceedings of the American Psychological Association. 1968:101-102.
- Eckel, K. 1951. Der Adaptationsverlauf unter verschieden starken Ausbleichung und kurzfristiger Blendung (sowie unter Sauerstoffatmung). Ophthalmologica. 122:325-334.
- Efron, N., and Carney, L. G. 1979. Oxygen levels beneath the closed eyelid. Investigative Ophthalmology and Visual Science. 18:93-95.
- Efron, N., and Carney, L. G. 1981. Oxygen tension beneath contact lenses under the closed eyelid: Human eye measurements. American Journal of Optometry and Physiological Optics. 58:806-809.
- Elsas, F. J., Anderson, B. Jr., and Lefler, W. H. 1968. Hyperbaric oxygen and dark adaptation in man. Aerospace Medicine. 39:970-971.
- Enroth-Cugell, C., Goldstick, T. K., and Linsenmeier, R. A. 1980. The contrast sensitivity of cat retinal ganglion cells at reduced oxygen tensions. Journal of Physiology. 304:59-81.

- Ernest, J. T., and Krill, A. E. 1971. The effect of hypoxia on visual function. Psychophysical studies. Investigative Ophthalmology. 10:323-328.
- Ernsting, J. 1965. The effects of anoxia on the central nervous system. In: J. A. Gillies (Ed.), A textbook of aviation physiology. New York and Oxford: Pergamon Press.
- Evans, J. N. 1938. An introduction to clinical scotometry. New Haven, CT: Yale University Press.
- Evans, J. N., and McFarland, R. A. 1938. The effects of oxygen deprivation on the central visual field. American Journal of Ophthalmology. 21:968-980.
- Eysel, U. T. 1978. Susceptibility of the cat's visual system to hypoxia, hypotonia and circulatory arrest. Pflugers Archiv für die Gesamte Physiologie. 375:251-256.
- Fatt, I., and Bieber, M. T. 1968. The steady distribution of oxygen and carbon dioxide in the in vivo cornea. Experimental Eye Research. 7:103-112.
- Fenn, W. O., Galambos, R., Otis, A. B., and Rahn, H. 1949. Corneo-retinal potential in anoxia and acapnia. Journal of Applied Physiology. 1:710-716.
- Ferree, C. E., and Rand, G. 1922. Perimetry: Variable factors influencing the breadth of the color fields. American Journal of Ophthalmology. 5:886-895.
- Fichter, H. 1940. Über das Verhalten der normalen und anomalen Trichromasie bei Hypoxämie. Doctoral dissertation. University of Freiburg.
- Fischer, F. P., and Jongbloed, J. 1935. Untersuchungen über die Dunkeladaptation bei herabgesetztem Sauerstoffdruck der Atmungsluft. Archiv für Augenheilkunde. 109:452-456.
- Flower, R. W., and Patz, A. 1971. The effect of hyperbaric oxygenation on retinal ischemia. Investigative Ophthalmology. 10:605-616.
- Fodor, G. G., and Winneke, G. 1972. Effect of low CO concentrations on resistance to monotony and on psychomotor capacity. Staub-Reinhaltung der Luft. 32:46-54.
- Forster, H. V., Soto, J., Dempsey, J. A., and Hosko, M. J. 1975. Effect of sojourn at 4,300 m altitude on electroencephalogram and visual evoked response. Journal of Applied Psychology. 39:109-113.

- Frantzen, B. S., and Yusfin, A. I. 1958. Alterations of Color Sensation under Hypoxic Conditions. Translated into English from Fiziologicheskii Zhurnal. 44:519-525. Glen Burnie, MD: Techtran Corporation. Report No. NASA-TT-F-15879, October 1974.
- Frayser, R., and Hickam, J. B. 1964. Retinal vascular response to breathing increased carbon dioxide and oxygen concentrations. Investigative Ophthalmology and Visual Science. 3:427-431.
- Frayser, R., Houston, C. S., Gray, G. W., Bryan, A. C., and Rennie, I. D. 1971. The response of the retinal circulation to altitude. Archives of Internal Medicine. 127:708-711.
- Fuelling, J. L. 1961. Aviation Ophthalmology, In: G. H. G. Armstrong (Ed.), Aerospace Medicine. Baltimore: Williams and Wilkins Co.
- Fujino, T., and Hamasaki, D. M. 1967. Effect of intraocular pressure on the electroretinogram of monkeys. Archives of Ophthalmology. 78:757-765.
- Furuya, G. 1936a. [The effects of low pressure on the human eye: I. The effects of low pressure on intraocular tension, particularly in sympathicotonic and vagotonic individuals.] Acta Societatis Ophthalmologicae Japonicae. 40:2432-2443; abstracted, *ibid.* (German summary) p. 159; Berichte über die gesamte Physiologie. 101:463, 1937.
- Furuya, G. 1936b. [The effects of low pressure on the human eye: II. Pupillary size.] Acta Societatis Ophthalmologicae Japonicae. 40:26362640; abstracted, *ibid.* (German summary) p. 172; Berichte über die gesamte Physiologie. 102:616, 1937.
- Furuya, G. 1937a. [The effects of low pressure on the human eye: III. Visual acuity.] Acta Societatis Ophthalmologicae Japonicae. 41:42-49; abstracted, *ibid.* (German summary) p. 6; Berichte über die gesamte Physiologie. 102:465, 1937.
- Furuya, G. 1937b. [The effects of low pressure on the human eye: IV. Accommodation.] Acta Societatis Ophthalmologicae Japonicae. 41:142-151; abstracted, *ibid.* (German summary) p. 14; Berichte über die gesamte Physiologie. 103:465, 1937.
- Furuya, G. 1937c. [The effects of low pressure on the human eye: V. Visual Field.] Acta Societatis Ophthalmologicae Japonicae. 41:415-433; abstracted, *ibid.* (German summary) p. 35; Berichte über die gesamte Physiologie. 103:465, 1937.

- Furuya, G. 1937d. [The effects of low pressure on the human eye: VI. Muscle balance.] Acta Societatis Ophthalmologicae Japonicae. 41:544-549; abstracted, *ibid.* (German summary) p. 44; Berichte über die gesamte Physiologie. 103:466, 1937.
- Furuya, G. 1937e. [The effects of low pressure on the human eye: VII. Summary and conclusions.] Acta Societatis Ophthalmologicae Japonicae. 41:680-683.
- Gabb, G., and Robin, E. D. 1987. Hyperbaric oxygen: A therapy in search of diseases. Chest. 92:1074-1082.
- Gallagher, T. J., Mammen, R. E., Nobrega, F. T., and Turaidis, T. 1965. The effect of various oxygen partial pressures on scotopic and photopic vision. Philadelphia: Naval Aviation Electronics Center. Report No. NAEC-ACEL-530.
- Gellhorn, E. 1936a. The effect of O₂-lack, variation in the CO₂-content of the inspired air, and hyperpnea on visual intensity discrimination. American Journal of Physiology. 115:679-684.
- Gellhorn, E. 1936b. The effectiveness of carbon dioxide in combating the changes in visual intensity discrimination produced by oxygen deficiency. American Journal of Physiology. 117:75-78.
- Gellhorn, E., and Hailman, H. 1943. Effect of anoxia on sense organs. Federation Proceedings. 2:122-126.
- Gellhorn, E., and Hailman, H. 1944. Parallelism in changes of sensory function and electroencephalogram in anoxia and effect of hypercapnia under these conditions. Psychosomatic Medicine. 6:23-30.
- Gellhorn, E., and Levin, J. 1945. The nature of pupillary dilation in anoxia. American Journal of Physiology. 143:282-289.
- Gellhorn, E., and Spiesman, I. G. 1935. The influence of hyperpnea and of variations of the O₂- and CO₂-tension in the inspired air upon afterimages. American Journal of Physiology. 112:620-626.
- Gerstle, C. L., Anderson, D., and Hamasaki, D. I. 1973. Pressure effect on ERG and optic nerve conduction of visual impulse. Archives of Ophthalmology. 90:121-124.
- Giardini, A. 1948. Ricerche sugli effetti della associazione alcool-anossia sul senso luminoso. Rivista di Medicina Aeronautica. 1:531-543.

- Giardini, A. 1949. Il comportamento dell'apparato oculare alle alte quote. Bollettino Oculistica. 28:649-676.
- Giardini, A. 1952. Permeabilita della barriera emato-oftalmica alla fluorescina in anossia acuta: (indagini sull'uomo). Rivista di Medicina Aeronautica. 15:49-60.
- Giardini, A., and Nizetic, B. 1949. Ricerche sulla permeabilita della barriera ematooftalmica in rapporto all'anossia. Atti del Congresso della Societa Oftalmologica Italiana. 111:444.
- Giardini, A., and Swanljung, H. 1951. Effects of anoxia on fluorescein permeability of the blood-aqueous barrier. British Journal of Ophthalmology. 35:114-118.
- Ginsburg, N. 1967. Ascending-descending differences in CFF-measurements as a function of eccentricity and starting point. Journal of Psychology. 67:161-167.
- Goldmann, H., and Schubert, G. 1933. Untersuchungen über das Gesichtsfeld bei herabgesetztem Sauerstoffdruck der Atmungs-luft. Archiv für Augenheilkunde. 107:216-237.
- Gouras, P., and Carr, R. E. 1965. Light-induced responses of monkey retina before and after central retinal artery interruption. Investigative Ophthalmology. 4:310-317.
- Granger, G. W., and Ikeda, H. 1961. Effect of hyperventilation on foveal critical flicker frequency. Vision Research. 1:287-300.
- Grehn, F. 1981. The sensitivity of the retinal nerve fibre layer to elevated intraocular pressure and graded hypoxia in the cat. Vision Research. 21:1697-701.
- Grehn, F., Grusser, O.-J., and Stange, D. 1984. Effect of short-term intraocular pressure increase on cat retinal ganglion cell activity. Behavioural Brain Research. 14:109-121.
- Greve, E. L., and Furuno, F. 1980. Myopia and glaucoma. Albrecht von Graefes Archiv für klinische und experimentelle Ophthalmologie. 213:33-41.
- Grüttner, R. 1944. Über das Verhalten des optokinetischen Nystagmus in akuten Sauerstoffmangel. Luftfahrtmedizin. 9:1-15.

- Grunwald, J. E., Riva C. E., Petrig, S. H., Sinclair, S. H., and Brucker, A. J. 1984. Effect of pure O₂-breathing on retinal blood flow in normals and in patients with background diabetic retinopathy. Current Eye Research. 3:239-241.
- Guest, A. D. L., Duncan, C., Lawther, P. J. 1970. Carbon monoxide and phenobarbitone: A comparison of effects on auditory flutter fusion threshold and critical flicker fusion threshold. Ergonomics. 13:587-594.
- Halperin, A. E., and Kilvin, M. M. 1959. Transient myopia during treatment with carbonic anhydrase inhibitors. American Journal of Ophthalmology. 48:534-535.
- Halperin, M. H., McFarland, R. A., Niven, J. I., and Roughton, F. J. W. 1959. The time course of the effects of carbon monoxide on visual thresholds. Journal of Physiology. 146:588-593.
- Halstead, W. C. 1944. The frontal lobes and the higher levels of consciousness. Archives of Neurology and Psychiatry. 52:252.
- Halstead, W. C. 1945a. Chronic intermittent anoxia and impairment of peripheral vision. Science, 101:615-616.
- Halstead, W. C. 1945b. Chronic intermittent anoxia in the dynamic visual field. Journal of Psychology. 20:49-56.
- Hecht, S., Henley, C. D., Frank, S. R., and Haig, C. 1946. Anoxia and brightness discrimination. Journal of General Physiology. 29:335-351.
- Hecht, S., and Schlaer, S. 1938. An adaptometer for measuring human dark adaptation. Journal of the Optical Society of America. 28:269-275.
- Heinke, E. 1942. Das Raumsehvermogen im Unterdruck. Luft-fahrtmedizin. 6:174-182.
- Herbstein, K., and Murchland, J. B. 1984. Retinal vascular changes after treatment with hyperbaric oxygen. Medical Journal of Australia. 140:728-729.
- Herlocher, J. E., Quigley, D. G., Behar, V. S., Shaw, E. G., and Welch, B. E. 1964. Physiologic response to increased oxygen partial pressure: I. Clinical observations. Aerospace Medicine. 35:613-618.
- Hess, R. F., and Garner, L. F. 1977. The effect of corneal edema on visual function. Investigative Ophthalmology and Visual Science. 16:5 13.

- Hickam, J. B., and Frayser, R. 1966. Studies of the retinal circulation in man. Circulation. 33:302-316.
- Holden, B. A., Sweeney, D. F., and Sanderson, G. 1984. The minimum precorneal oxygen tension to avoid corneal edema. Investigative Ophthalmology and Visual Science. 25:476-480.
- Hoorens, A. 1948. Influences de l'asphyxie, de l'anemie, de l'hypoxemie et du CO₂ sur la pupille. Archives Internationales de Pharmacodynamie et de Therapie. 77:464-467.
- Horsten, G. P. M., and Winkelman, J. E. 1957. Effect of temporary occlusion of the aorta on the electroretinogram. Archives of Ophthalmology. 57:557-565.
- Houston, C. S., and McFadden, M. 1979. Long-term effects of altitude on the eye. Lancet. 2:49.
- Howard, D. R., and Sawyer, D. C. 1975. Electroretinography of acute hypoxic and increased intraocular pressure status in the dog. American Journal of Veterinary Research. 36:81-84.
- Ingenito, A. I., and Durlacher, L. 1979. Effects of carbon monoxide on the b-wave of the cat electroretinogram: Comparisons with nitrogen hypoxia, epinephrine, vasodilator drugs and changes in respiratory tidal volume. Journal of Pharmacology and Experimental Therapeutics. 211:638-646.
- Izenberg, S., Fink, S., and Shoemaker, W. 1984. The eye as a peripheral sensor. Annals of Ophthalmology. 16:1105-1108.
- Jacobi, K. W., and Driest, J. 1966. Sauerstoffbestimmungen im Glaskorper des lebenden Auges. Bericht über die Zusammenkunft der Deutschen Ophthalmologischen Gesellschaft. 67:193-198.
- Jones, K. R., and Wilcott, T. I. 1977. Topographic impairment of night vision related to exercise. American Journal of Ophthalmology. 84:868-871.
- Jordancv, J., and Ruben, H. 1967. Reliability of pupillary changes as a clinical sign of hypoxia. Lancet. 2:915-917.
- Jorgensen, V. 1955. The effects of hyperventilation on flicker fusion frequencies with foveal images of different sizes. Acta Ophthalmologica. 33:615-621.
- Kahwaji, M. N., Mateossian, R., and Griffin, J. R. 1973. Visual field related to test target size and illuminance. American Journal of Optometry. 50:40-45.

- Kapp, J., and Paulson, G. 1966. Pupillary changes induced by circulatory arrest. Neurology. 16:225-229.
- Karlberg, B., Hedin, A., and Bjornberg, K. 1968. Electroretinography during short-term intraocular tension rise. Acta Ophthalmologica. 46:742-748.
- Kaskel, D., Ruther, U., and Fink, H. 1969. Experimentelle Untersuchungen am Kaninchen über den Zusammenhang zwischen intraokularem Druck, arteriellem Druck und Stromvolumen. Documenta Ophthalmologica. 27:212-219.
- Kaufmann, H., Kluxen, M., and Baumgart, W. 1973. Das Verhalten von Augentension und Rigiditäts-Koeffizient während Vergrößerung des funktionellen Totraums. Albrecht von Graefes Archiv für klinische und experimentelle Ophthalmologie. 186:191-202.
- Kaufmann, H., Schotte, J. F., and Holtmann, H. W. 1971. Ocular tension during hyperventilation. Ophthalmic Research. 2:261-265.
- Kayama, Y. 1974. Evoked potentials of the central visual system during and after hypoxia in cats. Electroencephalography and Clinical Neurophysiology. 36:619-628.
- Kenyon, E., Polse, K. A., and Sieger, R. G. 1986. Influence of wearing schedule on extended-wear complications. Ophthalmology. 93:231-236.
- Kent, P. R. 1966. Oxygen breathing effects upon night vision thresholds. Groton, CT: U. S. Naval Submarine Medical Research Center. Report No. 469.
- Kielar, R. A., Teraslinna, P., Kearney, J. T., and Barker, D. 1977. Effect of changes in PCO₂ on intraocular tension. Investigative Ophthalmology and Visual Science. 16:534-537.
- Kinney, J. A., Hammond, R., Gelfand, R., and Clark, J. 1978. Visual evoked cortical potentials in men during compression and saturation in He-O₂ equivalent to 400, 800, 1200 and 1600 feet of sea water. Electroencephalography and Clinical Neurophysiology. 44:157-171.
- Kinney, J. S., McKay, C. L., and Gordon, R. A. 1977. The use of fluorescein angiography to study oxygen toxicity. Annals of Ophthalmology. 9:989-995.
- Klyce, S. D. 1981. Stromal lactate accumulation can account for corneal edema osmotically following epithelial hypoxia in the rabbit. Journal of Physiology. 321:49-64.

- Kobrick, J. 1983. Effects of hypoxia on the luminance threshold for target detection. Aviation, Space, and Environmental Medicine. 54:112-115.
- Kobrick, J. L. 1968. Effects of exposure to 12,800 feet and acetazolamide on visual performance. Perceptual and Motor Skills. 27:939-944.
- Kobrick, J. L. 1970. Effects of hypoxia and acetazolamide on color sensitivity zones in the visual field. Journal of Applied Physiology. 28:741-747.
- Kobrick, J. L. 1976. Effects of prior hypoxia exposure on visual target detection during later more severe hypoxia. Perceptual and Motor Skills. 42:751-761.
- Kobrick, J. L., and Appleton, B. 1971. Effects of extended hypoxia on visual performance and retinal vascular state. Journal of Applied Physiology. 31:357-362.
- Kobrick, J. L., Zwick, H., Witt, C. E., and Devine, J. A. 1984. Effects of extended hypoxia on night vision. Aviation, Space, and Environmental Medicine. 55:191-195.
- Kolder, H. 1959. Spontane und experimentelle andernngen des Bestandpotentials des menschlichen Auges. Pflugers Archiv für die Gesamte Physiologie. 268:258-272.
- Kozousek, V. 1967. Elektroretinogram a hyperbaricka oxygenace. Ceskoslovenska Oftalmologie. 23:27-31.
- Kramar, P. O., Drinkwater, B. L., Folinsbee, L. J., and Bedi, J. F. 1983. Ocular functions and incidence of acute mountain sickness in women at altitude. Aviation, Space, and Environmental Medicine. 54:116-120.
- Krasno, L. R., and Ivy, A. C. 1950. The response of the flicker fusion threshold to nitroglycerin and its potential value in the diagnosis, prognosis, and therapy of subclinical and clinical cardiovascular disease. Circulation. 1:1267-1276.
- Krause, A. C., and Goren, S. B. 1956. The effects of hypoxia and hyperoxia upon the oxygen tension in the vitreous humor of the cat. American Journal of Ophthalmology. 42:764-769.
- Kreienbuhl B., and Niemeyer, G. 1985. Standing potential and c-wave during changes in PO₂ and flow in the perfused cat eye. Documenta Ophthalmologica. 60:353-360.

- Kronfeld, P. C. 1969. The gross anatomy and embryology of the eye. In: H. Davson (Ed.), The eye: Vegetative physiology and biochemistry (Vol. 1). New York: Academic Press.
- Krupin, T., Weiss, A., Becker, B., Holmberg, N., and Fritz, C. 1977. Increased intraocular pressure following topical azide or nitroprusside. Investigative Ophthalmology and Visual Science. 16:1002-1007
- Kwan, M., Niinikoski, J., and Hunt T. K. 1972. In vivo measurements of oxygen tension in the cornea, aqueous humor, and anterior lens of the open eye. Investigative Ophthalmology and Visual Science. 11:108-114.
- Kylstra, J. A., Wierzbicki, T., Wolbarsht, M. L., Landers, M. B. 3d., and Stefansson, E. 1986. The relationship between retinal vessel tortuosity, diameter, and transmural pressure. Graefe's Archive for Clinical and Experimental Ophthalmology. 1986. 224:477-480.
- Kyrieleis, W., Kyrieleis, A., and Siegert, P. 1935. Untersuchungen über das Gesichtsfeld bei Sauerstoffmangel und bei Unterdruck. Archiv für Augenheilkunde. 109:178-189.
- Lambert, E. H., and Bjurstedt, H. 1952. Effect of variation of oxygen and carbon dioxide tensions in inspired air on latency of blackout produced by pressure on eyeball. Federation Proceedings. 11:87.
- Lambert, S. R., and Klyce, S. D. 1981. The origins of Sattler's Veil. American Journal of Ophthalmology. 91:51-56.
- Landers, M. B. 3d. 1978. Retinal oxygenation via the choroidal circulation. Transactions of the American Ophthalmological Society. 76:528-556.
- Landis, C. 1954. Determinants of the critical flicker-fusion threshold. Physiological Reviews. 34:259-286.
- Langan, L. M., and Watkins, S. M. 1987. Pressure of menswear on the neck in relation to visual performance. Human Factors. 29:67-71.
- Larke, J. R., Parrish, S. T., and Wigham, C. G. 1981. Apparent human corneal oxygen uptake rate. American Journal of Optometry and Physiological Optics. 58:803-805.
- Lassen, N. A., Friberg, L., Kastrup, J., Rizzi, D., and Jensen, J. J. 1987. Effects of acetazolamide on cerebral blood flow and brain tissue oxygenation. Postgraduate Medical Journal. 63:185-187.

- Leber, L. L., Roscoe, S. N., and Southward, G. M. 1986. Mild hypoxia and visual performance with night vision goggles. Aviation, Space, and Environmental Medicine. 57:318-324.
- Lehmann, G. 1943. Nachtsehen bei ermüdung und Sauerstoffmangel. Mitteilungen aus der Gebote der Luftfahrtmedizin. Report No. 8/43, p. 41.
- Leibowitz, H. W., and Owens, D. A. 1978. New evidence for the intermediate position of relaxed accommodation. Documenta Ophthalmologica. 46:133-147.
- Leonardi, F. 1951. Sensibilita' corneale in anossia acuta. Rivista di Medicina Aeronautica. 14:416-419.
- Lilienthal, I. L., and Fugitt, C. H. 1946. Effect of low concentrations of carboxyhemoglobin on the "altitude tolerance" of man. American Journal of Physiology. 145:359-364.
- Linsenmeier, R. A. 1986. Effects of light and darkness on oxygen distribution and consumption in the cat retina. Journal of General Physiology. 88:521-542.
- Linsenmeier, R. A., Mines, A. H., and Steinberg, R. H. 1983. Effects of hypoxia and hypercapnia on the light peak and electroretinogram of the cat. Investigative Ophthalmology and Visual Science. 24:37-46.
- Linsenmeier, R. A., Smith, V. C., and Pokorny, J. In press. The light rise of the electrooculogram during hypoxia. Clinical Vision Sciences.
- Linsenmeier, R. A., and Steinberg, R. H. 1984. Effects of hypoxia on potassium homeostasis and pigment epithelial cells in the cat retina. Journal of General Physiology. 84:945-70.
- Linsenmeier, R. A., and Steinberg, R. H. 1986. Mechanism of hypoxic effects on the cat DC electroretinogram. Investigative Ophthalmology and Visual Science. 27:1385-1394.
- Livingston, P. C. 1944a. Visual problems of aerial warfare: I. "Night: Studies in the dark adapted eye." The Lancet. 2:33-38.
- Livingston, P. C. 1944b. Visual problems of aerial warfare: II. "Day: Studies in photopic vision." The Lancet. 2:67-73.
- Lowenstein, O., and Lowenfeld, I. E. 1969. The Pupil. In: H. Davson (Ed.), The eye. Muscular mechanisms (Vol. 3). New York: Academic Press.

- Luria, S. M., and Knight, D. R. 1987. Scotopic sensitivity with 10 % oxygen. Groton, CT: U. S. Naval Submarine Medical Research Center. Report No. 1097.
- Luria, S. M., and McKay, C. L. 1979. Effects of low levels of carbon monoxide on vision of smokers and nonsmokers. Archives of Environmental Health. 34:33-44.
- Lyne, A. J. 1978. Ocular effects of hyperbaric oxygen. Transactions of the Ophthalmological Society of the United Kingdom. 98:6-8.
- Malmejac, G. L., Ruffieuz, R., Chardon, G., and Serrell, E. 1944. Anoxie et aptitude a la differentiation des couleurs. Comptes Rendus des Seances de la Société de Biologie et de Ses Filiales. 138:966-967.
- Mandell, R. B., and Farrell, R. 1980. Corneal swelling at low atmospheric oxygen pressure. Investigative Ophthalmology and Visual Science. 19:697-702.
- Mapstone, R. 1981. Acute shallowing of the anterior chamber. British Journal of Ophthalmology. 65:446-451.
- Margolis, G., and Brown, I. W. Jr. 1966. Hyperbaric oxygenation: The eye as a limiting factor. Science. 151:466-468.
- Marmor, M. F., Donovan, W. J., and Gaba, D. M. 1985. Effects of hypoxia and hyperoxia on the human standing potential. Documenta Ophthalmologica. 60:347-352.
- Massopust, L. C., Wolin, L. R., and Barnas, H. W. 1966. The effect of hypoxia on electrical activity of the visual system in cats. Japanese Journal of Physiology. 16:450-461.
- Mathew, L., Purkayastha, S. S., Jayashankar, A., Radhakrishnan, U., Sen Gupta, J., and Nayar, H. S. 1985. Responses of the autonomic nervous system in altitude adapted and high altitude pulmonary oedema subjects. International Journal of Biometeorology. 29:131-143.
- McCluskey, D. J., Douglas, J. P., O'Connor, P. S., Story, K., Ivy, L. M., Harey, J. S. 1986. The effect of pilocarpine on the visual field in normals. Ophthalmology. 93:843-846.
- McDonald, R., and Adler, F. H. 1939. Effects of anoxia on the dark adaptation of the normal and of the vitamin A-deficient subject. Archives of Ophthalmology. 22:980-988.

- McFadden, D. M., Houston, C. S., Sutton, J. R., Powles, A. C., Gray, G. W., Roberts, R. S. 1981. High-altitude retinopathy. Journal of the American Medical Association. 245:581-586.
- McFarland, R. A. 1932. The psychological effects of oxygen deprivation (anoxemia) on human behavior. Archives of Psychology. 145:1-135.
- McFarland, R. A. 1937a. Psycho-physiological studies at high altitude in the Andes: I. The effects of rapid ascents by aeroplane and train. Journal of Comparative and Physiological Psychology. 23:191-224.
- McFarland, R. A. 1937b. Psycho-physiological studies at high altitude in the Andes: II. Sensory and motor responses during acclimatization. Journal of Comparative and Physiological Psychology. 23:227-258.
- McFarland, R. A. 1970. The effects of exposure to small quantities of carbon monoxide on vision. Annals of the New York Academy of Sciences. 174:301-312.
- McFarland, R. A., and Edwards, H. T. 1937. The effects of prolonged exposures to altitudes of 8,000 to 12,000 feet during trans-Pacific flights. Aviation Medicine. 8:156-177.
- McFarland, R. A., and Evans, J. N. 1939. Alterations in dark adaptation under reduced oxygen tensions. American Journal of Physiology. 127:37-50.
- McFarland, R. A., Evans, N. J., and Halperin, M. H. 1941. Ophthalmic aspects of acute oxygen deficiency. Archives of Ophthalmology. 26:886-913.
- McFarland, R. A., and Fisher, M. B. 1955. Dark adaptation as a function of age: I. A statistical analysis. Journal of Gerontology. 10:160-210.
- McFarland, R. A., and Forbes, W. H. 1940. The effects of variations in the concentration of oxygen and of glucose on dark adaptation. Journal of General Physiology. 24:69-98.
- McFarland, R. A., and Halperin, M. H. 1940. The relation between foveal visual acuity and illumination under reduced oxygen tension. Journal of General Physiology. 23:613-630.
- McFarland, R. A., Halperin, M. H., and Niven, J. I. 1944. Visual thresholds as an index of physiological imbalance during anoxia. American Journal of Physiology. 142:328-349.

- McFarland, R. A., Holway, A. H., and Hurvich, L. M. 1942. Studies of visual fatigue. Graduate School of Business Administration Report. Boston: Harvard University.
- McFarland, R. A., Hurvich, L. M., and Halperin, M. H. 1943. The effects of oxygen deprivation on the relation between stimulus intensity and the latency of visual after-images. American Journal of Physiology. 140:354-366.
- McFarland, R. A., Knehr, C. A., and Berens, C. 1937a. The effects of oxygen deprivation on eye movements in reading. Journal of Experimental Psychology. 21:1-25.
- McFarland, R. A., Knehr, C. A., and Berens, C. 1937b. The effects of anoxemia on ocular movements while reading. American Journal of Ophthalmology. 20:1204-1219, 1937b.
- McFarland, R. A., Roughton, F. J. W., Halperin, M. H., and Niven, J. I. 1944. The effects of carbon monoxide and altitude on visual thresholds. Journal of Aviation Medicine. 15:381-394.
- McFarland, R. A., Warren, A. B., and Karis, C. 1958. Alterations in critical flicker frequency as a function of age and light:dark ratio. Journal of Experimental Psychology. 56:529-538.
- Mercier, A., and Duguet, J. 1950. Physiopathology of the flyer's eye. [Translated from the French Physiopathologie oculaire de l'aviateur. 1947.] Randolph Field, TX: U. S. Air Force School of Aviation Medicine.
- Mercier, A., Perdriel, G., Sole, P., Chevaleraud, J., and Graveline, J. 1964. Glaucoma incidence and significance in aviation. Aerospace Medicine. 35:567-571.
- Michael, J. A. 1973. Neurophysiological effects of hypoxia. Monographs in Neural Sciences. 1:65-121.
- Miller, E. F. 1958. Effect of breathing 100 per cent oxygen upon visual field and visual acuity. Journal of Aviation Medicine. 29:598-602.
- Miller, E. M. 1956. Effect of acetazolamide on the dark adaptation function in glaucoma. AMA Archives of Ophthalmology. 56:869-877.
- Millodot, M., and O'Leary, D. J. 1980. effect of oxygen deprivation on corneal sensitivity. Acta Ophthalmologica. 58:434-439.

- Mitari, G., and Takagi, S. 1965. Effects of hypoxia on the visual pathway in rabbits. Annual Report of the Research Institute of Environmental Medicine, Nogoya University. 13:1-9.
- Nagaya, T., and Muneoka, A. 1963. [Effects of hypoxia on human visual function with particular reference to ERG, visual field, and CFF]. Acta Societatis Ophthalmologicae Japonicae. 67:257-269.
- Nair, C. S., Malhotra, M. S., and Gopinath, P. M. 1972. Effect of altitude acclimatization and simultaneous acclimatization to altitude and cold on critical flicker frequency at 11,000 ft. altitude in man. Aerospace Medicine. 43:1097-1100.
- Neely, J. C. 1951. The effect of high altitude on ocular muscle balance. Transactions of the Ophthalmological Society of the United Kingdom. 71:663-678.
- Neely, J. C. 1955. Practical aspects of heterophoria in aviation. In: Collected Papers on Aviation Medicine. London: Butterworth.
- Nelson, W. H. 1967. The effects of reduced partial pressures of oxygen (hypoxia) on the size of the visual field in humans. Dissertation Abstracts. 28(5-B):2163-2164.
- Neuschuler, R., and Palombi, R. 1966. Il tono oculare in ipossia: Indagini tonografiche. Rivista di Medicina Aeronautica. 29:402-411.
- Newberry, P. D., Johnson, W. H., and Smiley, J. R. 1965. Effect of hypoxic hypoxia on nystagmus induced by angular acceleration. Aerospace Medicine. 36:1090-1093.
- Newsome, D. A. 1971. Afterimage and pupillary activity following strong light exposure. Vision Research. 11:275-288.
- Newton, N. L., Clark, W. B., Culver, J. F., and Moore, J. T. 1963. Intraocular pressure, aqueous outflow and glaucoma at altitude. American Journal of Ophthalmology. 56:223-229.
- Nicholls, J. V. V. 1950a. The relationship of heterophoria to depth perception in aviation: Part I. American Journal of Ophthalmology. 33:1497-1515.
- Nicholls, J. V. V. 1950b. The relationship of heterophoria to depth perception in aviation: Part II. American Journal of Ophthalmology. 33:1775-1787.

- Nicholls, J. V. V. 1950c. The relationship of heterophoria to depth perception in aviation: Part III. American Journal of Ophthalmology. 33:1891-1903.
- Nicholls, J. V. V., and Minnes, J. F. 1943. Orthoptics in aviation. Ottawa: Royal Canadian Air Force. Interim Report No. C-2544, July 22, 1943.
- Nichols, C. W., and Lambertsen, C. J. 1969. Effects of high oxygen pressures on the eye. New England Journal of Medicine. 281:25-30.
- Nichols, C. W., Lambertsen, C. J., and Clark, J. M. 1969. Transient unilateral loss of vision associated with oxygen at high pressure. Archives of Ophthalmology. 81:548-552.
- Nichols, C. W., Yanoff, M., Hall, D. A., and Lambertsen, C. J. 1972. Histologic alterations produced in the eye by oxygen at high pressure. Archives of Ophthalmology. 87:417-421.
- Niemeyer, G., Nagahara, K., and Demant, E. 1982. Effects of changes in arterial PO_2 and PCO_2 on the electroretinogram in the cat. Investigative Ophthalmology and Visual Science. 23:678-683.
- Noell, W. K. 1951. Site of asphyxial block in mammalian retinae. Journal of Applied Physiology. 3:489-500.
- Noell, W. K. 1952. Azide-sensitive potential difference across the eye-bulb. American Journal of Physiology. 170:217-238.
- Noell, W. K. 1953. Studies on the electrophysiology and metabolism of vision. USAF School of Aviation Medicine. Project 21-1201.
- Noell, W. K. 1962. Effects of high and low oxygen tension on the visual system. In: K. E. Schaefer (Ed.), Environmental effects on consciousness. New York: MacMillan & Co.
- Noell, W. K., and Chinn, H. I. 1950. Failure of the visual pathway during anoxia. American Journal of Physiology. 161:573-590.
- O'Donnell, R. D., Chikos, P., and Theodore, J. 1971. Effect of carbon monoxide exposure on human sleep and psychomotor performance. Journal of Applied Physiology. 31:513-518.
- O'Hanlon, J. F., and Horvath, S. M. 1973. Neuroendocrine, cardiorespiratory, and performance reactions of hypoxic men during a monitoring task. Aerospace Medicine. 44:129-134.

- O'Mara, P. A., Zwick, H., Beatrice, E. S., and Lund, D. 1982. Microprocessor-controlled light-emitting diode dark adaptometer. Medical and Biological Engineering and Computing. 20:70-76.
- O'Neal, M. R., and Polse, K. A. 1985. In vivo assessment of mechanisms controlling corneal hydration. Investigative Ophthalmology and Visual Science. 26:849-856.
- O'Neal, M. R., and Polse, K. A. 1986. Decreased endothelial pump function with aging. Investigative Ophthalmology and Visual Science. 27:457-463.
- O'Neal, M. R., Polse, K. A., and Sarver, M. D. 1984. Corneal response to rigid and hydrogel lenses during eye closure. Investigative Ophthalmology and Visual Science. 25:837-842.
- Ohlbaum, M. K. 1969. The effects of hypoxia on certain aspects of visual performance. American Journal of Optometry. 46:235-249.
- Otis, A. B., Rahn, H., Epstein, M., and Fenn, W. O. 1946. Performance as related to composition of alveolar air. American Journal of Physiology. 146:207-221.
- Palmquist, B. M., Fagerholm, P. P., and Philipson, B. T. 1986. Nuclear vacuoles in nuclear cataract. Acta Ophthalmologica. 64:63-66.
- Palmquist, B. M., Philipson, B., and Barr, P. O. 1984. Nuclear cataract and myopia during hyperbaric oxygen therapy. British Journal of Ophthalmology. 68:110-117.
- Papst, N., Demant, E., and Niemeyer, G. 1982. Changes in pO_2 induce retinal autoregulation in vitro. Graefe's Archive for Clinical and Experimental Ophthalmology. 219:6-10.
- Paulson, H. M., and Ryan, A. P. 1981. The F-M 100-Hue Test for assessing the effect of oxygen on color vision. Groton, CT: U. S. Naval Submarine Medical Research Center. Report No. NSMRL-966.
- Pearlman, J. R. 1962. The c-wave of the human ERG. Archives of Ophthalmology. 68:823-830.
- Petajan, J. H., Packham, S. C., Frens, D. B., and Dinger, B. 1976. Sequelae of carbon monoxide-induced hypoxia in the cat. Archives of Neurology. 33:152-157.
- Pierson, W. R. 1967. Night vision and mild hypoxia. Aerospace Medicine. 38:993-994.

- Pinson, E. A. 1940. Intraocular pressure at high altitudes. Journal of Aviation Medicine. 11:108-111.
- Plewes, J. L., and Farhi, L. E. 1983. Peripheral circulatory responses to acute hyperoxia. Undersea Biomedical Research. 10:123-129.
- Pol, W. 1938. Przyczynek do badan nad zmianami czynnosci fizjologicznych oka w komorze niskich cisnien. Polski Przegląd Medycyny Lotniczej. 7:162-166.
- Polse, K. A. 1979. Tear flow under hydrogel contact lenses. Investigative Ophthalmology and Visual Science. 18:409-413.
- Polse, K. A., and Mandell, R. B. 1970. Critical oxygen tension at the corneal surface. Archives of Ophthalmology. 84:505-508.
- Polse, K. A., and Mandell, R. B. 1976. Etiology of corneal striae accompanying hydrogel lens wear. Investigative Ophthalmology and Visual Science. 5:553-556.
- Polse, K. A., and O'Neal, M. R. 1985. Oxygen requirements for extended wear. Proceedings of the VIIth Congress of the European Society of Ophthalmology, Helsinki-1985. 269-270.
- Polse, K. A., Sarver, M. D., and Harris, M. H. 1975. Corneal edema and vertical striae accompanying the wearing of hydrogel lenses. American Journal of Optometry. 52:185-190.
- Posternak, J. 1948a. L'adaptation visuelle a l'obscurité au Jungfraujoeh. Helvetica Physiologica et Pharmacologica Acta. 6:516-523.
- Posternak, J. 1948b. Le champ visuel a l'altitude. Helvetica Physiologica et Pharmacologica Acta. 6:524-527.
- Pretorius, H. A. 1970. Effect of oxygen on night vision. Aerospace Medicine. 41:560-562.
- Raber, F. 1941. Uber den Einfluss des Sauerstoffmangels auf das Dunkelsehen. Lilienthal-Gesellschaft. Report No. 146.
- Ramsey, J. M. 1972. Carbon monoxide, tissue hypoxia, and sensory psychomotor response in hypoxaemic subjects. Clinical Science. 42:619-625.
- Ramsey, J. M. 1973. Effects of single exposures of carbon monoxide on sensory and psychomotor response. American Industrial Hygiene Association Journal. 34:212-216.

- Ray, D. E., and Hawgood, B. J. 1977. Influence of systemic factors on hyperbaric oxygen toxicity in the rat visual system. Aviation, Space, and Environmental Medicine. 48:1046-1050.
- Rennie, D., and Morrissey, J. 1975. Retinal changes in Himalayan climbers. Archives of Ophthalmology. 93:395-400.
- Riva, C. E., Grunwald, J. E., and Sinclair, S. H. 1983. Laser Doppler Velocimetry study of the effect of pure oxygen breathing on retinal blood flow. Investigative Ophthalmology and Visual Science. 24:47-51.
- Riva, C. E., Pournaras, C. J., Tsacopoulos, M. 1986. Regulation of local oxygen tension and blood flow in the inner retina during hyperoxia. Journal of Applied Physiology. 61:592-598.
- Rokseth, R., and Lorentzen, F. V. 1954. Combined effect of alcohol and hypoxia on flicker fusion frequency. Journal of Applied Physiology. 6:559-565.
- Rose, H. W. 1949. Study of acclimatization during a two-week exposure to moderate altitude (10,000 feet): Effect of altitude adaptation on night vision and ocular muscle balance. March, 1949. Randolph Air Force Base, TX: School of Aviation Medicine. Report AD-491 745/6.
- Rose, H. W. 1950a. Depth perception (Chapter IX-E), In: German aviation medicine in World War II. Washington, DC: Department of the Air Force.
- Rose, H. W. 1950b. Night Vision (Chapter IX-F), In: German aviation medicine in World War II. Washington, DC: Department of the Air Force.
- Rosenberg, E., Shibata, H. K., and Maclean, L. D. 1966. Blood gas and neurological responses to inhalation of oxygen at 2 atmospheres. Proceedings of the Society for Experimental Biology and Medicine. 122:313-317.
- Rosenthal, C. M. 1939. Changes in angiostomias associated with inhalation of oxygen. Archives of Ophthalmology. 22:385-392.
- Saltzman, H. A., Anderson, B., Hart, L., Duffy, E., and Sieker, H. C. 1965a. The retinal vascular and functional response to hyperbaric oxygenation in normal subjects and in patients with retinal vascular disease. In: I. McA. Ledingham (Ed.), Hyperbaric oxygenation: Proceedings of the Second International Congress, Glasgow-September 1964. Edinburgh and London: E. & S. Livingstone Ltd.

- Saltzman, H. A., Hart, L., Sieker, H. O., and Duffy, E. J. 1965b. Retinal vascular response to hyperbaric oxygenation. Journal of the American Medical Association. 191:290-292.
- Sarver, M. D., Polse, K. A., Baggett, D. A. 1983. Intersubject difference in corneal edema response to hypoxia. American Journal of Optometry and Physiological Optics. 60:128-131.
- Sauer, W. W. 1924. The effects of altitude on the eyes of aviators and observers. Ohio State Medical Journal. 20:629-633.
- Scano, A., Bietti, G. B., and Schupfer, F. 1947. Influenza dell'anossia sul potere risolutivo retinico. Rivista di Medicina Aeronautica. 10:490-498.
- Scano, A., Mazza, G., and Caporale, R. 1966. Influence of mild hypoxia on visual perception during post-rotatory optical nystagmus. In: Assessment of skill and performance in flying. Advisory Group for Aerospace Research and Development. AGARD CP 14. 130p. September, 1966. Paris, France: Advisory Group for Aerospace Research and Development.
- Schaefer, K. E., and Carey, C. 1953. Effect of increased CO₂ concentrations on flicker fusion frequency and alpha blocking. Federation Proceedings. 12:125-126.
- Schmidt, I. 1937. Farbensinnuntersuchungen an normalen und anomalen Trichromaten im Unterdruck. Luftfahrtmedizin. 2:55-71.
- Schmidt, I. 1939. Farbensehen und Höhenwirkung. Klinische Wochenschrift. 1:139.
- Schmidt, I. 1950. Color vision (Chapter IX-D), In: German aviation medicine in World War II. Washington, DC: Department of the Air Force.
- Schmidt, I., and Bingel, A. G. A. 1953. Effect of oxygen deficiency and other factors on color saturation thresholds. Randolph Field, TX: U. S. Air Force School of Aviation Medicine. Report No. 21-31-002.
- Schocket, S. S., Esterson, J., Bradford, B., Michaelis, M., and Richards, R. D. 1972. Induction of cataracts in mice by exposure to oxygen. Israel Journal of Medical Science. 8:1596-1601.
- Schroeder, R. W. 1918. How I made the altitude record of 28,900 feet. Flying. 10:906-907.

- Schubert, G. 1932. Das Verhalten des Zentralnervensystems bei rascher Rückkehr aus kritischem Unterdruck. Pflügers Archiv für die Gesamte Physiologie. 231:1-19.
- Schull, W. J., Goldsmith, R. I., Clench, J., Ferrell, R. E., Barton, S. A., and Rothhammer, F. 1981. 2,3-diphosphoglycerate and night vision. Aviation, Space, and Environmental Medicine. 52:41-44.
- Schumacher, G. A., and Petajan, J. H. 1975. High altitude stress and retinal hemorrhages: Relation to vascular headache mechanisms. Archives of Environmental Health. 30:217-221.
- Scobee, R. G. 1944. The effects of exhaustion and of moderate anoxia on the ocular muscle balance. Randolph Field, TX: U. S. Air Force School of Aviation Medicine. Report No. 292-1.
- Scobee, R. G., and Chinn, H. T. 1944. The effect of carbon monoxide on night visual deficiency. Randolph Field, TX: U. S. Air Force School of Aviation Medicine. Report No. 234-1.
- Scow, J., Krasno, L. R., and Ivy, A. C. 1950. The immediate and accumulative effect on psychomotor performance of exposure to hypoxia, high altitude and hyperventilation. Journal of Aviation Medicine. 21:79-81.
- Scullica, L., and Bisantis, C. 1968. Modificazioni indotte dall'iperossia sull'epitelio lenticolare: Effetti immediati ed a distanza dopo esposizione di i oral ad iperossia normo ed iperbarica. Bollettino Oculistica. 47:281-299.
- Seitz, C. P. 1940. The effects of anoxia on visual function: A study of critical frequency. Archives of Psychology. 257:5-38.
- Seitz, C. P., and Rosenthal, C. M. 1941. Effects of oxygen deprivation and strychnine administration on visual function: A study of the angioscotomas. Archives of Ophthalmology. 26:276-287.
- Seki, K., and Hugon, M. 1976. Critical flicker frequency (CFF) and subjective fatigue during an oxyhelium saturation dive at 62 ATA. Undersea Biomedical Research. 3:235-247.
- Sen Gupta, J., Mathew, L., and Gopinath, P. M. 1979. Effect of physical training at moderate altitude (1850 m) on hypoxic tolerance. Aviation Space and Environmental Medicine. 50:714-716.

- Saapainen, A., Hakkinen, V., and Tenkku M. 1977. Effect of gradually increasing carboxyhaemoglobin saturation on visual perception and psycho-motor performance of smoking and nonsmoking subjects. Annals of Clinical Research. 9:314-319.
- Sheard, C. 1946. Effects of increased intrapulmonary pressure on dark adaptation. Journal of Aviation Medicine. 17:526-532.
- Shelburne, S. A. Jr., McLaurin, R. L., and McLaurin, A. N. 1976. Effects of graded hypoxia on visual evoked responses of rhesus monkeys. In: McLaurin, R. L. (Ed.), Head injuries. New York: Grune and Stratton.
- Shults, W. T., and Swan, K. C. 1975. High altitude retinopathy in mountain climbers. Archives of Ophthalmology. 93:404-408.
- Sieker, H. O., and Hickham, J. B. 1953. Normal and impaired retinal vascular reactivity. Circulation. 7:79-83.
- Simonson, E., and Brozek, J. 1952. Flicker Fusion Frequency: Background and applications. Physiological Reviews. 32:349-378.
- Simonson, E., and Winchell, P. 1951. Effect of high carbon dioxide and low oxygen concentration on fusion frequency of flicker. Journal of Applied Physiology. 3:637-641.
- Sipperley, J., Anderson, D. R., and Hamasaki, D. 1973. Short-term effect of intraocular pressure elevation on the human electroretinogram. Archives of Ophthalmology. 90:358-360.
- Smelser, G. K. 1952. Relation of factors involved in maintenance of optical properties of cornea to contact lens wear. Archives of Ophthalmology. 47:328-343.
- Smith, D. B., and Strawbridge, P. J. 1974. Auditory and visual evoked potentials during hyperoxia. Electroencephalography and Clinical Neurophysiology. 37:393-398.
- Smith, G. M., Seitz, C. P., and Clark, K. B. 1946. Variations in the angioscotoma in response to prolonged mild anoxia. Aviation Medicine. 17:590-595.
- Smith, V. C., Ernest, J. T., and Pokorny, J. 1976. Effect of hypoxia on FM 100-hue test performance. Modern Problems of Ophthalmology. 17:248-256.
- Smith, W. L. 1965. Recovery rates with descent from hypoxia-induced peripheral visual field loss. In: Collected Papers

Presented at the Meeting of the AGARD Aerospace Medical Panel (22ND), Fuerstenfeldbruck Air Base, Germany-September 1965.
Paris, France: Advisory Group for Aerospace Research and Development.

- Sohmer, H., Freeman, S., and Malachi, S. 1986. Multi-modality evoked potentials in hypoxaemia. Electroencephalography and Clinical Neurophysiology. 64:328-333.
- Stefansson, E., Wolbarsht, M. L., and Landers, M. B. 1983a. The corneal contact lens and aqueous humor hypoxia in cats. Investigative Ophthalmology and Visual Science. 24:1052-1054.
- Stefansson, E., Wolbarsht, M. L., and Landers, M. B. 1983b. In vivo O₂ consumption in rhesus monkeys in light and dark. Experimental Eye Research. 37:251-256.
- Steinberg, R. H. In press. Friedenwald Lecture: Monitoring communications between photoreceptors and pigment epithelial cells: Effects of "mild" systemic hypoxia. Investigative Ophthalmology and Visual Science.
- Stolze, B. 1943. "Das Raumsehen bei akuten Sauerstoffmangel." Doctoral dissertation. University of Giessen, Germany.
- Strughold, H. 1936. Das zentralnervensystem and die Sinnesorgane in grossen Hohen. Luftfahrtmedizin. 1:58-64.
- Sutton, J. R., Coates, G., Gray, G. W., Mansell, A. L., Powles, A. C. P., and Zahoruk, R. 1980. Retinal studies at 446 torr in a hypobaric chamber. Aviation, Space, and Environmental Medicine. 51:407-408.
- Tanaka, H., and Sekiguchi, E. 1935. Influence of low atmospheric pressure on optic sensitivity. Bulletin of the Naval Medical Association of Japan (Abstract Section). 24:7.
- Taumer, R., Tohde, N., and Pernice, D. 1976. The slow oscillation of the retinal potential. Bibliotheca Ophthalmologica. 85:40-56.
- Tazawa, Y., and Seaman, A. J. 1972. The electroretinogram of the living extracorporeal bovine eye: The influence of anoxia and hypothermia. Investigative Ophthalmology and Visual Science. 11:691-698.
- Ten Doesschate, G. 1955. Heterophoria. In: Collected papers on aviation medicine. London: Butterworth.
- Trokel, S. 1965. Effect of respiratory gases upon choroidal hemodynamics. Archives of Ophthalmology. 73:838-842.

- Tune, G. S. 1964. Psychological effects of hypoxia: Review of certain literature from the period 1950-1963. Perceptual and Motor Skills. 19:551-562.
- U. S. War Department. 1919. Manual of the medical research laboratory. Washington DC: Air Service Medical-Division of Military Aeronautics.
- Ury, Gellhorn, E. 1939. On the influences of anoxia on pupillary reflexes in the rabbit. Journal of Neurophysiology. 2:136-141.
- Van den Bos, G. C. 1968. L'electroretinogramme du chat en cas d'hypoxie. Journal de Physiologie. 60:199-216.
- Van Liere, E. J., and Stickney, J. C. 1963. Hypoxia. Chicago: University of Chicago Press.
- Velhagen, K. 1936. Die hypoxämische Farbenasthenopie, eine latente Störung des Farbensinnes. Archiv für Augenheilkunde. 109:605-621.
- Velhagen, K. 1937. Heterophorie unter den Bedingungen des Hohenfluges. Luftfahrtmedizin. 1:344.
- Vollmer, E., King, B. G., Birren, J. E., and Fisher, M. B. 1946. Effects of carbon monoxide on three types of performance at simulated altitudes of 10,000 and 15,000 feet. Journal of Experimental Psychology. 36:244-245.
- Von Post-Lingen, M. L. 1964. The significance of exposure to small concentrations of carbon monoxide. Proceedings of the Royal Society of Medicine (Supplement). 57:1021-1029.
- Von Tavel, F. 1943. Les effets du manque d'oxygene sur l'organisme humain dans un sejour de courte duree a de grandes altitudes. Helvetica Physiologica et Pharmacologica Acta (Supplementum).
- Wagner, L., Polse, K., and Mandell, R. 1980. Tear pumping and edema with soft contact lenses. Investigative Ophthalmology and Visual Science. 19:1397-1400.
- Wald, G., Harper, P. V., Goodman, H. C., and Krieger, H. P. 1942. Respiratory effects upon the visual threshold. Journal of General Physiology. 25:891-902.
- Waller, D., and Levander, S. 1980. Smoking and vigilance: The effects of tobacco smoking on CFF as related to personality and smoking habits. Psychopharmacology. 70:131-136.

- Weissman, B. A. 1986. Critical corneal oxygen values: A summary. Journal of the American Optometric Association. 57:595-598
- Weissman, B. A., and Fatt, I. 1982. External hypoxia and corneal hydration dynamics. American Journal of Optometry and Physiological Optics. 59:1-4.
- Weissman, B. A., Fatt, I., and Horn, B. 1982. Reversal of anoxic corneal swelling by breathing oxygen. Investigative Ophthalmology and Visual Science. 22:124-127.
- Weltman, G., Smith, J. E., and Egstrom, G. H. 1971. Perceptual narrowing during simulated pressure-chamber exposure. Human Factors. 13:99-107.
- White, W. J. 1961. Gravitational stress in aerospace medicine. Boston: Little, Brown, and Co.
- Whiteside, T. C. D. 1957. The problems of vision in flight at high altitude. Paris, France: Advisory Group for Aeronautical Research and Development. Report No. AGARD-OGGRAPH-13.
- Wiedman, M. 1973. Nouvelle recherche oculaire au Mont Everest. Bulletin et Memories de la Societe Franchaise d' Ophtalmologie. 86:201-207.
- Wiedman, M. 1975. High altitude retinal hemorrhage. Archives of Ophthalmology. 93:401-403.
- Wiesinger, K. 1948. Untersuchungen über die Bulbuslagen in der Orbita. Helvetica Physiologica et Pharmacologica Acta. 6:617-625.
- Wilmer, W. H., and Berens, C. 1918. The effect of altitude on ocular functions. Journal of the American Medical Association. 71:1394-1398.
- Wilson, G., and Fatt, I. 1980. Thickness of corneal epithelium during anoxia. American Journal of Optometry and Physiological Optics. 57:409-412.
- Wilson, G., and Stevenson, R. 1981. Measuring corneal recovery from osmotic and anoxic stress. American Journal of Optometry and Physiological Optics. 58:797-802.
- Winneke, G. 1974. Behavioral effects of methylene chloride and carbon monoxide as assessed by sensory and psychomotor performance. In: C. Xintaras, B. L. Johnson, and I. de

- Groot (Eds.), Behavioral toxicology: Early detection of occupational hazards. Washington DC: U. S. Department of Health, Education, and Welfare. HEW Publication No. (NIOSH) 74-126.
- Wischnewsky, N. A., and Zirlin, B. A. 1935. [Effect of decreased barometric pressure on dark adaptation, color vision, and electric excitability of the eye.] Fiziologicheskii Zhurnal. 18:237-249.
- Wolbarsht, M. L., Stefansson, E., and Landers, M. B. 1987. Retinal oxygenation from the choroid in hyperoxia. Experimental Biology. 47:49-52.
- Wolbarsht, M. L., White, C. W., and Anderson, W. B. Jr. 1973. Effect of elimination of nitrogen and/or hypoxia or restricted visual environment on color vision and range of accommodation. Durham, NC: Duke University. Department of Ophthalmology and Psychology Report No. NASA-CR-128896. 28 February 1973.
- Wright, G., Randell, P., and Shephard, R. J. 1973. Carbon monoxide and driving skills. Archives of Environmental Health. 27:349-354.
- Yancey, C. M., and Linsenmeier, R. A. In preparation. The electroretinogram and choroidal PO_2 in the cat during elevated intraocular pressure. Submitted to Investigative Ophthalmology and Visual Science.
- Yonemura, D., and Kawasake, K. 1979. New approaches to ophthalmic electrodiagnosis by retinal oscillatory potential, drug-induced responses from retinal pigment epithelium and cone potential. Documenta Ophthalmologica. 48:163-222.
- Yordanov, Y., and Ruben, H. 1968. Correlation of pupillary dimensions and partial oxygen pressure in experimental hypoxia. Nauchni Trudove Visshia Meditsinski Institute, Sofia. 47:79-84.
- Young, J. M. 1967. Acute oxygen toxicity in working man. In: C. J. Lambertson (Ed.), Underwater physiology: Proceedings of the 4th symposium on underwater physiology. New York: Academic Press.
- Züst, F. 1940. Das Verhalten der Pupille bei Abnahme des Luftdrucks. Luftfahrtmedizin. 4:209-224.
- Zwahlen, P., and Grandjean, E. 1948. Variation des sensibilités corneenne et cutanee a l'altitude. Helvetica Physiologica et Pharmacologica Acta. 6:471-473.

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French Army Liaison Office
Building 602
Fort Rucker, AL 36362

Commander
USAF Armstrong Aerospace
Medical Research Laboratory
ATTN: AAMRL/HEF (MAJ O'Neal)
Wright-Patterson AFB, OH 45433

Commander
USAF School of Aerospace Medicine
ATTN: USAFSAM/NGOP (LTC Miller)
Brooks AFB, TX 78235-5301

Commander
Naval Aerospace Medical
Research Laboratory
ATTN: Code 0-2 (Dr. Temme)
NAS Pensacola, FL 32508

Dr. Irving Biederman
Department of Psychology
University of Minnesota
75 East River Road
Minneapolis, MN 55455

Dr. R. L. DeValois
Department of Psychology
University of California
Berkeley, CA 94720

Dr. Ann B. Fulton
Department of Ophthalmology
300 Longwood Avenue
Boston, MA 02115

Dr. James Lackner
Provost
Brandeis University
Waltham, MA 02154

Dr. Thomas Poggio
Artificial Intelligence Laboratory
Mass. Institute of Technology
Cambridge, MA 02139

Dr. Louis Silverstein
Honeywell Inc.
P. O. Box 21111
Phoenix, AZ 85036

Dr. Anthony J. Adams
School of Optometry
University of California
Berkeley, CA 94720

Dr. Jo Ann Kinney
RDF 1 Box 156A
Morgan Bay Road
Surry, ME 04684

Dr. Pamela Ebert Flattau
Study Director
Committee on Vision
2101 Constitution Avenue, N.W.
Washington, D.C. 20418

Dr. Robert Shapley
Department of Psychology
6 Washington Place
New York, NY 10003

Dr. Andrew B. Watson
NASA Ames Research Center
Mail Stop 239-3
Moffett Field, CA 94035

Dr. Nigel Daw
Washington University
School of Medicine
660 S. Euclid Avenue
St. Louis, MO 63110

Dr. Donald G. Pitts
College of Optometry
University of Houston
Houston, TX 77004