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A STUDY OF VISION AS RELATED TO DARK ADAPTATION AND NIGHT VISION IN THE SOLDIER

AUGUST 1969

Prepared for

LIFE SCIENCES DIVISION, ARMY RESEARCH OFFICE
OFFICE OF THE CHIEF OF RESEARCH AND DEVELOPMENT
DEPARTMENT OF THE ARMY
WASHINGTON, D. C. 20310

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9650 Rockville Pike
Bethesda, Maryland 20014

FOREWORD

This is a technical report prepared for the Life Sciences Division, Army Research Office, Office of the Chief of Research and Development, Department of the Army, by the Staff of the Life Sciences Research Office, Office of Biomedical Studies, Federation of American Societies for Experimental Biology (FASEB), in accordance with the provisions of U.S. Army Contract No. DA-HC19-68-C-0001. The text of the report contains a critical literature review and reflects the opinions of an ad hoc study group that met at Beaumont, FASEB, on October 8 and 9, 1968. The report has been approved by the majority, not necessarily by all, of the participants.

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SUMMARY

This technical report was prepared to provide the Life Sciences Division, Army Research Office, with a succinct summarization of recent advances in the understanding of dark adaptation and night vision capability.

The scope of the study included: current knowledge of the biochemical and physiological aspects of dark adaptation and night vision, the role of nutrition as it affects dark adaptation, pharmacologically induced alterations of night vision, the effects of smoking and noxious environmental agents on night vision, and individual variability in dark adaptation and night vision.

A synopsis of the review discussions is given (p 99). Suggestions are made for future research in these areas.

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I. THE PROBLEM

This study was undertaken to provide the Life Sciences Division, Army Research Office, Office of the Chief of Research and Development, Department of the Army, with a comprehensive review of the state of knowledge on vision as related to dark adaptation and night vision in the soldier.

Military history and current tactical doctrine stress the importance of both night and day operations. The advantage of a 24-hour capability for the soldier emphasizes the importance of studies on night vision. Military night operations basically depend upon the ability of the individual soldier to successfully accomplish his assigned task. In recent years, emphasis has been placed on development of devices that externally aid night vision capability (1). The Army has recently introduced a new family of electronic devices, e.g. image intensifiers, that enhance visual acuity and pattern recognition under reduced levels of illumination. However, the night vision devices depend upon both rod and cone functioning rather than scotopic capability of the user alone. The efficient use of these devices depends upon the recognition of the limitations of the visual capabilities of the man.

Vision involves the capacity of the eye to adapt to enormous variations in ambient illumination. This adaptation is mediated by the two interspersed photoreceptive systems of the retina. Cone cells are involved with perception of color and vision at higher levels of ambient illumination; rod cells at reduced illumination. Visual ability in reduced ambient illumination is, in part, dependent on the efficiency of dark adaptation. The process of dark adaptation refers to the increased visual sensitivity that accrues following a rapid decrease in the quantity of visible light reaching the retina. This process includes an increase in pupil diameter, increased photosensitivity of the retina, conversion from cone to rod vision and a shift in the neural pathways within the retina.

An individual's ability and confidence in his night vision capability can be enhanced by training in dark adaptation techniques and in the use of peripheral scanning for night vision. There are individual variations in the rate of dark adaptation and the final threshold of night vision capacity. However, selection of individuals with

superior scotopic vision, training to enhance night vision capability, and use of accessory optical equipment can be employed to better meet military requirements for night vision capability.

For these reasons, the principal concerns of this study were (a) to review the mechanisms of dark adaptation and night vision, (b) to assess the effects of nutrition, drugs, and environmental factors on night vision, and (c) to suggest guidelines for future research leading to a better understanding of the fundamental aspects of dark adaptation and night vision in the soldier.

II. SCOPE OF THE STUDY

In the preliminary reviews of this subject, the interrelationships of the physiological, biological, behavioral, and physical factors that affect vision were considered. Subjects such as visual cognition and the biological effects of monochromatic light constitute an important but separate body of knowledge and are not a part of this study. Emphasis in this study has been placed on the current biochemical and biophysical concepts of dark adaptation and night vision, the role of nutrition as it affects dark adaptation, and the pharmacologically induced alterations of night vision. In addition, the effects of smoking and noxious environmental agents are considered as well as the poorly understood individual variability in night vision capacity. Night operations as well as the most effective use of night vision devices may depend upon the individual soldier's capacity for dark adaptation and night vision.

III. REVIEW DISCUSSIONS

A. INTRODUCTION

The review discussions represent a comprehensive evaluation of state of knowledge on the physiology of dark adaptation and night vision. Emphasis has been given to recent research as it impinges on the necessity for adequate night vision capacity in the soldier. Because these aspects encompass only a small portion of the subject of vision, it is appropriate to briefly characterize the anatomy of the normal vertebrate eye and the processes of dark adaptation and night vision.

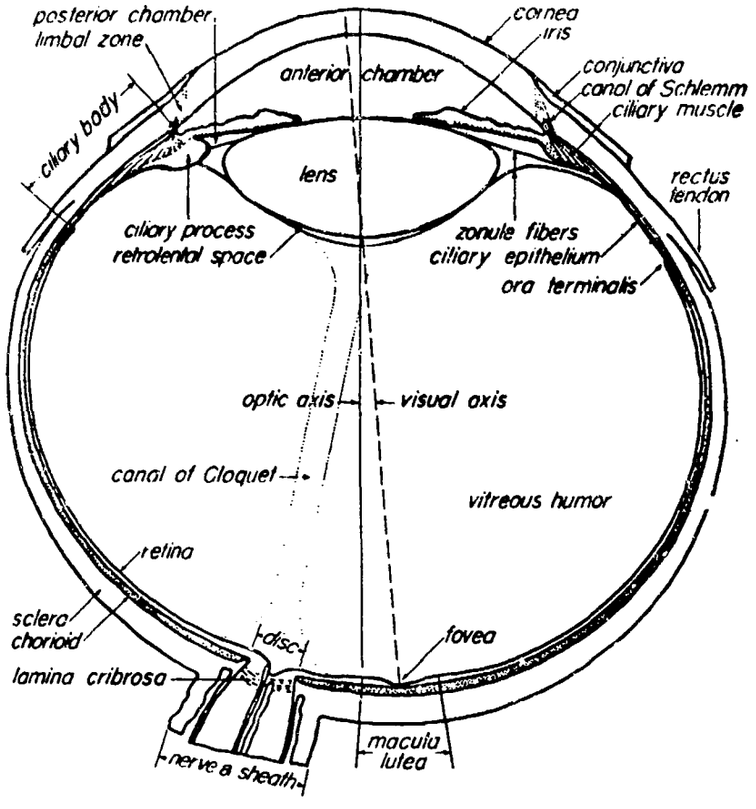
1. Anatomy of the Normal Eye

The adult human eye is roughly spherical (24 mm diameter) and is located in the orbital cavity. The bony structure of the orbit and the areolar tissue of the orbital cavity serve as a protective cushion for the eyeball. Approximately one-fifth of the anterior portion of the eyeball is exposed beyond the orbit. This portion is protected by a delicate mucous membrane, the conjunctiva, which continues anteriorly to the inner surface of the eyelids. When the eyelids open and close, the opposed conjunctival membranes slide over one another. These surfaces are continually lubricated by the fluid secreted by the lacrimal glands.

The eyeball is moved within the orbital cavity by 3 pairs of ocular muscles which are attached to the eyeball. Binocular vision requires a high degree of coordination between the musculature of the two eyes. Normally, visual images fall on corresponding sections of the two retinas at all times; fusion of the two retinal images is a higher cortical process.

A horizontal section reveals the tripartite nature of the wall of the eyeball (Figure 1). The outer layer or tunic is primarily fibrous and protects the internal vascular and neural tissues. The anterior portion of this tunic, the cornea, is transparent, allowing light to enter the eyeball. The cornea is continuous with the opaque

FIGURE 1



Horizontal Section of Right Human Eye. x 4. On the left, the section contains a ciliary process behind which the zonule fibers are partly concealed; on the right, the section has passed between two ciliary processes and the full extent of the zonule fibers can be seen. The limbal zone (transition between cornea and sclera) is stippled to emphasize that it is broader internally than externally. (Reprinted from Ref. 2, p 7. Copyright 1963 by the Cranbrook Institute of Science. Reprinted by permission of the copyright owner).

elastic sclera which surrounds the posterior five-sixths of the eye. The anterior chamber that separates the outer and second layer, the vascular tunic, contains the aqueous humor. This fluid supplies nutrients to those anterior ocular tissues that have no blood supply, e. g. the cornea.

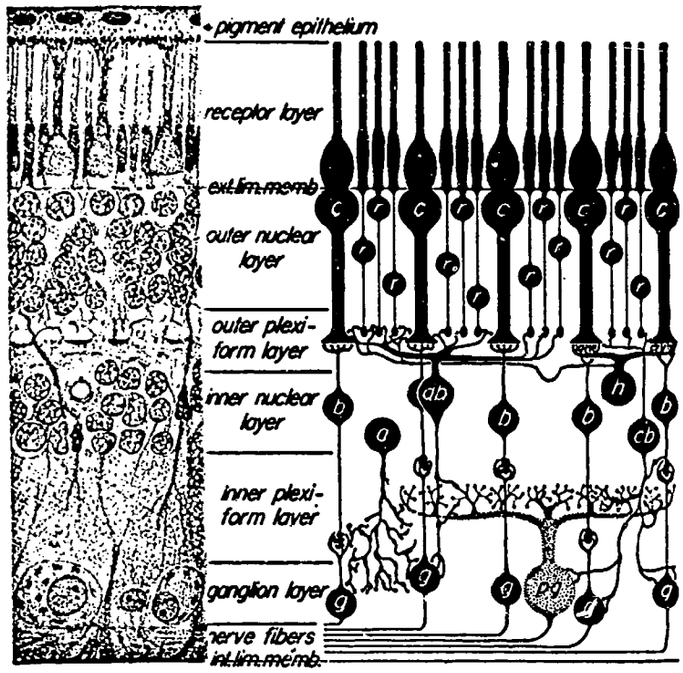
The middle vascular tunic consists of the iris anteriorly, the ciliary body, and the choroid posteriorly. The pigmented iris functions as a diaphragm opening or closing the pupil. The pupillary diameter changes with intensity of illumination and accommodation of the eye for near or far vision. The thickened anterior portion of the choroid is the ciliary body. The crystalline lens is held immediately behind the iris by zonules to the ciliary body. Muscles of the ciliary body control tension on zonule fibers which, in conjunction with the elastic properties of the lens, serve to alter the optical strength of the lens. The choroid is internal to the sclera and contains an extensive capillary plexus.

Posterior to the lens the main body of the eyeball is filled with the vitreous humor. This gelatinous vitreous is transparent and functions in maintenance of the spherical shape of the eyeball.

The inner tunic, or retina, is an extension of the central nervous system. It functions primarily in photoreception and initiation of neural transmission of photoreceptive stimulation to the higher visual centers of the forebrain. These neural impulses are carried by the optic nerve to the lateral geniculate body. Fibers of each nasal portion of the two retinas decussate in the optic chiasma. In the lateral geniculate body, nerve fibers of the nasal portion of one retina and the temporal portion of the other synapse in a highly complicated manner. These synaptic processes are connected to the occipital lobe of the cerebral cortex where visual perception occurs. Some optic nerve fibers synapse in the pretectal region and the superior colliculus, mediating visual reflexes and oculomotor responses.

The retina is a complex multilayered structure (Figure 2) (3, 4, 5, 6). Approximately 20% of light entering the cornea ultimately reaches the retina. A single ray of light entering the retina would pass sequentially through the following layers:

FIGURE 2



The Human Retina. At the left, a vertical section through the retina in the nasal fundus, x 500. At the right, a "wiring diagram" of the retina showing examples of its principal elements, as revealed in material impregnated with silver by the methods of Golgi. Based largely upon the work of Polyak.
a = amacrine cell (diffuse type); b = bipolar cells (ordinary, "midget" type); c = cones; cb = "centrifugal" bipolar, believed by Polyak to conduct outward through the retina rather than inward; db = diffuse bipolar, connecting with many visual cells - chiefly rods; g = ganglion cells (ordinary, "midget" type); h = horizontal cell - its dendrites connecting only with cones and its axon with both rods and cones at some distance from the cell-body; pg = "parasol" ganglion cell (one of several giant types, connecting with many bipolars); r = rods.
(Reprinted from Ref. 2, p 43. Copyright 1963 by the Cranbrook Institute of Science. Reprinted by permission of the copyright owner).

(a) the internal limiting membrane which separates the vitreous humor from the neural and photoreceptive cells. It is in part composed of neuroglial cell processes, the Müller fibers;

(b) optic nerve fibers, or more correctly, the axons of ganglion cells;

(c) ganglion layer which constitutes the inner cellular layer of the retina. Ganglion cells have been classified on the basis of shape, size, and extent of dendritic arborization. The ganglion cells are characterized by spontaneous activity; that is, the cells "fire" at random without external stimulation. The histological separation of ganglion cell types was reviewed recently (4);

(d) the inner plexiform layer where synaptic connections between bipolar, amacrine, and ganglion cells occur;

(e) inner nuclear layer that contains primarily the bipolar cells, but also the horizontal and amacrine cells as well as the cells of the Müller fibers. While Polyak (7) suggested that bipolar cells could be grouped as either monosynaptic or polysynaptic, this classification is incomplete (3, 6). Rod bipolar cells synapse exclusively with numerous rod photoreceptors; diffuse bipolar cells synapse with a limited number of cone cells, and the midget bipolar cells synapse with individual cone cells (3, 4). In addition to synaptic connections with the respective photoreceptive cells, bipolar cells synapse with amacrine cells and dendrites of ganglion cells. Amacrine cells also have reciprocal junctions back onto bipolar terminals (4, 6);

(f) outer plexiform layer, which is characterized by the connections of bipolar cells with horizontal photoreceptor cells;

(g) outer nuclear layer, containing the nuclear region of the photoreceptive cells;

(h) the outer limiting membrane;

(i) the outer segment of the photoreceptive cells containing the membrane bound visual pigments responsible for photoreception. The outer segment of the typical vertebrate rod cell is comprised of a stack of tightly packed discs, each of which represents a double layer of in-folded plasma membrane (3). Rhodopsin, the visual pigment, is a constituent of this plasma membrane disc and is not found in the other portions of the cell. The outer segment is connected to the inner segment through a narrow cylindrical stalk which contains a modified cilium. Within the inner segment, ellipsoid and myloid regions are evident. The former is characterized by numerous mitochondria; the latter by Golgi bodies, ribosomes, and various other vesicular inclusions. Below the myloid region, the inner segment is axon-like, contains the nucleus, and terminates synaptically in the outer plexiform layer (4); and

(j) the pigment epithelium which interdigitates with the adjacent layer anteriorly to the external limiting membrane. The light that is not absorbed by the photoreceptive cells is partially absorbed in the pigment epithelium and the choroid; both tissues contain melanin.

There are no photoreceptive cells at the optic disc, thus a "blind spot" occurs where the optic nerve passes from the anterior retinal surface posteriorly through the sclera. Immediately adjacent at the posterior pole of the eyeball is the fovea centralis. The retinal surface thins and most cells and layers are absent except for the cone photoreceptors. Visual acuity in man is greatest in the highly developed foveal area.

In the normal eye, the cornea and lens function to present an image on the receptive outer segment of the rods and cones which extend behind the external limiting membrane. The retina may be considered to have two distinct visual systems, the rod and cone cells. The former function at low levels of illumination; the latter perceive color and function at higher levels of illumination.

In man there are approximately 7 million cone cells and 125 million rod cells per eye. The cone cells are concentrated mainly in the foveal area and their distribution falls sharply to a minimum in the peripheral region of the retina (Figure 3). The cone cells which occur in the fovea are elongated and appear to be slightly different than cone cells immediately adjacent. There is no evidence that this anatomical difference affects the cellular physiology and photoreceptive functioning. Each photoreceptive cell acts individually; thus, a visual image cast upon the retina is divided into approximately 132 million separate fragments. Initial integration of this image occurs in the neural layer of the retina following the photochemical stimulation of the outer segment of the rod and cone cells.

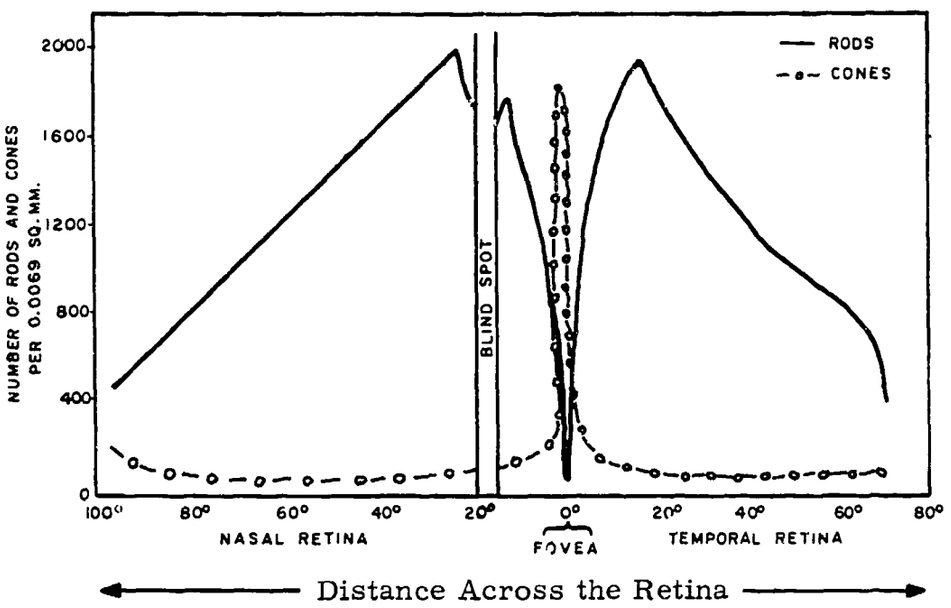
2. Dark Adaptation and Night Vision

The human visual system is capable of functioning over a wide range of luminance (Table 1). A change from the fully dark adapted state to higher luminance normally occurs in less than one minute. Conversely, adaptation of the eye to the fully dark adapted state requires approximately 30-40 minutes. Light adaptation is a loss of visual sensitivity while dark adaptation represents a gain of visual sensitivity. Dark adaptation involves a sequential process of anatomic, photochemical, and neurophysiological events. The details of these processes are incompletely understood.

The visibility of an object depends upon (a) the angular size of the object, (b) the quantity and direction of illumination of the object, (c) the field contrast, (d) the length of time it is viewed, (e) the state of retinal adaptation, and (f) interposing environmental conditions. The visibility of an object would decrease as any or all of the above factors are decreased. However, in the dark adapted eye, a reduction in any one of these factors may be compensated for by an increase in one of the others. The perception of color in the dark adapted eye is limited to shades of gray; perception of fine detail is poor. Thus night vision involves a greater summation of visual stimuli by the retinal rod cells, but visual acuity is reduced.

Night vision has been termed rod or peripheral vision. The foveal area contains only cone cells which do not function in vision under reduced ambient light levels. Thus night vision is best peripheral to the fovea. The number of rod cells is greatest 20 to

FIGURE 3



Density of rod and cone cells along a horizontal line through the human retina. (Modified from Ref. 9 and Ref. 10).

TABLE 1

LUMINANCE LEVEL AND CHARACTERISTICS OF HUMAN VISION

Type	Luminance in millilamberts	Remarks
Scotopic Vision (Rods)	10^{-7}	Absolute threshold, fully dark adapted
	10^{-6}	
	10^{-5}	
	10^{-4}	Starlight, moonless night
	10^{-3}	
Mesopic Vision (Transition Zone)	10^{-2}	Moonlight
	10^{-1}	
	1	Read with difficulty
	10	Room light, adequate for reading and critical work
	10^{2}	
Photopic Vision (Cones)	10^{3}	Sunlight, bright day
	10^{4}	
	10^{5}	
	10^{6}	Carbon arc
	10^{7}	
	10^{8}	Sun viewed from earth, clear day
	10^{9}	Detonation of A-Bomb and flash viewed from about 5 miles
Retinal Damage	10^{10}	

25 degrees from the foveal center (Figure 3). Scotopic visual capability relies upon this so-called "peripheral vision." Some evidence suggests that peripheral vision in man can be enhanced by training (11).

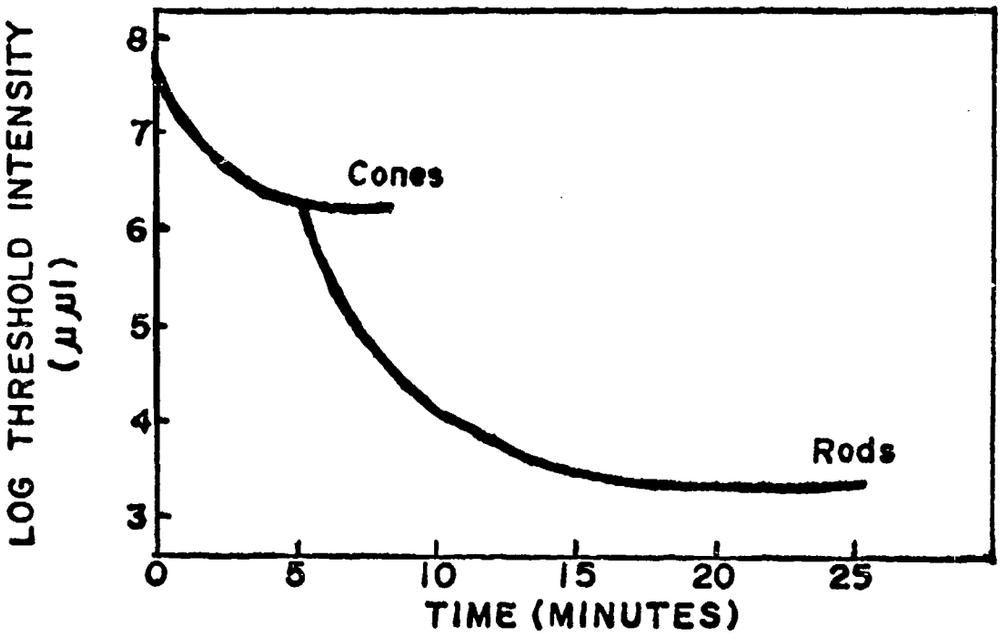
The most apparent change in the dark adapted eye is the increased pupillary diameter. As the ambient or background light decreases, pupillary dilation allows up to a 16-fold increase in the area of exposed lens. This change can account for adaptation of approximately one logarithmic unit of luminance in both mesopic and scotopic vision. While the increase in pupillary diameter does allow more light to enter the eye, the major contribution to night vision capacity is found within the retina itself.

In man, adaptation to decreasing luminance involves first the cone and then the rod cells (Figure 4). Cone cells are normally associated with photopic vision and rod cells with scotopic vision. Following general acceptance of the duplicity theory of vision, it was a natural consequence that anatomical characteristics, as viewed by light microscopy, led to the distinction of two classes of retinal photoreceptors. Utilizing electron microphotographic data, Pedler (13) suggested that more than two types of photoreceptive cells are present in the vertebrate eye. However, most investigators, acknowledging that the structure and neurophysiology of photoreceptive cells are highly complex, agree that scotopic vision involves rod cells and photopic vision depends exclusively on cone cells (4, 13, 14, 15). Both rods and cones as well as the adaptive mechanism of each system interact in the mesopic range (16).

The minimum threshold of light perception is normally determined by following changes in the absolute threshold of that luminance which is just perceptible to the dark adapting eye. Under standard conditions, the subject observes the occurrence of a stimulus light in a dark background. The luminance of the stimulus light is reduced by uniform increments until it is no longer visible. Classically, dark adaptation is measured by reducing the stimulus luminance from the photopic to the scotopic range. Complete dark adaptation occurs within 30-40 minutes. The luminance at which the fully dark adapted eye can barely discern a stimulus light is the minimum threshold value.

Numerous modifications of the methods for following the course of dark adaptation have been developed (11, 17). The minimum

FIGURE 4



The normal course of dark adaptation in man. Threshold light intensity observed plotted against time in the dark. (Modified from Ref. 12).

threshold can be determined psychophysically as above, or by measuring the luminance that evokes an electroretinogram (ERG) b-wave of constant size. Coupled with retinal densitometric determinations, both measures can be compared with the actual quantity of visual pigment in a certain specified area of the retina (16).

3. Ophthalmologic Aspects

Normal binocular vision is dependent upon oculomotor control and maintenance of the convergent relationship of the two eyes. In addition, for normal vision each eye independently adjusts to produce the sharpest possible retinal image. The adjustment or accommodation of the eye depends upon complex motor processes. These ophthalmologic considerations involve the mechanics of vision and therefore are of importance in night vision.

Approximately 80% of the light which enters the corneal surface does not reach the surface of the retina. While most is lost by absorption, some light is reflected or refracted during passage through the cornea, aqueous humor, lens, and vitreous humor. Since refractive indices of these tissues are approximately equal, for all practical purposes the eye has two refractive surfaces: the anterior corneal surface in contact with the air, and the lens surrounded by the two liquid media (9). Because of light refraction and the fact that the eye is not absolutely spherical, optical defects of the eye from curvature of refractive surfaces may be significant. In addition, dispersion of light by refractive media will influence the transmission of light and thus the nature of the image formed on the retina.

The importance of ophthalmologic disorders as influencing night vision capacity is significant when one considers that approximately 75% of adult Americans over 21 years of age wear eye glasses or use contact lenses (18). Projection of these figures suggests that approximately one out of every three servicemen (33%) does or should use some form of refractive correction.

The external and internal surfaces of both the cornea and the lens are not perfectly curved. In addition, the optical density of the lens varies from one point to another and this variation in optical density increases with age (18). The process of accommodation, i.e. focus of the image on the retina, includes the change

in curvature of the lens surface. Spherical aberration is greatest at the periphery of the cornea and the lens. Thus, spherical aberration defects are largest when the pupillary diameter is greatest. Myopia in the dark adapted eye has been attributed to spherical aberration (19) as well as accommodation (20).

Chromatic aberration is of negligible significance at night because of low luminance level and the physical size of the aperture (pupillary diameter of 4 mm). Uncorrected astigmatism may be important in night vision. It is conceivable that astigmatism would interfere with the efficient use of night-seeing devices. Errors of diffraction may be more important than spherical aberration or astigmatism (21). The fully dark adapted eye would have maximal pupil diameter. Thus any reduction in night vision acuity as a result of diffraction might be offset by increased aberrations. Pomerantzeff (22) has shown that the correction of optical aberrations arising in the dilated pupils of the dark adapted eye enhances night vision. The occurrence of a severe diffractive condition might affect night vision similarly, but it would be correctable.

While these ophthalmologic conditions affecting night vision are probably less significant than those involving the physiology and neurophysiology of the eye, they nevertheless represent factors which must be taken into account when considering the night vision capability of individuals.

(See Section V, Suggested Areas for Future Research, pp 119, 123).

B. VITAMIN A

The relation of night blindness[1] to a nutritional deficiency has been known since antiquity, but the relationships of vitamin A[2] with the provitamin carotenoids, and their role in the visual pigments were established only within the past 55 years (23). While several ophthalmologic disorders may precipitate night blindness, the commonly encountered reversible condition involves vitamin A deficiency (23). The pathology of vitamin A deficiency is exceedingly complex and has been the subject of several reviews (24, 25, 26, 27, 28, 240). Damage to the epithelial tissues, especially in the eye, is the most obvious clinical manifestation of deficiency.

The effects of vitamin A imbalance are summarized in Table 2. The occurrence and severity of clinical symptoms varies with species, sex, age, and environment (24). In man, pre- and post-natal vitamin A deficiency results in night blindness as a prelude to xerophthalmia and permanent degeneration of the eye (26). In man and several animal species, the clinically evident symptom of night blindness suggests corrective therapy. Reduction in dark adaptive capacity is a primary symptom, and is not usually used by itself to establish vitamin A deficiency. Night blindness does not cause death. Vitamin A deficiency in man is probably always complicated by other nutritional deficiencies as well as infectious diseases (25, 29).

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[1] Night blindness refers to the inability to see under dim or reduced light. Technically termed "nyctalopia," it implies no impairment of visual capacity under bright or daylight conditions. Unfortunately, "hemeralopia," or ability to see in dim light but not in bright or daylight, has been erroneously used in synonymy with night blindness. While both nyctalopia and hemeralopia occur often interchangeably in the literature, their correct definitions mean exactly the opposite.

[2] See p 30 for definition of vitamin A terminology.

TABLE 2

GENERAL CONSEQUENCES OF VITAMIN A IMBALANCE

Site	Hypovitaminosis A	Hypervitaminosis A
General	Growth retardation; susceptibility to infection; death	Malaise; lethargy; deposition of carotenoids; death
Skin and mucous membranes	Xerosis; keratinizing metaplasia; xerophthalmia; keratomalacia	Mucous cell formation, desquamation
Skeletal tissues and bone	Cancellous structure; defective remodelling	Decalcification, fractures, early epiphyseal closure; cortical thickening
Reproductive system	Degeneration of testes, gonadal resorption, congenital malformation	Resorption, congenital malformation
Nervous system	Compression by bone, increased cerebrospinal pressure, atrophy and ataxia	Elevated intracranial pressure
Retina	Night blindness	--

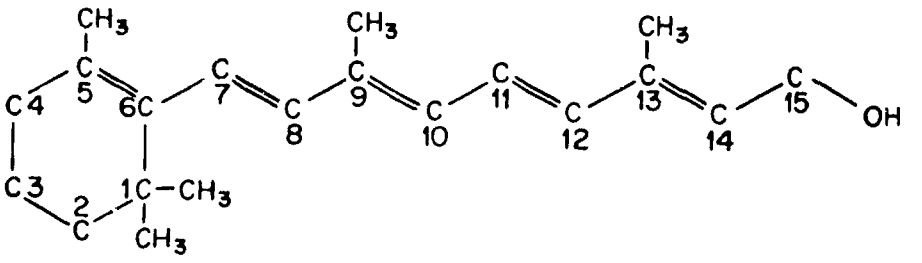
(Modified from Ref. 26).

The occurrence of endemic night blindness is commonly associated with dietary inadequacies, individual susceptibility, and environmental circumstances. For example, night blindness has been noted in prisoner of war camps, mental and penal institutions, and in geographic areas where there is insufficient food consumption (25). Night blindness may be precipitated in individuals with low vitamin A reserves when exposed to high intensity light flashes or prolonged exposure to bright light. The ability to absorb retinol and its carotenoid precursors, or store and transport vitamin A to the eye, involves several complex and interrelated physiological mechanisms. Recent studies suggest that the dietary intake and body stores of vitamin A in certain North American populations may be less than expected (30, 31, 32). While no recent data on the extent of nutritional night blindness in North America are available, the assumption that it is rare may be erroneous.

1. Chemistry of the Vitamin A Group

The chemistry of the A vitamins has been studied extensively in the quest for an understanding of their biological role. Several reviews on the chemistry of the vitamin A group are available (33, 34, 35, 36).

In accordance with modern nomenclature (37), the parent substance [3, 7-dimethyl-9-(2, 6, 6-trimethyl-1-cyclohexen-1-yl)-2, 4, 6, 8-nonatetraen-1-ol] is called "trans-retinol" (trans-vitamin A alcohol). In carotenoid chemistry, numbering begins in the ring rather than in the side chain (34). Following this nomenclature, the structure of the colorless, water insoluble, lipid soluble, unsaturated alcohol is:



The term "vitamin A" is in common use. In general, vitamin A is used generically to refer to the related group of chemicals which possess trans-retinol activity (38). Some confusion exists because there are several systems of nomenclature of vitamin A derivatives (Table 3). In this report, the terms "vitamin A" and "vitamin A activity" are used to denote the active forms of the vitamin and the visual pigment precursor when the exact chemical structures are unknown. Where chemically identifiable "retinol" is used for vitamin A alcohol and "retinal" for the aldehyde.

The 11-cis isomer of retinal is the active form of vitamin A that constitutes a portion of most vertebrate visual pigments. Retinal is bound to one of a series of proteins, the opsins, in each of the visual pigments, e.g. the rod pigment, rhodopsin. In addition to the vertebrate visual pigments, two other groups of retinol derivatives have been studied in some detail. The photosensitive pigment, porphyropsin, of true freshwater fish contains 11-cis-dehydroretinal in place of 11-cis-retinal. Dehydroretinal contains a second conjugated double bond in the β-ionone ring (C3-C4). Dehydroretinal forms stereoisomeric derivatives that are important in the visual processes of those animals which have porphyropsin (39). A second series of isomers have been synthesized which are derivatives of α-retinol, where the conjugated double bond is C2-C3 in the β-ionone ring.

Stereoisomerization of trans-retinal to 11-cis-retinal and the reverse are crucial reactions in the photoisomerization of rhodopsin. Numerous stereoisomers of trans-retinal have been synthesized, but the 11-cis form is considered the most important in the biochemistry of the visual process (40).

In animal sources such as milk, butter, eggs, and fish liver oils, the vitamin A activity is in the form of a retinyl ester or retinol bound to protein. The ultimate sources of all vitamin A activity are the carotenoid pigments contained in plant tissues, e.g. carrots, tomatoes, and spinach. These carotenoids, or provitamins A, occur in several chemical forms of which β-carotene is the most active (23).

TABLE 3

SYNONYMY OF TERMINOLOGY WITHIN THE VITAMIN A GROUP

trans-retinol	trans-vitamin A
11-cis-retinol	11-cis-vitamin A, neo-b vitamin A
trans-retinal	trans-vitamin A aldehyde, trans-retinene, trans-retinaldehyde, trans-retinald
11-cis-retinal	11-cis vitamin A aldehyde, 11-cis-retinene, 11-cis retinaldehyde, neo-b retinene, 11-cis-retinald
retinoic acid	vitamin A acid
retinyl palmitate	vitamin A palmitate
retinoyl β-glucuronide	vitamin A acid β-glucuronide
rhodopsin	visual purple, rod visual pigment, $retinene_1$ pigment
porphyropsin	$visual\ purple_2$ and $retinene_2$ pigment

2. Dietary Allowances

Although vitamin A is recognized as an essential component of the human diet, minimal and optimal daily requirements are not known precisely. In addition to the role of retinal in the visual pigment, retinyl derivatives are known to be essential in development and maintenance of epithelial tissues in the eye, gastrointestinal, respiratory, and urogenital tracts (38). Vitamin A may also function in mucopolysaccharide biosynthesis (41) and by interacting with vitamin E may play an important role in membrane permeability (42, 43). The quantitative aspects of the nutritional requirements of vitamin A are less well known than the qualitative effects. In general, vitamin A influences growth and maturation by affecting vision, bone growth, reproduction, and keratinization of mucous membranes (27).

In the human diet, retinol and retinal are derived from preformed retinol and carotenoids. Beta-carotene is the most prevalent and active natural form of vitamin A. The provitamins A (carotenoids) are active only after conversion to retinol. The activity of provitamins A and retinol are best known from animal studies (44). Absorption of carotenoids and retinol by man are thought to be similar to those processes known from animal investigations.

An exact definition of vitamin A activity or deficiency level in man is not possible. Originally defined from bioassay data, one international unit (IU) of β-carotene is established as that amount (0.600 μg of trans-β-carotene) equivalent to the activity of one IU of retinol (0.344 μg of trans-retinyl acetate or 0.300 μg of trans-β-retinol). Recent studies suggest that β-carotene can be enzymatically cleaved to yield 2 retinol moieties. In addition, carotenoid availability is highly variable, depending in part on the isomeric configuration, the ability of the absorptive mechanism to convert it to retinol, and particularly upon the chemical nature of the food source.

Daily allowances for vitamin A have been established by several responsible agencies. The Food and Agriculture Organization of the United Nations and the World Health Organization (FAO/WHO) (45) recommendations for an "average adult" include a daily dietary intake of 2500 IU as retinol, with the assumption

that availability of β-carotene is 0.33. Thus, the overall utilization efficiency of 1 μg of β-carotene is set as equal to 0.167 μg retinol. In a recent revision of recommended daily dietary intake levels, the Food and Nutrition Board of the National Research Council (FNB/NRC) (44) established the recommended daily allowances for young adults at 5000 IU of vitamin A. The revision noted that the average adult in the United States receives approximately one-half of this dietary intake in the form of carotenoids. The FNB/NRC suggested it was not practical to adjust the allowance of 5000 IU of vitamin A in terms of the proportions of provitamins versus actual retinol.

In an effort to establish human requirements for vitamin A activity, deficiency studies have led to conflicting results (25, 35, 38). Recommendations are currently based on the British Medical Research Council investigations reported by Hume and Krebs in 1949 (46). In this study, 16 adult volunteers were placed on a vitamin A-free diet; seven were placed on the diet supplemented by 2500 IU of retinol per day. Reduction in serum vitamin A levels varied widely with season and the individual subjects. The dark adaptation response showed a closer relationship to season of the year than to reduced serum vitamin A levels. After 11 months on the vitamin A-free diet, only 3 of the 16 subjects had a reduction in dark adaptive thresholds which could be attributed to depletion of vitamin A body stores (< 50 IU vitamin A/100 ml serum). Dietary supplementation for these 3 subjects and measurement of fecal carotene excretion led to the conclusion that a daily dosage of 1330 IU of vitamin A or 2600 IU of β-carotene restored normal scotopic capability. These dosage levels were inadequate for maintenance of acceptable serum and liver vitamin A levels, and thus 2500 IU of vitamin A was established as the minimal daily adult allowance (46).

It has been assumed that North American populations receive adequate dietary vitamin A. Schaefer (31) in a study of 12,000 low-income people in the United States (44% age 6 or below) reported that 33% have serum vitamin A levels below 19 μg (approximately 66 IU) per 100 ml. The studies of Hoppner et al. (30) of the vitamin A liver storage levels in Canadians were revealing. These constituted a portion of an overall assessment of the nutritional status of Canadians in relation to age, sex, disease, and environment. Vitamin A analyses were performed on livers collected at necropsy. Sampling, handling, and analysis methodology were rigidly standardized. As expected, age and sex were related to

liver vitamin A level (30) (Table 4). Of particular interest is the observation that 32 of the 100 subjects had liver vitamin A levels of 0-40 μg/g. The clinical significance of the level of 0-40 μg/g is unknown. The average vitamin A content of the normal liver is reported to be 100-300 μg/g (47).

In an extension of these studies to a wider geographic area, the investigators noted a trend to low vitamin A storage levels in the inland urban resident. While data on the cause of death was essentially similar to that reported in previous studies (Table 5), again 0-40 μg/g vitamin A was detected in 30.6% of the necropsy liver samples (Table 6). Utilizing food consumption figures, the "apparent" vitamin A intake for Canadians in 1964 was estimated at 2040 μg (6800 IU) per person per day. Hoppner et al. (30) concluded that in view of this estimate it must be assumed that diseases, nutritional habits, and other unknown environmental factors influence vitamin A storage in the liver.

3. Absorption

The absorption of retinol and the provitamins has been studied extensively in both animals and man (26, 38, 48). Typically, retinyl esters are converted to retinol in the gastrointestinal tract where retinol is absorbed. Carotenoids are converted to retinol, mostly in the small intestine, prior to absorption through the intestinal wall (48). However, there is considerable difference among vertebrates with respect to the ability to absorb carotenoids directly. In the rat, direct absorption of ingested carotenoids is minimal; in man and several ruminants both retinol and carotenoids are absorbed. Most vertebrates convert the provitamin to retinol. Simultaneous absorption of fat appears necessary for absorption of β-carotene, but not for absorption of retinol (48). Similarly, presence of bile salts, α-tocopherol, or lecithin, enhance absorption, but do not appear to be essential to the absorptive process. In normal adult individuals, retinol and retinyl esters are absorbed in either aqueous or lipid dispersion; however, absorption is more rapid from the aqueous phase. The primary site of absorption is the duodenum and the jejunum, although other gastrointestinal tissues may absorb retinol (48). In this connection, Adams et al. (49) observed low serum vitamin A levels and night blindness in 5 patients following total gastrectomy.

TABLE 4

VITAMIN A LEVELS IN LIVERS OF CANADIANS
IN RELATION TO AGE AND SEX

Age (years)	No. of Subjects	Vitamin A (μg/g liver) Range	Mean	Standard Deviation
Stillborn	4	6.2 - 104.2	38.0	± 45.0
0 - 1	7	*ND - 129.6	44.6	± 41.0
1 - 10	8	15.2 - 533.6	223.0	± 173.8
11 - 20	3	105.0 - 233.8	152.3	± 70.9
21 - 30	8	ND - 230.0	76.9	± 79.9
31 - 40	7	21.4 - 95.8	52.5	± 28.7
41 - 50	10	12.0 - 411.2	98.8	± 113.6
51 - 60	16	ND - 535.5	105.8	± 149.0
61 - 70	11	ND - 191.7	69.5	± 47.0
71 - 80	15	ND - 173.8	65.2	± 52.7
81 and over	11	ND - 438.0	92.0	± 128.3
Male	55	ND - 535.5	105.4	± 120.5
Female	45	ND - 438.0	89.8	± 95.9

* ND = not detectable

(Courtesy W. E. J. Phillips; data from Ref. 30).

TABLE 5

VITAMIN A LEVELS IN LIVER SAMPLES OF 379 CANADIANS IN RELATION TO DISEASE

Cause of Death	Number of Subjects	Vitamin A/liver (µg/g)	
		Range	Mean
Accidental	28	20.4 - 533.6	101.7
Heart & Coronary Diseases	142	ND[a] - 1325.2	131.9
Cancer	73	ND - 690.0	96.3
Respiratory Diseases	52	ND - 764.5	95.2
Miscellaneous Disorders[b]	84	ND - 686.3	117.3

a) ND = not detectable

b) in subjects over 1 year of age.

(Courtesy W.E.J. Phillips; data from Ref. 30).

TABLE 6

LIVER VITAMIN A LEVELS IN 369 CANADIANS
OVER 10 YEARS OF AGE

Vitamin A Content of liver (μg/g)	Number of Subjects	Percent of Total
0	37	10.0
1 - 40	76	20.6
41 - 80	85	23.0
81 - 120	63	17.1
121 - 160	30	8.1
161 - 200	20	5.4
201 - 240	15	4.1
over 240	43	11.7

(Courtesy W.E.J. Phillips; data from Ref. 30).

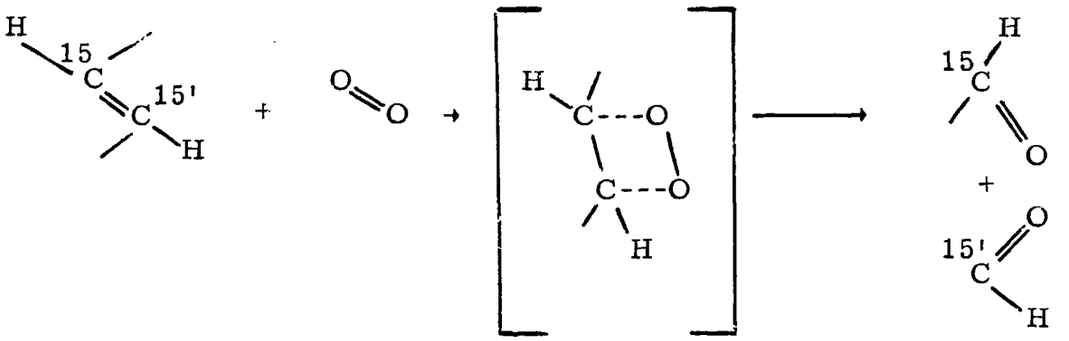
The absorption of retinol requires normal function and structure of the small intestine. Faulty retinol absorption is evident in numerous diseases, e.g. cirrhosis, hepatitis, sprue, celiac disease, as well as gastric and enteric infections (23). However, the effects of disease-induced malabsorption of retinol on occurrence and prevalence of impaired night vision are not completely documented. Typically, therapy of infectious diseases does not include critical study of the after-effects of the disease on the somatic and ocular metabolism of retinol.

In man and the rat, retinol is esterified as it passes through the intestinal mucosa. The predominant saturated fatty acid esters involved are palmitate and stearate (50, 51). The retinyl esters are transported via the intestinal lymphatics in chylomicrons. Recently, the pathway of absorption has been further clarified by use of retinol-15-^{14}C, retinyl-15-^{3}H acetate, and labeled β-carotene. Maximum absorption into the lymph occurred 3 to 10 hours following ingestion; washed chylomicrons contained 70-80% of the absorbed radioactivity. Approximately 90% of the labeled vitamin A found in the lymph was present as retinyl esters, both in the rat and man (50, 52). The fatty acid composition of the retinyl esters in the lymph was fairly uniform and did not change with alterations in the composition of the fatty acids ingested. The retinyl ester composition showed a consistent predominance of saturated fatty acids regardless of whether analyses followed absorption of retinol or β-carotene, or whether the chylomicron or non-chylomicron fraction was studied. Highest radioactive labeling occurred in retinyl palmitate and retinyl stearate in a ratio of 2.4 to 1.0 respectively; less than 20-25% of the radioactivity was observed in the unsaturated retinyl esters. A small quantity of unchanged labeled β-carotene (20-30% of the total lymph radioactivity) was observed in human lymph following ingestion of labeled β-carotene; in contrast, unchanged labeled β-carotene was not found in rat lymph. Goodman et al. (50) concluded that the human intestine has a limited capacity to absorb dietary β-carotene directly into the lymph. The fatty acid composition of the intestinal mucosa is known to be similar to that found in the retinyl esters of the liver and the retina (53).

The specificity of the fatty acid composition in retinyl esters is intriguing. When different types of fat were fed, large variations in total fatty acid composition of the chylomicrons

occurred (48). Lymphatic triglycerides and cholesterol esters normally reflect the composition of ingested fat (48). The consistency in predominance of palmitate and stearate retinyl esters in lymph suggests that further investigation of the mechanism of retinol esterification is required. Mahadevan et al. (54) recently reported that a retinyl ester hydrolase from rat liver exhibited marked specificity for retinyl palmitate. The similarity of retinyl ester composition in numerous vertebrates warrants further study of the acyl donor pool to clarify the mechanism of lymphatic transport of retinyl esters.

Carotenoids have been known as precursors of retinol for many years (55) and one mechanism of conversion has been clarified recently (50, 52, 56, 57). The site of conversion in vivo is apparently the intestinal mucosal wall. Working with labeled precursor, Goodman et al. (58, 59) showed that β-carotene is cleaved centrally (15-15' bond) to form two moieties of retinal which are then reduced to retinol. The action is mediated by a dioxygenase enzyme system which is thought to proceed as follows:



The dioxygenase system requires molecular oxygen. In vitro preparations also require a lipid detergent mixture; the reasons are not fully understood. Olson and Hayaishi (57) have observed in vitro conversion of one molecule of β-carotene to two molecules of retinal in rat liver preparations. Further studies on the enzyme from rat and hog duodenal mucosa have established additional characteristics of the enzyme system. The specificity of the dioxygenase enzyme system for carotenoids other than β-carotene is currently under investigation (38). To date, other postulated mechanisms of carotene cleavage have not been observed in vivo.

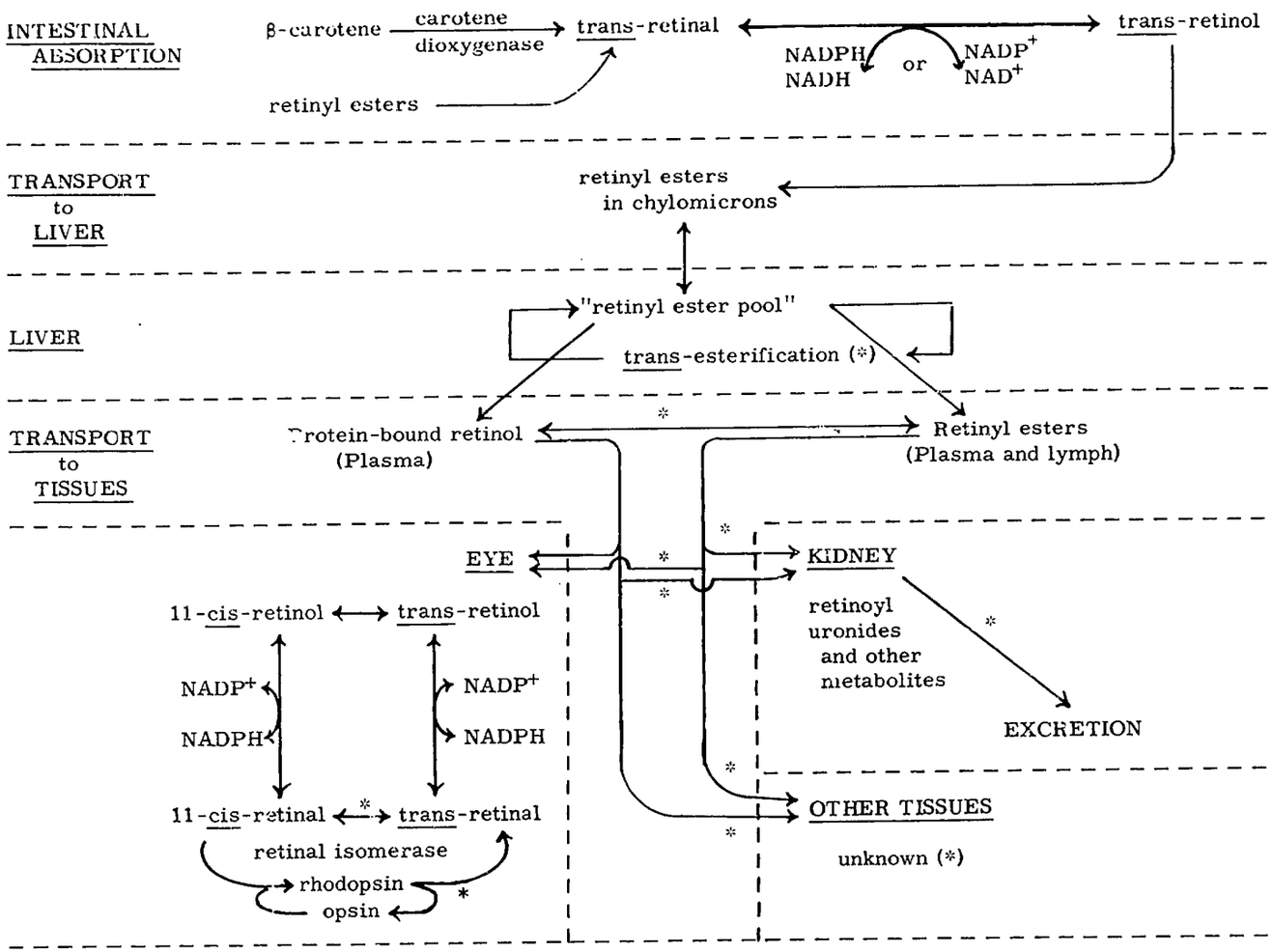
Following cleavage of β-carotene to 2 molecules of retinal, reduction to retinol takes place in the mucosal wall. This reaction is mediated by a second soluble protein enzyme. In the rat, Fidge and Goodman (60) found the enzyme to be an aldehyde reductase requiring as a cofactor either reduced nicotinamide adenine dinucleotide (NADH) or reduced nicotinamide adenine dinucleotide phosphate (NADPH). The former is more active at low nucleotide concentrations; at higher concentrations NADPH was slightly more active. The reduction reaction is stimulated by glutathione and hindered by thiol inhibitors. The mucosal enzyme is relatively nonspecific with respect to the aldehyde substrate as well as the pyridine nucleotide cofactor. However, the enzyme exhibited stereospecificity for the hydrogen atom at the 4A position of NADH. Thus, the mucosal reductase resembles the alcohol dehydrogenase enzymes isolated from many tissues (60).

Previous investigators have reported the reduction of retinal to retinol in preparations of liver and the retina (40, 61, 62). Originally, an NADH dependent reduction was noted in preparations from frog and bovine retinas (61). Futterman (62) examined retinal reduction in preparations from calf retina and found the reductase activity localized in the outer segment of the visual cells. Furthermore, NADPH was more effective than NADH in mediating the reduction. These data suggested that the enzyme system in the outer segment of the photoreceptive cells is in close proximity to the visual pigment and is sterically oriented for rapid reduction of photochemically released trans-retinal to trans-retinol (62).

4. Transport and Storage

The classical concept of retinyl ester transport and storage (Figure 5) includes movement of retinyl palmitate in chylomicrons through the lymphatic system, via the thoracic duct, to the blood stream, and finally to the liver where storage occurs. Subsequently, liver reserves of retinyl esters are enzymatically hydrolyzed and the retinol is carried to various body tissues in specific protein fractions of the blood. Finally, the serum retinol level is thought to be maintained by mobilization of stored liver reserves. Symptoms of dietary deficiency of vitamin A are not evident in the visual system until liver reserves are exhausted or at least severely depleted (23, 51). In this scheme, night blindness

FIGURE 5



* Needs further clarification.

Schematic Outline of Major Pathways of Vitamin A Metabolism.

should be preceded first by a depletion of liver reserves, and second by a decrease in serum retinol levels. This classical pattern has been produced experimentally in the rat (63). However, since plasmal retinol levels are regulated, in part, by the concentration of the carrier proteins, the retinol supply to the tissues may not depend solely on the amount stored in the liver. The subject of net retinol transport requires further investigation. These studies should include further work on the mechanisms of plasma transport, for example, the possibility and effect of carrier protein saturation (50, 60, 64).

Plasma retinol levels in the rat are altered by protein and/or caloric deprivation (65). These effects may be a result of the dietary deprivation on the level of protein-bound retinol. Arroyave et al. (66) have demonstrated a possibly related phenomenon in children recovering from severe protein-caloric malnutrition. Initially, plasma vitamin A levels were depressed even though measurable liver reserves were present. When a protein supplement (free of vitamin A) was added to the diet, plasma levels of vitamin A increased, suggesting that dietary deficiencies or alterations may have a marked effect on vitamin A transport. Furthermore, protein deficiency is known to impair carotene utilization in the rat (67). The mechanisms of vitamin A release from the liver and other tissues are poorly understood. Thus, protein-calorie deprivation may influence absorption, mobilization of liver reserves, and transport of vitamin A to the various tissues (23, 55).

The major portion of vitamin A activity in fasting blood is present as retinol, bound to a specific protein, retinol-binding protein (RBP), rather than to a lipoprotein fraction (64). RBP has a molecular weight of 21,000 to 22,000 and electrophoretic mobility characteristic of the α_1 protein fraction. RBP contains approximately one molecule of retinol per molecule of RBP, suggesting that there is one retinol binding site per RBP molecule. Retinol can be extracted from RBP with organic solvents, indicating that it is neither covalently bonded nor is the molecular configuration markedly altered by binding to RBP (64). The RBP amino acid composition includes a high proportion of aromatic amino acids and may be representative of a specific group of plasma proteins.

RBP circulates in the plasma bound to a larger protein that exhibits prealbumin electrophoretic mobility. From electrophoretic and immunologic studies, Kanai et al. (64) concluded that the prealbumin protein (PA) is identical to the "thyroxine-binding" PA of human plasma. This observation is of interest as thyroxine is known to affect carotene conversion to retinol (23). The retinol-binding protein-prealbumin complex (RBP-PA) contains one molecule of each component (1:1).

The transport of retinol in the plasma involves interaction of two proteins, RBP and PA. The interaction of RBP with retinol not only solubilizes the insoluble retinol, but protects it during transport (64). The binding of RBP to PA may also protect the RBP from glomerular filtration during circulation through the kidney.

These fundamental studies on the binding and transport of retinol are of great importance. The isolation, purification, and identification of the retinol-RBP complex and the RBP-PA complex have helped to clarify the mechanism of retinol transport in the plasma to body tissues. Further study of RBP-PA transport will be useful in understanding several other facets of retinol metabolism. For example, the eye contains only a minute proportion of the total body reserves of vitamin A (68). The possible role of RBP in regulation of ocular vitamin A levels should be investigated.

Similarly, mobilization of retinol from the liver could be a consequence of increased RBP synthesis. Dietary protein supplementation in severe malnutrition often precipitates vitamin A deficiency (66). While this is probably due to the stimulation of growth and the concomitant increased vitamin A requirement, it may be related to synthesis and utilization of RBP. If both protein and vitamin A reserves were low, night blindness and other deficiency symptoms might become evident when the increased rate of RBP synthesis exceeded the supply of vitamin A.

The existence of a retinol carrier within the blood stream could explain why dietary supplementation with excessive retinol does not enhance scotopic vision, but rather may induce hypervitaminosis A. It seems reasonable to assume that the RBP-carrier system normally functions in the fully saturated state; i.e.

it carries as much retinol as possible. Then any administered excess retinol could not reach the ocular tissues, but would be transported to the liver via the β-lipoproteins and ultimately could reach toxic levels in that organ.

Numerous studies have shown that about 90% of body retinol stores occur in the liver as retinyl esters (23, 47). There is little evidence that liver storage of retinyl compounds has an upper limit. Liver reserves of retinyl esters would be protective, but retinol storage could be toxic depending on the magnitude of storage. There is little direct relationship between the level of retinol in the blood and the level of retinyl esters held in the liver (47).

Animal experimentation has established that infections or hyperthermia produce a significant reduction of plasma vitamin A levels, regardless of liver reserves (23, 69). Ironically, in depletion studies, blood levels do not exhibit significant decrease until liver stores are drastically reduced or eliminated (23, 70). It is paradoxical that accurate determination of vitamin A levels in the liver do not reflect the actual supply of retinol to body tissues, and plasma vitamin A levels do not closely reflect total body reserves. There is need for reevaluation of the interrelationships of liver stores of retinyl esters and transport of retinol in the blood.

In the normal adult, carotenoids and vitamin A metabolites are eliminated in the feces, urine, and expired air. Fecal excretion reflects, in part, carotenoid passage through the gastrointestinal tract in excess of that quantity converted to retinol and absorbed. Radioactively labeled retinol and retinyl esters are eliminated by all 3 routes, but primarily by fecal and urinary excretion (71). Similarly, retinoic acid metabolites appear to be excreted in both urine and feces (38). The urinary metabolites are water-soluble and contain retinoyl glucuronides as a major constituent. Fecal glucuronides originate via the biliary route as a consequence of enterohepatic circulation. The importance of enterohepatic circulation should be further investigated (38).

Urinary excretion of retinyl derivatives increases following infection, and is thought to be related to the concomitant decrease that occurs in plasma vitamin A (23, 38). There is a

paucity of data on the nutritional sequelae and significance of vitamin A excretion following infection and disease. Particularly relevant to night visual capability would be the investigation of the increased urinary excretion of vitamin A following severe infectious diseases, e.g. chronic diarrhea. Model animal systems could be utilized to study the interrelationships of decreased plasma levels and increased urinary excretion together with impairment of dark adaptation and night vision.

5. Measurement of Retinol and Carotenoids

When liver and blood vitamin A have been depleted, the first overt deficiency symptom in man and other animals is night blindness. Initially, a rise in minimal visual threshold occurs. Lack of visual pigment is thought to result from insufficient retinal precursor. Prolonged retinol deficiency results in progressively severe night blindness and ultimately degenerative retinopathy. Analyses of vitamin A levels in the blood and liver are indicated when scotopic sensitivity is reduced without apparent cause. Similarly, nutritional surveys of dietary adequacy often include plasma vitamin A analyses. However, night blindness is but one sequela of vitamin A deficiency, and analyses of liver and blood levels have received primary attention rather than the measurement of elevated visual threshold.

Two major methods are utilized in vitamin A analysis. The procedures for extraction, separation, and determination have recently been reviewed (72). While there are several methods for analysis of carotenoids, retinol, and retinyl derivatives, only the micromethods of Bessey et al. (73) and the Neeld-Pearson modification of the Carr-Price method (74) are used routinely. Micromethods, in this context, refer to an analysis of a small sample (<200 mg) irrespective of the concentration of the substance to be measured.

The Bessey et al. (73) method is based upon determination of vitamin A content in a nonpolar solvent by measuring the absorption at 326 nm[3]. Interference by hemolysis can be overcome by chromatographic separation prior to analysis. However, this

[3] nanometers (nm), 10^{-9} meters or millimicrons (mμ).

procedure is subject to error in that retinol is not the only substance destroyed in the acidic solution by ultraviolet irradiation treatment. Substances other than retinol that are affected by ultraviolet irradiation contribute to absorption at 326 nm.

The Carr-Price method for determination of retinol (74) is also subject to experimental errors. The procedure depends upon the formation of a transient blue reaction product between retinol and antimony trichloride in chloroform solution. While the Carr-Price reaction can be obscured by turbidity and may be of limited usefulness as a micromethod, the Neeld-Pearson modification (74) is used as a micromethod. Serum retinol is calculated from absorbance at 620 nm after subtraction of a value for nonretinyl sera components. This latter value is calculated by assuming that the interfering material consists primarily of β-carotene. However, mammalian blood and other tissues contain carotenoids other than β-carotene which interfere with the accuracy of the correction factor (72). In sera more than 40 days old, a large percentage of the samples contain an artifact which will produce the transient color with the chromogenic reagent trifluoroacetic acid. This may result in erroneously high spectrophotometric readings.

There is a need to compare these two methods in a large population containing a wide range of liver or blood retinol levels. The accuracy of these analyses as well as assessment of the actual levels in relation to liver storage and retinol binding in blood plasma should be considered.

Ideally, vitamin A analysis should indicate retinol and retinyl ester concentrations rather than total vitamin A activity. For example, plasma levels of retinyl esters fluctuate widely following ingestion of vitamin A. Plasma retinol levels are more stable, probably reflecting the binding in RBP-PA. There is an urgent requirement for more precise analytical methodology that measures tissue retinol and retinyl ester concentrations.

(See Section V, Suggested Areas for Future Research, p 113).

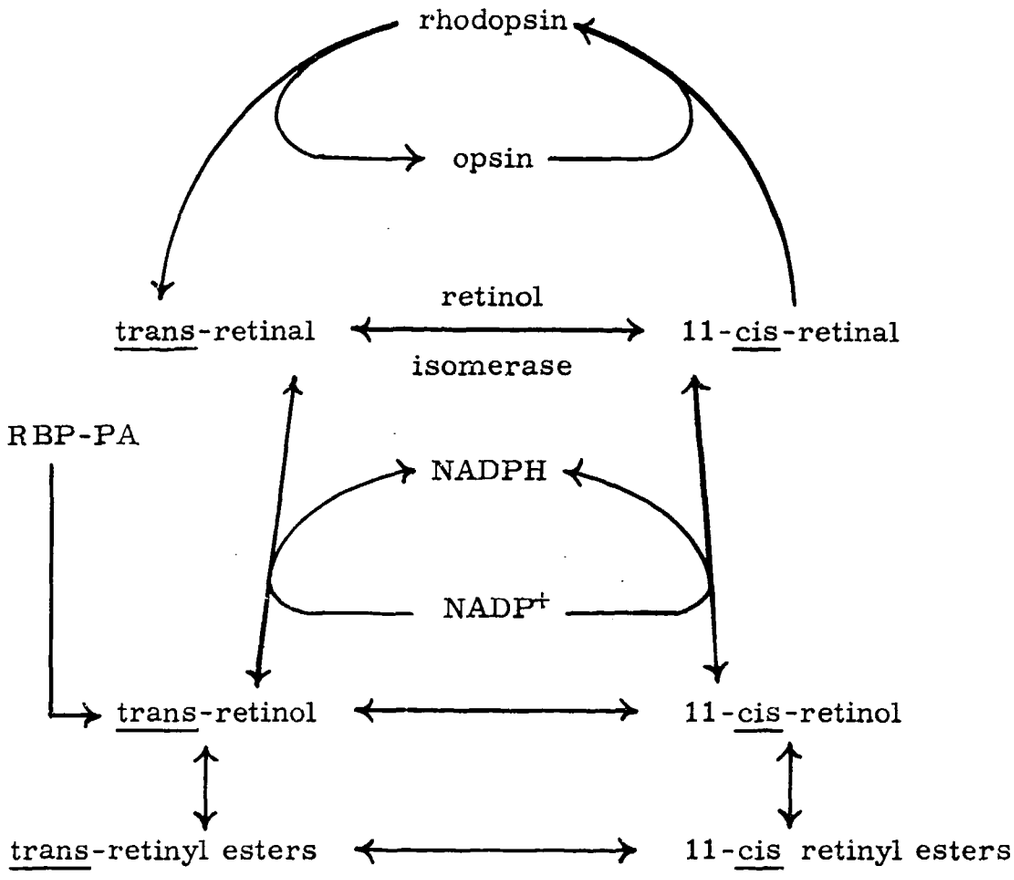
C. OCULAR METABOLISM OF VITAMIN A

The retina and related ocular tissues receive a rich supply of blood from the internal carotid and ophthalmic arteries. Presumably retinol is delivered to these tissues by the retinol-binding protein-prealbumin complex (RBP-PA) (Figure 6). The mechanisms of retinol release from the liver to the blood and from the RBP-PA complex to the ocular tissues have not received due consideration.

The location of retinol in the ocular tissues has been determined for the most part by animal experimentation. The characteristic fluorescence of retinol was found in the pigment epithelium of the rat eye in the light adapted state (75). In the dark adapted eye, the pigment epithelium showed reduced fluorescence. The retina exhibited maximum fluorescence when dark adapted, although actual fluorescence was less than that observed in the light adapted pigment epithelium due to conversion in the retina to the nonfluorescent retinal. Greenberg and Popper (75) observed that the retinol is tenaciously held by the eye when animals are retinol depleted. These and other studies (63) indicate that retinol metabolism within the eye is, to a great extent, separate and distinct from other somatic pathways of retinol metabolism. Moore (68) pointed out that less than 0.01% of the vitamin A content of the adult human is present in the ocular tissues. This suggests that ocular concentration is metabolically controlled and that dietary supplementation with retinol or its precursors would not enhance the visual process in an individual already receiving an adequate supply of vitamin A.

Krinsky (76) studied an enzyme from the particulate fraction of bovine pigment epithelium that esterified retinol. Hydrolysis of the retinyl acetate appeared to occur in the retina but not in the pigment epithelium. Rapid and selective esterification of retinol in the pigment epithelium would allow subsequent diffusion to photoreceptor cells where hydrolysis occurs. Oxidation and isomerization to 11-cis-retinal would then provide the retinyl moiety available for formation of rhodopsin (Figure 6). Krinsky (76) showed that over 60% of the retinyl ester formed in preparations of bovine retina was the 11-cis isomer. The enzymic activity of the pigment epithelium to selectively produce an 11-cis isomeric ester implies a mechanism that separates vitamin A metabolism of the eye from other body tissues. Several investigators (63, 76) have observed that the

FIGURE 6



Schematic Diagram of Retinol Metabolism in Ocular Tissues.

11-cis isomer was present only in preparations of vertebrate eyes and always absent in plasma and liver preparations.

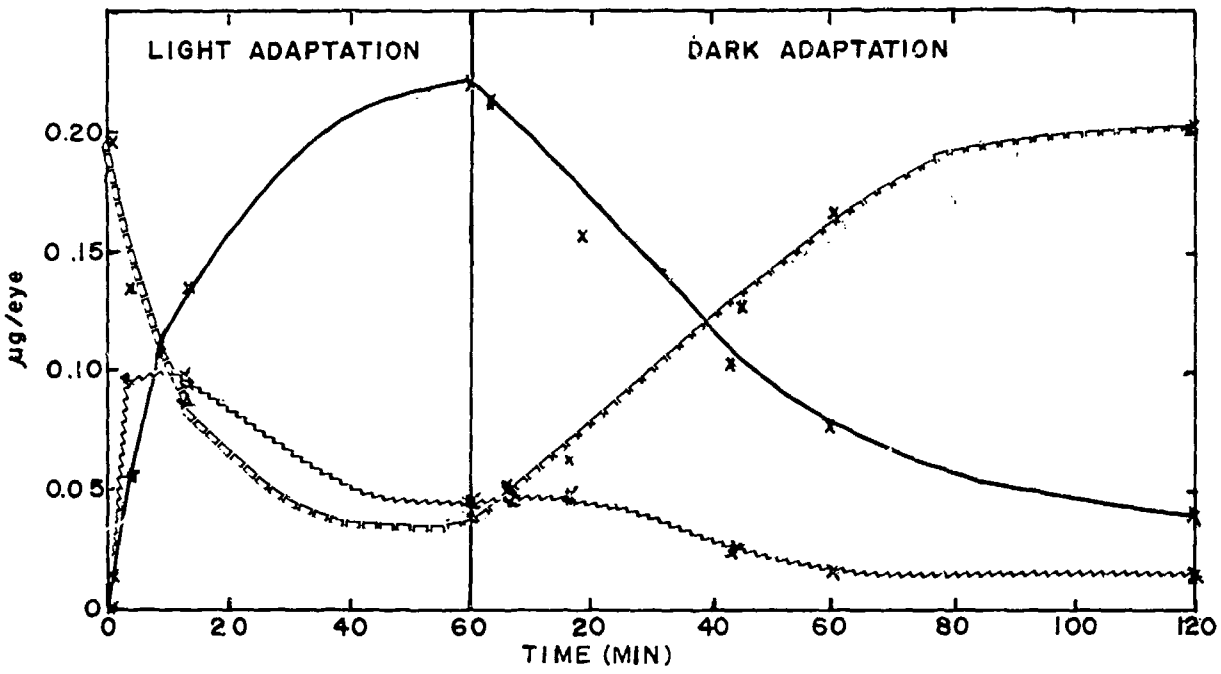
Isomerization of trans-retinal to 11-cis-retinal is thought to be enzymically mediated (77). Enzyme preparations from both frog and bovine pigment epithelium exhibited equilibrium kinetics producing 5% 11-cis and 95% trans-retinal in the dark. Hubbard (77) concluded that since opsin was present to trap the 11-cis-retinal, retinal isomerase would normally provide sufficient 11-cis-retinal for rhodopsin synthesis. Dowling and Hubbard (78) suggested that all vertebrates may regenerate rhodopsin in the dark only from free 11-cis-retinal and opsin.

In a study of retinol and retinal distribution in the retina and pigment epithelium of the albino rat, total vitamin A activity in the two tissues remained relatively constant and the interconversion of retinol and retinal could be quantified (70) (Figure 7). Analyses of retinol and retinal indicated the retinol content of the pigment epithelium decreased in dark adaptation while a concomitant increase of retinal occurred in the retina. In the light adapted state, less total vitamin A activity is present in the retina (Figure 7).

These observations are consistent with the cyclic processes of rhodopsin metabolism. In the dark adapted eye, increased synthesis of rhodopsin would account for the elevated level of total vitamin A in the retina and the reduced level in the pigment epithelium. Following photolysis and bleaching, the reduction of trans-retinal to trans-retinol in the outer segment of the rod cell would theoretically be decreased by an equilibrium favoring synthesis of rhodopsin from 11-cis-retinal. In a subsequent period of light adaptation, release of trans-retinol, conversion to retinyl esters, and storage in the pigment epithelium would be expected (Figure 7). About 90% of the vitamin A activity of the eye after light adaptation was found to be present as retinyl esters in the pigment epithelium (70, 76).

Vitamin A metabolism in the light adapted retina has been studied (53, 62, 79). Removal of trans-retinal after photolysis is related to oxidative metabolic activity of the outer segment of the photoreceptors (62). Futterman (62) suggested that removal of trans-retinal prevented buildup of a potentially toxic concentration

FIGURE 7



Retinol in retina

Retinol in pigment epithelium

Retinal in retina

Concentration of retinol and retinal (µg/eye) during light- and dark adaptation. During light adaptation, the retinal content of the eye falls, as the retinal, liberated on bleaching of rhodopsin, is reduced to retinol. Retinol in the retina rises for a time, and then declines, while the bulk of the retinol moves into the pigment layers. During dark adaptation, these processes are reversed. The retinal content of the eye increases, as rhodopsin is re-formed; and reciprocally the retinol in the pigment layers and retina declines. Dark adaptation is completed in about 100-120 min. (Modified with permission from J.E. Dowling; Ref. 70).

of trans-retinol. The released trans-retinal is reduced to trans-retinol in the outer segment, accompanied by an oxidation of NADPH to $NADP^+$ mediated by an alcohol dehydrogenase enzyme, retinal reductase (62). In the sequence of the rhodopsin cycle, N-retinylidene opsin could be either the substrate or an intermediate in this reaction. This possibility does not appear to have been investigated.

The glycolytic pathway and hexose monosphophate shunt both contributed to generation of NADPH. These reactions are summarized in Figure 8. Retinal reduction in the visual cycle appears to be dependent on glucose metabolism primarily by way of the pentose cycle. In the light adapted eye, the presence of trans retinal results in reoxidation of the nicotinamide nucleotide, NADPH (62). Thus, pentose cycle activity and ultimately the requirement for both oxygen and glucose are stimulated. The retina exhibits a rapid rate of respiration, as well as a high rate of CO_2 fixation and glucose utilization (80). Even when the oxygen supply is not limited, retinal tissues accumulate some lactic acid, indicating aerobic as well as anaerobic glycolysis. Because glycogen storage is limited, the human retina is almost entirely dependent on an uninterrupted supply of blood glucose.

Andrews and Futterman (79) demonstrated that the microsomal fraction of the retina is active in esterification of trans-retinol. The observation that outer segment preparations are unable to induce esterification led these investigators to conclude that the reduced retinal diffuses out of the outer segment and into the microsomes of the photoreceptive or related neural cells. This process is summarized as follows:

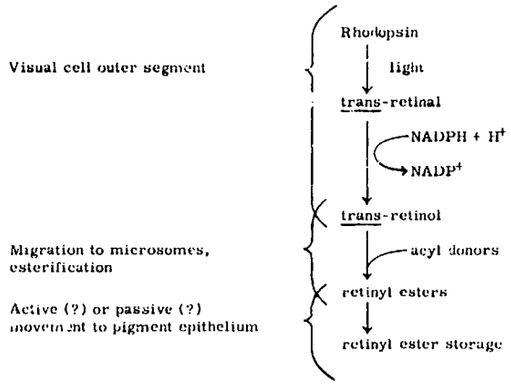


FIGURE 8

a) Glucose + ATP $\xrightarrow{\text{hexokinase}}$ Glucose-6-Phosphate (G-6-P) + ADP

b) G-6-P + $NADP^+$ $\xrightarrow{\text{G-6-P dehydrogenase}}$ 6-phosphogluconate (6-PG) + NADPH + H^+

c) 6-PG + $NADP^+$ $\xrightarrow{\text{6-PG dehydrogenase}}$ ribulose-5-phosphate + CO_2 + NADPH + H^+

d) 2 trans-retinal + 2 NADPH $\xrightarrow{\text{retinal reductase}}$ 2 trans-retinol + 2 $NADP^+$

In Summary:

Glucose + ATP + 2 trans-retinal $\longrightarrow$ Ribulose-5-phosphate + ADP + 2 trans-retinol + CO_2

The Interrelationship of Glucose Metabolism and Retinal Reduction. (Modified from Ref. 62).

The esterification mechanism does not require adenosine triphosphate (ATP), coenzyme A (CoA) or other cofactors. The formation of retinyl esters is greater when preparations are incubated in the light (79). This would be expected since the increased synthesis of rhodopsin in the dark adapted retina would tie up most of the vitamin A, inhibiting esterification. Futterman and Andrews (53) found that retinyl palmitate, stearate, and oleate esters comprised about 85% of the total retinyl esters formed. The ratio (6.5 palmitate : 2.5 stearate : 1.0 oleate) produced was quite similar in retinal preparations from trout, frog, cat, sheep, calf, and man. Addition of excess trans-retinol increased the ester synthesis rate but did not alter the fatty acid composition of the ester (79). These data suggest that the esterification mechanism exceeds that required for esterification of endogenous retinol produced in the visual process and that an acyl donor and carrier system may exist within the retina.

Futterman and Andrews (81) reported that the fatty acid composition of esters synthesized in the retina is similar to that of liver retinyl esters. Esterification of retinol in the liver is mediated by components in the microsomal fraction and appears similar to that found in the microsomes of the retina. In addition, the similarity of retinyl ester composition in several animal species implies a common pathway of retinyl esterification may exist. A common mechanism, involving RBP-PA, that transports retinol to the pigment epithelium could also be present in vertebrates.

Extension of these studies on vitamin A interconversion to the pigment epithelium and adjacent tissues is desirable. The existence of an esterification mechanism in the pigment epithelium has been assumed, but not conclusively proved. Similarly, the mechanism of retinol and retinyl ester movement to the pigment epithelium requires further investigation. Consideration should be given to elucidation of the specific tissues of the eye in which these metabolic processes occur. Data on vitamin A metabolism in the eye has been derived mainly from animal experimentation. Additional studies in man are required.

(See Section V, Suggested Areas for Future Research, p 116).

D. OTHER NUTRITIONAL FACTORS

1. Proteins and Lipids

There is a close relationship between vitamin A and protein metabolism. Dietary protein influences absorption, transport, and storage of retinol; vitamin A affects synthesis of muscle and serum proteins (23, 38, 48). While these interrelationships are outside the scope of this review, they impinge upon these discussions since the visual pigments are composed of specific proteins bound to the vitamin A derivative, 11-cis-retinal.

As noted previously, protein and vitamin A deficiencies often occur simultaneously. Where symptoms of kwashiorkor are present, serum vitamin A levels are usually low (48, 82, 83). Where protein deficiency is present, the absorption and conversion of dietary carotenoids as well as the absorption of retinol may be impaired. Similarly, it would appear that utilization of liver vitamin A reserves could be impaired by low protein intake. This could be due to a depletion of retinol-binding protein (RBP) or an indirect effect, e.g. alterations in vitamin A absorption or rates of turnover within the liver. When growth is inhibited, reduction of vitamin A utilization from the liver may be related to a lowered requirement or to actual disturbance in retinol transport. Protein supplementation in the diet of protein-deficient individuals leads to an increase in serum vitamin A, presumably through mobilization of liver stores (48, 66). Protein supplementation also increases the overall vitamin A requirement by stimulation of growth. When low storage reserves are depleted, protein supplementation could induce symptoms of vitamin A deficiency. These observations emphasize the importance of retinol supplementation when previously protein malnourished individuals receive dietary protein supplementation (48, 82).

While severe protein and retinol deficiencies are not endemic in the United States, nutrition surveys suggest that prolonged voluntary or economically produced dietary insufficiency exists within certain population groups (31). An inadequate diet throughout childhood coupled with the occurrence of chronic intestinal infestations and infectious diseases will aggravate further any existing or potential nutritional deficiencies. Recently, Schaefer (31)

reported that in addition to other deficiencies of the surveyed population, 33% had reduced serum vitamin A levels and 16% had serum protein levels below values considered acceptable. While dark adaptation was not studied, it is possible that the visual capability of some of these individuals could be compromised. These observations of substandard nutritional levels within the United States call for a complete assessment of the dietary adequacy of the American population. Some young, ostensibly healthy males inducted into military service could have reduced night vision ability as the result of prior long-term nutritional insufficiency.

Wald, in 1955 (84), prophetically noted that the role of opsin had been neglected in favor of the prosthetic group of rhodopsin derived from retinol. Theoretically, the impairment of opsin synthesis could induce nutritional night blindness. Auerbach et al. (85) showed a rise of visual threshold in albino rats fed a diet deficient only in protein. The effects of protein and amino acid deficiencies on ocular function in man have been summarized by McLaren (26).

Protein metabolism may also have indirect effects upon retinal metabolism within the visual system (38, 48). Continuous light exposure is detrimental to the structural integrity of the photoreceptors of the retina. Chronic visual pigment bleaching in the rat can lead to histologically and electrophysiologically evident damage in the pigment epithelium and the photoreceptors (86, 87). Presumably, synthesis of the visual pigment proteins is adversely affected. Noell et al. (86) noted that the effect of prolonged light exposure simulates the buildup of toxic retinol levels within the retina. Such a condition is possibly related to the accumulation of the toxic products of bleaching, notably trans-retinol. Accumulation of trans-retinol might occur in severe protein deficiency if esterification or opsin synthesis were disrupted. The indirect effects of protein deficiency on ocular metabolism require further critical study.

Injected labeled amino acids are incorporated in vertebrate visual pigments (8, 88, 89). The labeled protein, synthesized in the inner segment, is concentrated in the membranous discs at the base of the outer segment of the receptor cell. Protein synthesis is a continuous process and thus, protein turnover, as well as the ribonucleic acid (RNA) translation mechanism of protein synthesis

in the eye, may be of greater importance to vision than previously realized. The synthesis of the membranous discs and opsin would depend on a metabolic system which included the correctly coded messenger ribonucleic acid (m-RNA). There are few published reports on the availability of m-RNA or actual synthesis of the m-RNA prior to protein synthesis in the receptor cells.

Dietary fat intake is another closely related factor in production of vitamin A deficiency and night blindness. The level of fat intake may have little or no effect upon the utilization of preformed vitamin A. However, factors interfering with fat absorption would influence the absorption of both vitamin A and carotenoids. Several investigators (48, 82, 90) have noted low fat intake and inefficient absorption of dietary carotenoids occurred simultaneously in a vegetarian population. In one study the diet was supplemented with both fat and carotene and the incidence of night blindness was reduced (91).

While dietary proteins and lipids appear to be important in absorption of carotenoids and retinol, the quantitative and qualitative aspects are not completely understood. There appears to be an upper limit to the rate at which β-carotene can be absorbed while retinol is absorbed rapidly. Liver vitamin A levels following β-carotene administration vary with intake of both protein and lipid (24, 48). This variation may be due to differences in absorption, hydrolysis of retinyl esters, conversion of β-carotene, synthesis of retinyl esters, or transport to the liver. For example, using isocaloric diets with differing levels of protein, optimal cleavage of β-carotene was observed on a 10% protein diet. In this one case, the effect of the dietary protein level was interpreted as a direct effect upon synthesis of the cleavage enzyme, carotene dioxygenase, in the intestinal mucosa. Interaction between vitamin A and other lipoproteins has been investigated. Vitamin A metabolism influences the metabolism of coenzyme Q, vitamin D, α-tocopherol (vitamin E), squalene, and various sterols (48). Stability of biological membranes depends, in part, on the interactions of vitamins A and E (42).

2. Vitamins and Minerals

The obvious importance of vitamin A in the visual process has overshadowed the role of other vitamins and nutritional factors. Deficiency of several vitamins and minerals produces

clinically evident syndromes that include ocular symptoms. The nutritional effects of various deficiencies (92) as well as deficiency effects on the eye have been cataloged (25). The conclusions with respect to B-vitamin deficiencies may be applied to other nutrients as well. McLaren (25) suggested that the specific effects of single dietary factors on the eye are difficult to interpret for several reasons:

> "Deficiency of closely related vitamins may have a similar end result, circumstances have varied considerably in which the disease states have been studied, single vitamin preparations have often not been available for trial, and isolated vitamin deficiencies are not encountered outside the laboratory."

In general, the B-vitamins function catalytically in various steps in intermediary metabolism and thus are important with respect to normal functioning of oxidative metabolic processes of the retina (80, 93). Riboflavin (vitamin B_2) in flavine adenine nucleotides and nicotinic acid (niacin) in nicotinamide adenine nucleotides (NAD^+, $NADP^+$) as well as Coenzyme Q and the cytochrome system are important in supplying tissues with adequate amounts of adenosine triphosphate (ATP). As discussed previously, the enzymatic interconversion of both isomers of retinal $\rightleftarrows$ retinol is known to be NADH or NADPH dependent (62). Therefore, nicotinic acid deficiency might induce reduced visual capability by elevation of the absolute visual threshold as the result of insufficient visual pigment synthesis. However, no experimental evidence exists that corroborates this hypothesis. Riboflavin does not appear to function as a photosensitive intermediary metabolic substance in the human eye (25).

While deficiencies of the B-vitamins are known to induce ocular disturbances, their influence on the visual process and the metabolism of the dark adapted retina are essentially unknown. Lack of dietary thiamine (vitamin B_1) precipitates visual disorders; however, night blindness is not a typical symptom. Deficiency results in insufficient cocarboxylase, leading to neurophysiological disturbances, such as the Wernicke-Korsakoff syndrome (25, 94). The clinical features of severe nicotinic acid deficiency are similar to Wernicke's encephalopathy; visual disturbances, such as loss of visual acuity, are often reported in pellagra patients (25). In the

rat, degeneration of ro and cones occurs with pantothenic acid deficiency, especially during pregnancy. Slight degeneration of the ganglion cell layer was observed in pyridoxine (vitamin B_6) deficient rats.

Several nutrition studies have been made on the effects of riboflavin deficiency on dark adaptation. However, no recent data confirms the observations of early field studies (25). In 1939, Kimble and Gordon (95) reported that individuals with elevated dark adaptation thresholds and low serum retinol did not show improved dark adaptive capability nor did the serum vitamin A level increase until riboflavin was administered with the vitamin A. Similarly, McLaren (25) noted that Pock-Steen reported sprue patients with nutritional amblyopia and impaired dark adaptation required riboflavin rather than retinol therapy.

Additional data are available from animal studies. Saito (96) investigated the influence of riboflavin on metabolism and oxygen consumption in rat tissues of the retina and liver. In deficient animals, oxygen consumption and riboflavin in the retina decreased rapidly. Yet, liver riboflavin decreased gradually and this deficiency could be reversed by inclusion of riboflavin in the diet. Saito concluded that retinal oxygen consumption was thus influenced by the availability of dietary riboflavin. Similarly, Koyanagi et al. (97) observed changes in the ERG of rats that were riboflavin-deficient. Referring to the earlier work of Kimble and Gordon (95) on riboflavin deficiency in man, Koyanagi et al. (97) noted that in the rat, thiamine, riboflavin, ascorbic acid (vitamin C) or protein deficiency resulted in delayed dark adaptation as measured with the ERG.

Study of an abnormality in cyanocobalamin (vitamin B_{12}) metabolism in patients with diabetic retinopathy did not indicate any effects of vitamin B_{12} deficiency on dark adaptation and night vision. However, in rats, vitamin B_{12} deficiency is known to produce dilation of retinal veins and pallor of the fundus (25).

Investigations on the role of vitamin C suggest numerous effects on various ocular processes and structures; however, the literature is contradictory (25). One report has noted an improvement in dark adaptation in subjects receiving vitamin C in addition to retinol. There was no improvement in dark adaptation when retinol alone was fed (25). Hodges et al. (98) showed that scorbutic

human volunteers have impaired dark adaptation despite normal retinol levels in the blood. These examples of vitamin C effects on night vision indicate the need for further research.

Alpha-tocopherol (vitamin E) exerts an important role in the stability and integrity of biological membranes (42, 99). Vitamin E is known to reverse or block the lysis of the rat liver lysosomal membrane that can be precipitated by retinol deficiency (99).

There is a paucity of information concerning the direct effects of vitamin D and vitamin K on dark adaptation and night vision. The clinical recognition of vitamin D and vitamin K deficiencies depends on symptoms other than visual disturbances (23). No reports of alterations in scotopic visual capability related to deficiency or excess of either vitamin D or K were found.

The direct effects of mineral elements on night vision are obscure. Calcium, phosphorus, potassium, and sodium are ubiquitous in body tissues. The deficiency or marked imbalance of any one of these minerals leads to recognized clinical manifestations. Visual disturbances, notably in the cornea, lens, and conjunctiva, are evident in abnormal metabolism of calcium and phosphorus (25). Both zinc and selenium are known to be present in relatively high concentrations in certain parts of the vertebrate eye. Deficiency states for these elements might occur, but evidence is lacking. Since zinc is an essential portion of the enzyme alcohol dehydrogenase, oxidizing trans-retinol to trans-retinal, it is conceivable that zinc deficiency might reduce the rate of rhodopsin regeneration during dark adaptation. Experimental data that support this deduction were not found. The role of selenium in vision is obscure. Sirén (100) postulated that selenium might be important in the neural excitation mechanism in vision. If the selenium ion were protein bound, then the rhodopsin might function in excitation of the selenium ion following absorption of light quanta by rhodopsin. Taussky et al. (101) have shown that selenium is present in ocular tissues, especially the retina. However, Sirén's hypothesis (100) has not been investigated in any detail, primarily because the early evidence supporting the concept is circumstantial.

(See Section V, Suggested Areas for Future Research, p 117).

E. PHOTOCHEMISTRY OF VISION

1. Visual Cycle

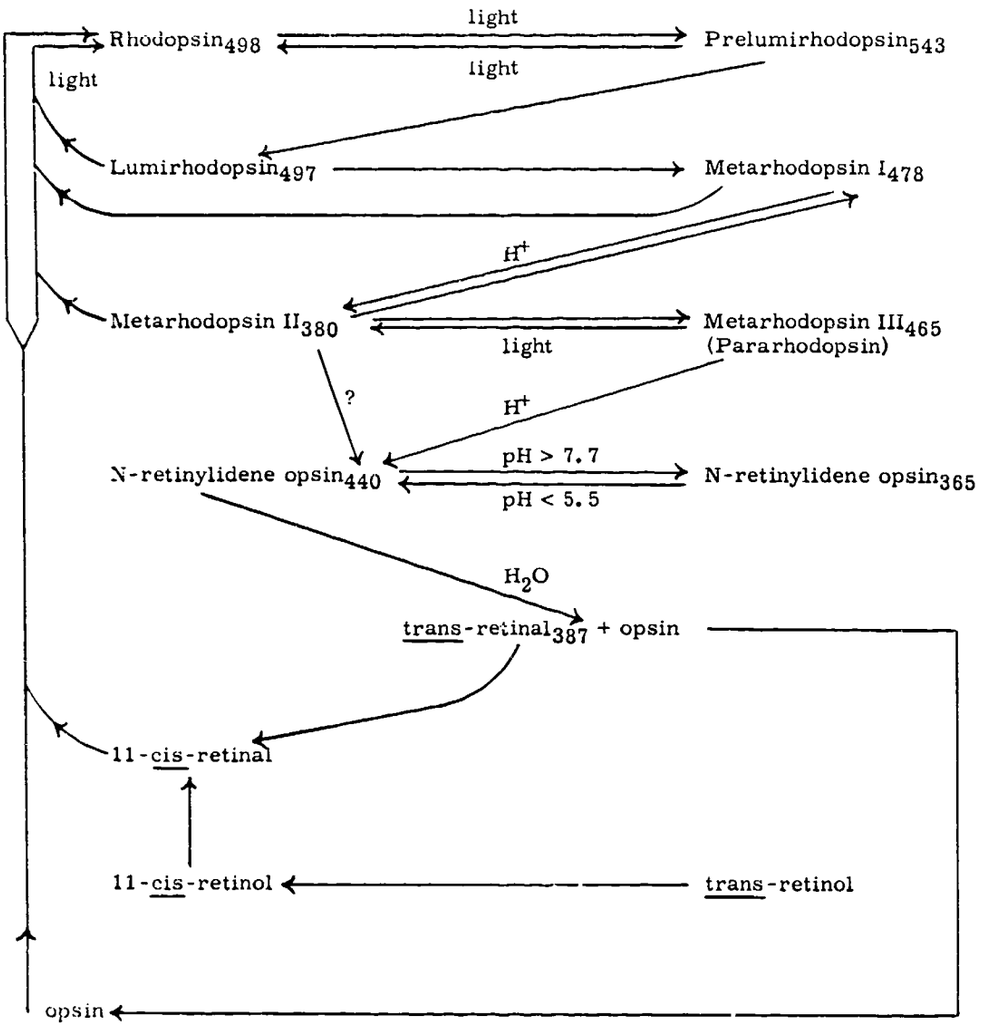
The chemistry and biochemistry of the visual pigments and their intermediate transformations in the visual process have been investigated in great detail (102, 103, 104, 105). While certain structural and transformational processes are incompletely understood, the sequential steps in rhodopsin photolysis are well established (102, 104). The photolytic transformations of other visual pigments, e.g. amphibians and vertebrate cone cells, are considered to be similar to rhodopsin. The absorption of light by rhodopsin produces photoisomerization of the chromophore and an apparently spontaneous series of endothermic transformations (Figure 9). The transformations following photoisomerization produce a series of unstable intermediates, but each contains trans-retinal attached to opsin. Hydrolysis of the final intermediate, N-retinylidene opsin, yields the two final products, trans-retinal and opsin.

The absorption of light isomerizes the chromophore from the 11-cis to the trans configuration; subsequent conversions yielding N-retinylidene opsin do not require light. Changes in protein configuration that occur during the transformations are initiated by the light-induced isomerization of retinal (102, 103, 241). The isomerization and conformational changes exposing active sites, e.g. sulfhydryl groups, on the protein are considered critical to the initiation of visual excitation (102, 106, 107). Subsequent transformations are too slow to be involved in excitation (106). Bleaching, in the literal sense, i.e. loss of color, occurs primarily before the formation of metarhodopsin II[4]. The transformations of rhodopsin photoproducts and excitation of the visual response have been reviewed (102, 103, 104, 108).

In addition to inducing stereoisomerization of 11-cis retinal in rhodopsin, light isomerizes the trans-retinal of the photoproducts back to the 11-cis-retinal form (Figure 9) (78, 102).

[4] The widespread use of the terms "bleached photopigment" and "bleaching" is chemically ambiguous for there is no indication that the retinal moiety is still attached to the protein.

FIGURE 9



Reactions in the Synthesis and Photolysis of Rhodopsin. (Modified from Ref. 104).

Trans-retinal remains attached to the opsin at the same site in the intermediates up to and including metarhodopsin II (102). If a second photon is absorbed by that molecule, the trans configuration is converted to 11-cis, regenerating rhodopsin. Thus, mechanisms exist for regeneration of rhodopsin from the intermediate as well as the final photoproducts.

2. Visual Pigment Structure

Studies on retinal isomerization and opsin conformation changes have stimulated investigations of visual pigment structure. The pigment, rhodopsin, constitutes approximately 35% of the dry weight of the outer segment and the remainder is essentially lipid (104). The rod outer segment consists of multiple double membrane discs, one above the other in a stack. The rhodopsin molecule is an integral part of each disc. The entire stack of discs is enclosed by the plasma membrane. Some question exists as to whether the membrane of each disc is continuous with the plasma membrane of the outer segment. Sjöstrand (109) proposed that each disc had two double layers of lipid in between two layers of protein. He suggested that rhodopsin was located in the middle of the disc, presumably in the intra-space between the double layers of the membrane. Wolken (110) has developed an alternate hypothesis from interpretation of electron photomicrographs. He proposed that the electron-dense layers contain a double layer of lipid and lipoprotein, and the interdisc space represents soluble protein in an aqueous phase. From other data on molecular size, he concluded that rhodopsin molecules are loosely arranged perpendicularly to the disc stack axis on the interface of the interdisc spaces and lipoprotein. The orientation of the rhodopsin molecule, relative to the axis of the outer segment is critical to the ability of the system to trap light. Continued investigation of the molecular architecture of the lipoprotein-visual pigment discs within the photoreceptor cells will enhance understanding of the molecular basis of visual excitation.

3. Synthesis of Rhodopsin

Visual pigment synthesis within the photoreceptive cells has been investigated only recently although Kühne, in 1879 (111),

had postulated rapid regeneration of rhodopsin from decomposition products, and a slower de novo synthesis from materials associated with the pigment epithelium. The investigations of Futterman (62) and Andrews and Futterman (79) clarified the metabolic pathways of trans-retinal after photolysis. A reverse route from retinyl esters in the pigment epithelium, oxidation, and subsequent isomerization to 11-cis-retinal in the rod outer segment has been postulated (112). Autoradiographic techniques have been used to establish the pattern of in vivo rhodopsin synthesis in frog rod cells (8, 88, 113, 114). Using radioactively labeled protein precursors, Young and Droz (88) observed that protein synthesis occurred in the ergastoplasm of the myloid region of the inner segment of the rod cell. The labeled protein is transported through the Golgi apparatus and to the mitochondrial region. The protein moves through the connecting ciliary region to the base of the outer segment where it is assembled into discs (8, 112). Synthesis of discs in rods is affected by light and temperature (8). In cones, basal accumulation and disc synthesis were not observed (114). Continual disc synthesis moved previously synthesized discs distally. Electron photomicrography and autoradiography suggested that discs at the distal apex of the outer segment entered inclusion bodies, termed phagosomes, in the pigment epithelium. The disintegration in the phagosomes suggests that proteolysis is occurring although the mechanisms of movement through the outer segment plasma membrane and destruction in the phagosomes requires further clarification.

Using autoradiography, Hall et al. (89) demonstrated that injected amino acids are rapidly incorporated into rhodopsin in the outer segment of the rod cell. The protein formed after injection of amino acids contained the labeled precursors and moved distally as synthesis was allowed to continue. These data support the hypothesis that the visual pigment in the outer segments of the retinal rod cells is constantly being renewed. Presumably the protein synthesized in the inner segment makes up the lipoprotein of the disc as well as the visual pigment rhodopsin (89).

4. Binding of Retinal and Opsin.

Closely related to the study of visual pigment structure within the outer segment are investigations of the protein of the

visual pigment. It is generally assumed that the several vertebrate visual pigments are composed of 11-cis-retinal, bound to an apoprotein, opsin (115). Numerous studies have established that one 11-cis-retinal moiety and one opsin moiety constitute a molecule of the visual pigment rhodopsin (103, 116). While the prosthetic groups, retinal or 3-dehydroretinal, have been studied in great detail, little information is available about the opsin portion of the visual pigment molecule (103). The opsin is thought to vary with animal species and type of photoreceptor.

A major difficulty in the study of visual pigments is the relative insolubility of the molecule. It can be solubilized in the form of a micelle by extraction with synthetic detergents or aqueous digitonin (104). Hubbard (117) calculated a molecular weight of 40,000 for bovine visual pigment; Wolken (110) obtained similar data, but calculated the molecular weight as 32,000 to adjust for lipoprotein density differences. Several investigators have prepared digitonin extracts of frog rhodopsin and the estimated molecular weights are in good agreement (104, 110).

Krinsky (118) found that a phospholipid fraction bound to the opsin could not be separated even by exhaustive degradative procedures. He concluded that rhodopsin is a lipoprotein with a molecular weight of 32,000, with 18,000 considered as the protein portion. More phospholipid could be extracted from rhodopsin after photolysis, suggesting that the lipid moiety might be associated with either the isomerization of retinal or the conformational changes in opsin.

Recently, Heller (119) reexamined the molecular weight and composition of a bovine visual pigment using gel filtration chromatography and polyacrylamide gel disc electrophoresis. He suggests the bovine visual pigment is a conjugated glycoprotein rather than a lipoprotein. The molecular weight calculated from amino acid analysis was 27,707, with a minimal molecular weight of the opsin molecule of 26,397. The opsin was found to contain 235 amino acids, 118 had nonpolar side chains. Heller (119) suggested that the covalently bonded carbohydrate moiety (3-glucosamine, 2-mannose, and 1-galactose residues) may function in sterically orienting the visual pigment molecule in the hydrophilic insoluble membrane matrix.

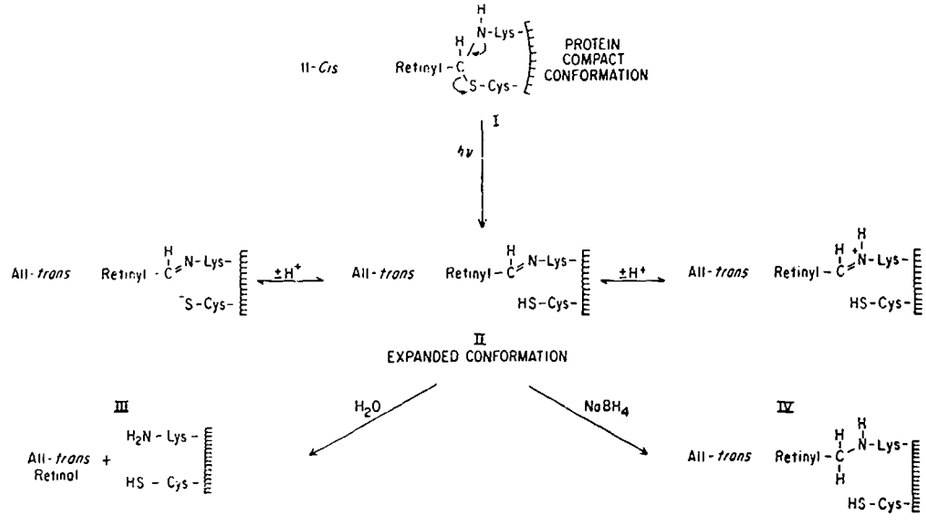
The chemistry of opsin is critical to understanding the effects of quantum absorption by the visual pigments. Theoretical explanation of the configurational changes of opsin following stereoisomerization of 11-cis-retinal have been based upon the existence of a specific aldehydic linkage between retinal and a lipoprotein opsin. Most investigators assume this binding as a protonated or unprotonated Schiff-base linkage (104).

Isolation and purification of the bovine visual pigment led Heller (120) to investigate the binding of retinal to the glycoprotein opsin and the rearrangement induced by exposure to light. Previously, Bownds (103, 121) showed that the retinal was bound to the ε-amino of a lysine residue of rhodopsin. Heller (120) suggested that the intact visual pigment does not contain a Schiff-base linkage, but rather a substituted aldimine bond (Figure 10, I). The bonding is to both the ε-amino group of lysine and to a sulfur of a cysteine moiety. Upon absorption of light, two chemical reactions were postulated; the substituted aldimine (the C-S bond) reverts to a Schiff-base linkage (Figure 10, II), and isomerization of the 11-cis-retinal to trans-retinal occurs. The major consequence of these reactions would be transformation of the glycoprotein opsin from the compact to the expanded form. The photochemical degradation of the bond between the terminal carbon of 11-cis-retinal and the sulfur of cysteine in opsin could be by free radical mechanism (120).

The prevailing opinion is that retinal is bound to a free ε-amino group of lysine in a lipoprotein; the resulting Schiff-base may be either protonated or unprotonated (104, 110). However, other types of linkage can not be ruled out. Opsin may be a glycoprotein with 11-cis-retinal linked to lysine and cysteine moieties of the glycoprotein by a substituted aldiminic linkage (120). In addition, retinal may be bound by phosphatidal ethanolamine of the phospholipid-protein prior to photolysis and to the lysine residue of opsin following photolysis (122). At the present time, the exact nature of the primary binding between 11-cis-retinal and opsin, both before and after light absorption, is not entirely clarified (104). Investigations on the exact nature of these bonds and the light-induced bonding rearrangements should be continued. It would be of interest to determine the nature of the protein (opsin) in vertebrate systems other than bovine visual pigment. These studies are critical to understanding of the basic photochemical processes of vision.

(See Section V, Suggested Areas for Future Research, p 118).

FIGURE 10



Linkage between the retinal and opsin in bovine visual pigment as postulated by Heller. The expanded conformation indicates the Schiff-base linkage. (Reprinted from Ref. 120, p 2918. Copyright 1968 by the American Chemical Society. Reprinted by permission of the copyright owner).

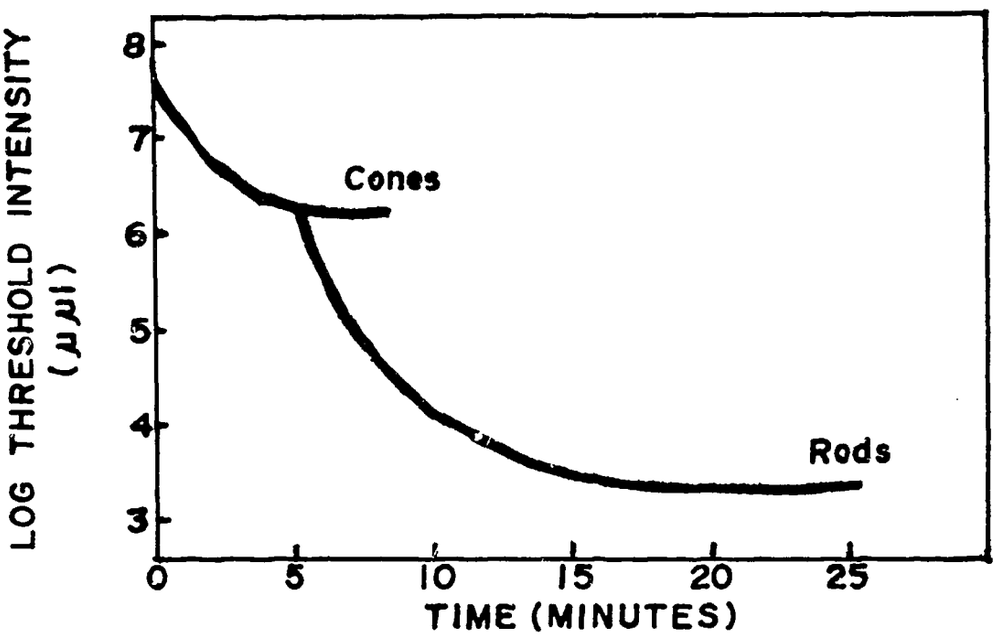
F. DARK ADAPTATION

1. Mechanisms

Visual adaptation to variations in ambient luminance has been studied in great detail (102, 123, 124). The characterization of the visual pigment, rhodopsin, was critical in the study of dark adaptation. Although the exact relationship was not apparent, Hecht et. al. (125) concluded in 1942 that the process of dark adaptation in man involved the accumulation of rhodopsin in the photosensitive cells of the retina. If the dark adaptation curve (Figure 11) were to reflect only an increased rate of visual pigment regeneration, it should be unaffected by changes in test methodology, except for vertical displacement due to variation in background luminance (126). The minimal threshold value is partially dependent upon the size, duration, and wavelength of the stimulus flash (16, 127). Since the maximum absorption of rhodopsin is 497-500 nm, a change in the wavelength of the adapting flash will alter the final threshold, but not the rate of dark adaptation (126). Moreover, alteration of the retinal area exposed or duration of the stimulus light will affect both the ultimate threshold and the rate of dark adaptation (126, 128). These observations suggest that while rhodopsin regeneration is critical to dark adaptation, other biochemical and neurophysiological factors are involved in dark adaptation. Photosensitive pigments regenerate in the dark, but the increase in amount of pigment is insufficient to account for the decrease in threshold.

Although the half-life of these intermediates is brief, some investigators have suggested that the concentrations of the metarhodopsins affect visual sensitivity. Donner and Reuter (129) observed the thermal decay rate of metarhodopsin II parallels the rate of increase in sensitivity of the ganglion cells in the excised frog retina. They suggested that the metarhodopsin II concentration may determine threshold in the frog eye during the initial period of dark adaptation. However, the neurophysiology of the human retina may differ from that of the frog (4). Furthermore, Frank and Dowling (130) were unable to observe any photoproduct effects on scotopic sensitivity in preparations of rat retinas. Investigations of these and related photoproduct effects have used different electrophysiological measurements of visual sensitivity (127, 129, 130, 131), and are not comparable. The several electrophysiological responses

FIGURE 11



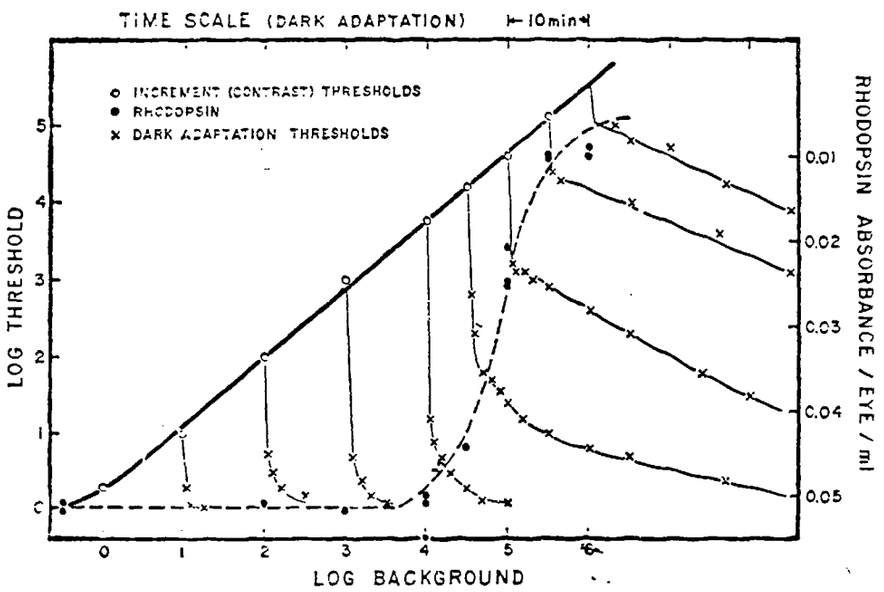
Typical Curve of Human Dark Adaptation. (Modified from Ref. 12. Figure 11 is identical to Figure 4; reproduced for convenience).

that record changes in visual sensitivity may be involved in separate aspects of the visual process (132, 133). Additional studies are required to clarify the effects of photoproduct concentrations and shifts in conversion equilibria on adaptation, sensitivity, and regeneration of visual pigments.

The mechanisms involved in adaptation have been studied extensively in several vertebrate systems (16, 70, 123, 124, 129, 134). With some exceptions, the processes are quite similar; perhaps the best model system is the predominantly rod system of the rat retina (124). The process of dark adaptation is thought to be similar in the rod cells of the human retina. Dark adaptation is slower in the rat, affording more opportunity for experimental observation of the underlying processes. When changes in visual adaptation are recorded from low to high levels of background luminance, one is measuring adaptation to light (Figure 12). On the other hand, starting at higher levels of background light and decreasing the luminance level, the course of dark adaptation can be observed. When the logarithm of the background luminance is plotted against the logarithm of the threshold, the change of the threshold is linearly proportional over a wide range of background or adapting light intensities; the slope of the line being almost 1.0. Adaptation to higher ambient light levels is extremely rapid and does not appear to be directly related with the concentration of the visual pigment, rhodopsin (Figure 12). No measurable loss of rhodopsin occurs until luminance of the background light is 4 to 5 logarithmic units above the absolute threshold value. At this point, photolysis of rhodopsin is rapid. Thus, the rapid elevation of threshold in the process of light adaptation appears to be regulated by the relative increase in luminance level.

Even in the predominantly rod retina of the rat, dark adaptation is not simply the reversal of light adaptation. Two distinct phases in sensitivity gain can be observed (Figure 12). The rapid phase has been termed the neural adaptation phase; the slower phase, photochemical dark adaptation (124). The rapid phase is thought to be the reverse of the swift loss of sensitivity which occurs during light adaptation (124). Dark adaptation is rapid (Figure 12) until the rods are adapted to luminance levels where significant photolysis of rhodopsin can be measured. At this point, rhodopsin concentration has a significant effect upon dark adaptation. Thus, the slower phase of dark adaptation is closely related to the regeneration of rhodopsin; the rapid phase probably is localized in the bipolar processes of the inner nuclear and plexiform layers (124).

FIGURE 12



Visual adaptation in the rat as determined by sensitivity of the b-wave of the electroretinogram. During light adaptation (open circles), the increase in the threshold logarithm is linearly proportional to the background luminance logarithm, except at the lowest background luminances. Dark adaptation (crosses) is rapid until the eye is adapted to background luminances which bleach significant quantities of rhodopsin (solid circles) in a 5-minute adaptation period. With bright background luminances, the slow component of dark adaptation is observed. (Courtesy J. E. Dowling; Ref. 124).

Although the two phases of dark adaptation can be distinguished experimentally, common neural control mechanisms are present. For example, after light adaptation of one previously dark adapted eye, the pupil of the other eye will constrict even when covered to prevent loss of dark adaptation. Subsequently, if the pupil of this still dark adapted eye is dilated, the pupillary enlargement follows the course of slow dark adaptation of the light adapted eye, even when the light adapted eye has been temporarily blinded during light adaptation (124). Since the slow phase of dark adaptation is related to the concentration of rhodopsin, some signal is presumably arising in the retina of the light adapted retina indicating the amount of rhodopsin present in the photoreceptor cells.

Another suggestion of the interrelation between the two phases of dark adaptation is the observation of "after-images." These phenomena are thought to originate from rod receptor cells in which photolysis of rhodopsin has already occurred (135). In the light adapted state, a positive after-image can be perceived for several minutes when dark adaptation is initiated. The after-image may be associated with a signal from a bleached photoreceptive pigment (135). This after-image represents continued activity in the receptors and is conceived as "noise" or "dark light" of the retina. The decrease in dark adaptation threshold is similar to the fading of the stabilized after-image on the retina. This suggests that the elevated threshold during photochemical dark adaptation is simulated on a dark adapted eye when a light is present that matches in luminance the brightness of the stabilized after-image. It is not certain whether a common mechanism exists, but the evidence suggests either a common mechanism or a common pathway is involved.

2. Measurement

a. Psychophysical Measurement

The necessity for accurate assessment of visual sensitivity has led to the development of various quantitative and qualitative methods for measuring dark adaptation. Historically, the psychophysical methods were developed first; electrical and optical methods were developed later. These methods have been utilized for both experimental and clinical purposes (11, 136, 137). Considerable confusion has resulted from attempts at direct com-

parison of the changes in visual sensitivity with these different methods. These difficulties arise mainly from differences in methodology (11).

The sensitivity of the eye to light depends upon several interrelated critical factors utilized as experimental variables:

- the duration of exposure to the critical levels of illumination;
- the mean luminance of pre-test exposures;
- the duration of the test exposure;
- the size, shape, and contrast of the test object;
- the region (size and shape) of the retina stimulated;
- the spectrum of the pre-exposure and test exposure lights; and
- the general physiological state and psychological condition of the test subject.

Thus the conclusions from investigations in this field must be interpreted with care as it is often difficult to predict the dark adaptation rate or final visual threshold from one set of experimental conditions.

Numerous investigative and clinical test methods for the determination of dark adaptation rate have been developed, including increment, contrast, or absolute visual threshold, as well as size and shape of the visual field. Most of these tests require active participation of the subject because he must respond (positively or negatively) to a flash of light. The most frequently tested aspect of scotopic vision is the absolute light sense. This involves either determination of the visual threshold at time intervals during the course of dark adaptation or the perception of decreasing or increasing luminance to a threshold value. The latter tests are normally 30 minutes in duration to allow for complete dark adaptation of the visual system (11). The most recent review of the methodology of visual psychophysical tests was published in 1959 (11).

Because psychophysical measurement is subjective, it can be valuable in determining the presence of visual defects. Each step of the total visual system must function properly to evoke the subjective response. Certain practical aspects of standardization often interfere with critical evaluation of scotopic vision using these methods. Primarily, psychophysical methods measure threshold, but the subject must recognize and discriminate the test objects at suprathreshold levels. The tests are markedly affected by the prior visual experience of the eye as well as the spectrum, size, duration, and position of the test light. Adaptometers that standardize these variables are available.

Since dark adaptation involves the entire eye, including both the rod and cone systems, the psychophysical methods are affected by individual differences in ocular as well as retinal morphology and physiology. Because the response is subjective, motivation, stress, and other psychological factors may influence measurement. There is also a wide normal response range (138). Threshold differences of 0.2 to 0.3 log unit have been reported for normal individuals tested repeatedly. For normal subjects of the same age, the threshold range between subjects may vary 0.5 to 0.6 log unit. Variation with age may be up to 1.5 log units, but is primarily associated with senescence of the lens rather than changes in the retina.

Need for psychophysical tests to determine night vision capacity rather than dark adaptation has resulted in the development of several testing devices. These tests are employed to determine the practical ability of individuals to maintain adequate task performance under reduced or negligible luminance. After reviewing the subject, Berry (139) concluded that capacity for night vision was too complex to be determined by any one single test.

Recent work has suggested night vision can be measured accurately in the field by the use of a portable scotopic sensitivity test developed by the Naval Medical Research Laboratory (NMRL) (140, 141). The test procedure measures scotopic sensitivity over a known area of the retina using objects of different size or brightness in several locations of the visual field. The test has been used to establish seasonal and individual differences in scotopic sensitivity (142). In a prolonged study on 3 individuals, scotopic sensitivity was found to be greatest in winter and lowest in midsummer.

The seasonal variations occur independently of individual differences; that is, the individual with the greatest scotopic sensitivity was always superior to the one with lowest sensitivity, regardless of season. These observations confirm results of other studies that indicate night vision testing may be complicated by previous exposure to sunlight, seasonal variation, or rapid movement from one latitude or hemisphere to another.

The Army Night Seeing Tester (ANST) was developed to measure brightness contrast sensitivity and visual acuity detail (143). Although compact and portable for field use, the ANST has not been widely used. The ANST was successfully field-tested in conjunction with training for enhancement of night vision capability. Previously, several testing procedures revealed that training produced only minor enhancement of night vision (144). However, the efficacy of the ANST has not been determined with a large number of subjects where the normal range of scotopic vision would be present.

Military utilization of the NMRL test, the ANST, as well as previously developed night vision test procedures, has been influenced by the question of the validity of night vision testing (141). Originally test procedures were of questionable value because there was a lack of correlation between tests; however, these newer methods appear to test night vision sensitivity during both simple and complex tasks (141). Unfortunately, extensive field testing using both methods has been limited. The apparent lack of use of these devices suggests some question as to the need for testing per se rather than the inherent validity or reliability of the devices. The test methods can only measure the parameters the test is designed to assess. These devices may reliably test the night vision capacity of a soldier, but it is possible that the response that is tested, by itself, is insufficient in meeting military requirements for night vision.

b. Electrophysiological Responses

The electrical responses of the eye are of value in studying rod function. The most widely used is the electroretinogram (ERG); however, the electro-oculogram (EOG) and the early receptor potential (ERP) record other electrical parameters of the

eye. These methods obviate the necessity for subjective response because they depend on evoked changes in the electrical potential within the eye. These electrophysiological methods were developed as clinical and research tools, and can be used to assess accurately the rate of dark adaptation and the threshold of scotopic sensitivity (18, 145).

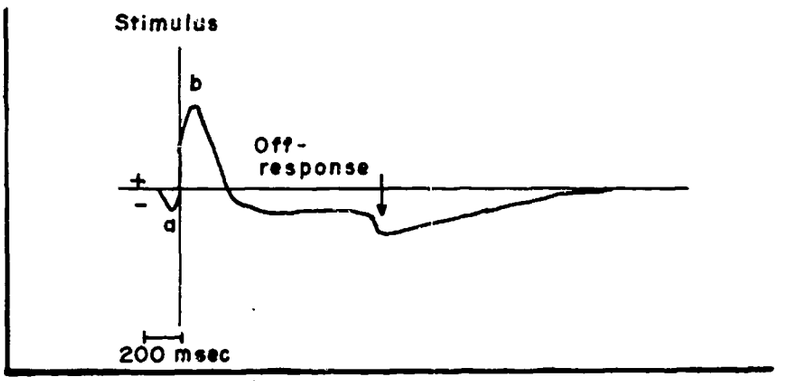
The ERG measures the gross response of the retina rather than the electrical activity of individual cells. The ERG largely reflects the rod response, because the rods outnumber cones approximately 20 to 1. However, by varying the luminance of the adapting flash, it is possible to separate cone and rod components (18, 145). Objective assessment of the rate of dark adaptation or scotopic threshold is thus possible without subjective influence (136). The usual technique for recording the ERG involves one electrode on the cornea and a second on the forehead. The corneal electrode is positive to the forehead and the potential difference increases when the eye is illuminated. Brown (145) published a comprehensive review of the ERG neural components, their origin within the retina, and their relation to the visual process. The clinical use of the ERG has been reviewed by Carr and Gouras (136). The character of the evoked b-wave (Figure 13A) is utilized as a reference in studies of dark adaptation and scotopic threshold determinations.

The electro-oculogram (EOG) records the variation with eye movement of a standing corneoretinal electrical potential. The EOG is highly sensitive and therefore subject to considerable experimental error. However, it is widely used clinically in testing ocular fixation or tracking acuity. Since the potential across the eye varies with the adaptation status, the EOG has theoretical utility in studies of light and dark adaptation. Because these functions can be tested more directly by use of the adaptometer, the ERG response, or by reflection densitometry, the EOG has met with limited use in testing dark or light adaptation.

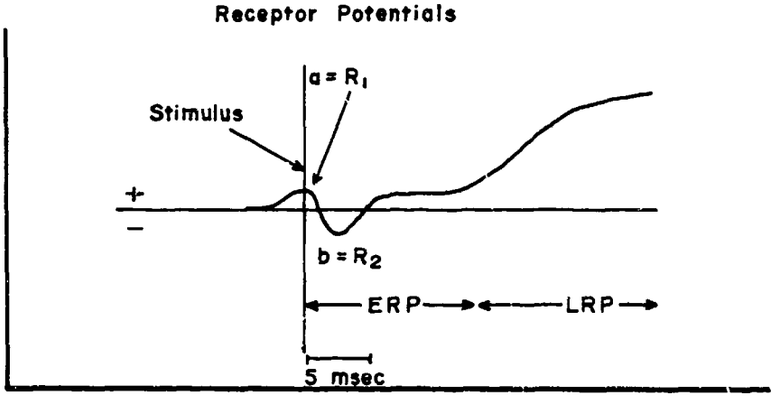
In 1964, Brown and Murakami (146) discovered the presence of another electrophysiological potential, the early receptor potential (ERP) (Figure 13B). Subsequent studies showed that the ERP has an action spectrum similar to that of rhodopsin in the rod retina of the rat and other vertebrates (18). In the all-cone retina of the ground squirrel, the ERP has the action spectrum of the cone pigment. Thus, the ERP is closely related to photochemical reactions

FIGURE 13

A. The Components of the Predominantly Rod Electroretinogram



B. The Components of the Early and Late Receptor Potentials



(Modified from Ref. 10).

and linearly related in magnitude with the number of visual pigment molecules that actually absorb light energy. Since the ERP is directly related to photochemical events in the eye, theoretically it could be used in adaptation studies. However, the ERP arises within two milliseconds after flash stimulation, limiting its practicality as a tool for measurement of the relatively long time period of the dark adaptation process. The ERP has been used primarily in connection with studies on the initiation of electrophysiological response to light stimulation and initiation of the neural response to photochemical events.

The surface of the living retina can be observed with the ophthalmoscope. When the ophthalmoscope is connected to a suitable recorder, a quantitative measure of the reflected light from the retina can be made. In 1952, Brindley and Willmer (147) utilized this instrument to compare the reflection of light from the macular and peripheral areas of the human retina. Photolysis of rhodopsin in the dark adapted peripheral area of the eye was followed. These early studies led to the development of reflection densitometry. This technique has been used for the detection of visual pigments in the retina (148) and stimulated the study of the pigment layer and the changes which occur during vision (149).

Reflection densitometry involves a measurement of polarized light which is reflected back from the pigment epithelium behind the retina. The reflection densitometry apparatus has been described in detail by Rushton (148, 150, 151) and Weale (152, 153, 154). The most critical aspect of reflection densitometry is the requirement for complete immobility of the head during examination. Any movement of the head will cause a change in the angle of reflection and interferes with the electro-optical balance of the system.

The measurement of visual pigment in either rod or cone cells by reflection densitometry represents a more accurate measure of the rate of dark adaptation or the threshold level than adaptometers that rely upon the subjective response. It should be noted, however, that reflection densitometry, as well as the psychophysical tests, measure photochemical dark adaptation and do not directly measure the initial rapid (neural) phase of dark adaptation. This latter phase can be measured by following the course of dark adaptation at decreasing intensities of background light and computation of the actual threshold. Measurement of rhodopsin by reflection

densitometry will indicate quantitative changes in the visual pigment concentration. The initial rapid phase of dark adaptation can be computed by plotting the ERG measurements and the reflection densitometric or psychophysical data on the same scale against time. The advantage in using the ERG is that it actually measures the course of dark adaptation during the period when the background light is being decreased prior to measurable changes in rhodopsin concentration. Thus a more direct measure of both phases of dark adaptation can be made (Figure 12).

As indicated previously, the ERG and other electrophysiological methods and retinal densitometry are research methods. These techniques theoretically measure dark adaptation and night vision capability. However, current instrumentation and methodology are so complex that assessment of dark adaptation in a large number of individuals in a short period of time is not possible. Thus, the less objective psychophysical methods (adaptometers) are used to measure large numbers of individuals. Unfortunately, the inherent variability of these devices precludes extremely sensitive measurement of dark adaptation and night vision capability. Further refinements of these techniques could lead to practical and sensitive methods of measuring dark adaptation.

3. Theoretical Aspects

The existence of the rapid phase of dark adaptation in the rods can be determined by plotting the ERG b-wave changes (124). Historically, experimentation with human dark adaptation curves has involved only the latter slow phase, although the existence of the slow phase and the neural or rapid phase have been known for many years (126, 155). According to the "simple photochemical" theory of dark adaptation, the absorbed light at threshold intensity should vary inversely with the rhodopsin concentration that is not photochemically destroyed. This simplified theory of inverse proportionality is insufficient to explain the course of dark adaptation. Rushton (126) demonstrated that photolysis of only 10% of the rhodopsin in human rod cells resulted in elevation of the rod threshold value by a factor of at least 100. In addition, during dark adaptation, rhodopsin regeneration is rapid, but the logarithm of the threshold falls with the decrease in the concentration of unregenerated rhodopsin or free opsin (16). These studies suggest that dark adaptation

involves mechanisms other than a direct photochemically induced arithmetic difference in rhodopsin content of the rod cells. In 1940, Lythgoe (156) noted that light bleaching only a small fraction of the rhodopsin causes large changes in increment thresholds. Other aspects of visual function that change during adaptation cannot be accounted for in terms of photochemical change alone. The area of the stimulus flash or the adapting light used to test sensitivity of the retina influences the extent of dark adaptation (157). Evidence opposing the simple photochemical theory of adaptation led to the development of the neural theory; however, little evidence has been accumulated to support a theory based on neural changes alone (158).

Extensive studies of visual pigment regeneration rates demonstrated that the regeneration rate of in vitro rhodopsin preparations and dark adaptation in vivo are nearly identical (40, 103). Dark adaptation of the cones occurs initially, followed by increased sensitivity to lowered luminance by dark adaptation of rod cells (Figure 11). Furthermore, in several vertebrate species, the logarithm of the threshold, not the threshold itself, depended upon the concentration of the visual pigment. In an attempt to correlate the physiological findings with anatomical studies, Wald and colleagues (159) suggested that the visual pigment in each rod was held in distinct compartments. The logarithmic relationship of visual threshold and rhodopsin level in man has been supported by other investigators and the logarithmic relationship between visual threshold and bleached rhodopsin has been found in several vertebrate and the human visual systems (70, 126). However, the evidence is consistent with the basis of the slower phase of dark adaptation and does not necessarily support the theory of rhodopsin compartmentalization.

Accumulated evidence suggests that compartmentalization within the photoreceptor is incorrect (158). First, the empirically determined value for the size of the compartment is not supported by anatomical and electron photomicrographs of the photoreceptive cells. Second, the logarithmic relationship is valid only for small amounts of bleaching, but does not hold for larger bleachings. Third, Barlow (158) indicated that the theory does not adequately predict quantum efficiency changes, nor does it adequately explain the observations of lateral stimulation or inhibition from one rod cell to the next (16). Finally, this explanation did not account

for lateral spreading of retinal stimulation. Rushton and Westheimer (128) adapted retinas with a light that passed through a grating. Rods in the region covered by the grating bars were not exposed to the adapting light, yet were unable to respond to subsequent stimulation. Light falling on certain rods (exposed areas) did raise the threshold of adjacent (unexposed) rod cells.

Barlow (158) developed a theory of adaptation that relies upon the occurrence of background noise or "dark light" in the retina. The theory is based upon the concept that continued exposure to increasing intensities of light causes a persistent loss in sensitivity, i.e. light adaptation. This explanation assumes the test exposure causes subsequent light-evoked signals to be attenuated. However, at least two factors affect the visual system; the initial stimulus may attenuate subsequent capacity of the photoreceptors to respond but, in addition, the level of retinal activity, that is background noise, could change. Barlow suggested that light adaptation raises the background of spontaneous activity of photoreceptors so that previously detectable photochemical signals become submerged in this spontaneous noise. Furthermore, if retinal noise induced changes in photoreceptors similar to changes induced by light, then the effects of noise will be the same as the effects of uniform light of similar intensity and thus should be reproducible by supplying such a light.

Historical evidence supports Barlow's theory of dark adaptation. A uniform background light differentially affects the increment threshold level when a large area of the retina is exposed. Comparing large and small areas of exposure, Crawford (160) demonstrated that the differential effect exactly balances the greater dark adaptation for large targets. The intensity of the background light needed to increase the threshold to a particular value is called "the equivalent background brightness." If the equivalent background brightness rather than the logarithm of the threshold luminance is plotted as a function of time, the dark adaptation curves from large and small targets become quite similar.

Barlow (158) suggested that "noise" could conceivably arise from the photosensitive pigment absorption of light quanta during the chemical transformations that occur following the photolysis of rhodopsin. Recent studies with dark adapted frog retinas have suggested that rhodopsin bleaching involves a biphasic rate (127). The relatively rapid phase appeared linearly related to the logarithm of

the threshold and quantitatively dependent upon the concentrations of visual cycle intermediate, metarhodopsin II. In the second slower phase, the threshold is proportional to the rate of rhodopsin regeneration. The results that Donner and Reuter (127) have reported in the frog eye have not been confirmed in either the rat or the human visual system. However, Hubbard et al. (103) suggested that metarhodopsin I and metarhodopsin II could be photochemically converted to rhodopsin. In addition, metarhodopsin III (pararhodopsin) is known to be converted to metarhodopsin II in the presence of light, and tautomeric shifts in the configuration of the metarhodopsins might constitute a component of neural adaptation.

Dowling has shown that in the rat the neural phase of dark adaptation may occur when no rhodopsin regeneration is apparent (124). The majority of the current data supports the concept that dark adaptation in man involves neurophysiological mechanisms rather than photochemical intermediates alone. The a-wave of the ERG probably arises in the outer plexiform layer of the retina in neural receptor terminals (124, 145). The b-wave of the ERG arises in the bipolar cells in the inner nuclear layer. Thus the a-wave originates more peripherally than the b-wave. Both ERG responses are measurable subsequent to reception of the light stimulus, but only the b-wave follows a course similar to that found for psychophysical adaptation. The b-wave is the first electrical response of the visual system which shows adaptation to changes in background light, and this site of adaptation in the visual system is associated with cells located in the bipolar cell layer that give rise to the b-wave.

A more complete understanding of the detailed processes of dark adaptation will be possible with additional investigations of both neuroanatomy and neurophysiology of the retina and the process of neural excitation following photolysis of visual pigments both in the light and dark adapted eye. Currently, there is considerable interest and research in these areas.

(See Section V, Suggested Areas for Future Research, p 119).

G. INITIATION OF NEURAL RESPONSE

Absorption of a light quantum by the rhodopsin molecule results in both internal bonding rearrangements within the absorbing pigment and initiation of the neural response to visual excitation. While the neural pathways within the vertebrate retina have been studied extensively, the details of the mechanisms by which rhodopsin photolysis leads to neural excitation are not fully understood.

Several hypotheses have been proposed to explain the mechanism whereby neural stimilation results from absorption of one light quantum by one molecule of visual pigment. In 1956, Wald (161) suggested rhodopsin could be a proenzyme converted to an active enzyme by light absorption. The active enzyme would catalyze a reaction resulting in neural excitation in the bipolar cell layer. Thus, the visual excitation and neural stimulus was thought to involve a series of enzymes (161), and that rhodopsin was an adenosine triphosphatase with 11-cis retinal as a cofactor (110, 162). Most experimental evidence does not support this concept of rhodopsin as a proenzyme or component of an enzyme system (122).

The solid state concept is based on the semicrystalline structure of the rod outer segments where localization of rhodopsin in specific areas suggests that resonance or photoconductivity is the visual excitatory phenomenon (163). This theory proposes that photochemical products are not involved in neural impulse generation. Rather, light absorption produces mobile electrons by promotion into a conductivity band. The theory requires a measurable quantity of the excited triplet state (see glossary). Measurable semiconductive activation energies in rod cells are related to the photoisomerization step (163). However, Abrahamson and Ostroy (104) suggest that the high quantum yield of the photolytic reactions of the retina would rule out participation of a triplet state as the initial excitatory phenomenon. Similarly, the relatively low quantum current gain found in photoconducting solids argues against the solid state hypothesis (122).

Bonting and Bangham (122) attempted to relate the biochemical events following rhodopsin photolysis to neural excitation by means of an ionic mechanism. The ionic theory suggests that visual excitation is somewhat analogous to the changes in ionic balance that

occur across the axonic membrane (104, 122). The rhodopsin within the discs of the outer segment are thought to be bound to a membraneous structure. In addition, light absorption does produce rhodopsin intermediates which ultimately undergo protein conformational changes, volume loss, and charge displacement phenomena as well as stereoisomerization of the retinal.

These investigators suggest that photoisomerization, alone or coupled with other processes, might depolarize a small area of a rod membrane creating an ionic change in potential which is then propagated along the rod (122). The trans-retinal liberated by photolysis of rhodopsin reacts with an amino group of phosphatidylserine or phosphatidylethanolamine in the outer segment membrane. Bonding of the free amino group leads to a more negatively charged membrane, resulting in increased cation permeability. As potassium ions (K^+) are removed and sodium ions (Na^+) enter the outer segment, a current is generated triggering a cholinergic response at the base of the photoreceptor cell. Energy (from ATP) is released following the change in ionic balance and produces a cationic flow reversal. Trans-retinal is released by the phospholipid, isomerized to 11-cis retinal, and combines with opsin to reform rhodopsin.

As yet there is insufficient experimental evidence to substantiate that visual excitation depends solely upon ionic movement. However, the possible role of ion migration in visual excitation deserves continued investigation. For example, exposure to light induces a receptor current in the outer segment of the squid photoreceptor cells (164). Concomitantly an influx of Na^+ and an outward flux of K^+ occur in that portion of the photoreceptor cell. This is similar to the changes observed in muscle and nerve tissues following stimulation. The presence of a highly active Na^+ - K^+ activated adenosine triphosphatase in the outer segment is further evidence that the adenosine triphosphatase functions in repolarization of the outer segment membrane by active transport of Na^+ out and K^+ into the rhodopsin bearing structure (122, 165). Similarly, observations of active Na^+ extrusion (129, 134), Na^+ absorption in dark adapted retinas (166), Na^+ and K^+ turnover rates (167), and the effect of Na^+ concentration on the ERG (168, 169), indicate that ionic changes do occur in the light stimulated photoreceptive cell layer. While the ionic hypothesis does not offer proof of how the regeneration of rhodopsin and opsin synthesis are involved in neural excitation, it does afford a basis for further study of these phenomena.

Photochemical stimulation initiates changes in electrical potential within the retina and between retinal cells and adjacent cells. Several of these electrical potentials of the eye have been measured with great precision, for example: the electroretinogram (ERG), the early receptor potential (ERP), and the late receptor potential (LRP) (145, 170). As suggested, these measurable electrical phenomena may be associated with initiation of the neural signal. Most evidence indicates changes in electrical potential within the retina are only indirectly related to the actual initiation of the neural signal evoked by light stimulation of the photoreceptor cells (15, 104).

The resting potential recorded in the ERG has a latency period of several milliseconds and thus is not directly involved with initiation of neural response (Figure 13A) (104, 145). In 1964, Brown and Murakami (146) discovered another electrophysiological phenomenon, the early receptor potential (ERP), arising during the latent period preceding the ERG a-wave. The ERP occurs within 2 milliseconds following a brief intense flash stimulus (Figure 13B). The ERP is initiated only by flash intensities which are approximately 10^6 times that necessary to induce an ERG response of similar magnitude (170). Additional studies have shown that the ERP does not depend on ion distribution across a membrane (171), although it is generated during the absorption of light by the visual pigment (172, 173). Cone (174) concluded that the similarity of the ERP electrical responses and the photochemical changes of rhodopsin suggests that each response is generated by charge displacement in the visual pigment as the result of photon absorption. It may be that this charge displacement phenomenon occurs upon the surface of the outer segment discs at the site of rhodopsin attachment.

Another electrophysiological response, the slow (S) potential, has been observed in intracellular recordings of receptor and horizontal cells of lower vertebrate retinas (175, 176, 177, 178, 179). The luminosity (L-type) S-potentials are sustained, vary with illumination over a limited range of luminance, and are always hyperpolarizing (180). L-type S-potentials have been related to dark adaptation (177, 178), while a second type of S-potential, the C-type, appears to have a role in color vision (175, 176). Recent studies suggest that visual excitation could involve either a hyperpolarizing (L-type S-potential) or depolarizing signal arising in the horizontal and receptor cells (180).

Investigations of the spatial organization within the retina have clarified the process of functional organization of retinal transmission of the visual stimulus (3, 4, 6, 180, 181, 182). Using light and electron microscopy (181) and intracellular recording and staining (180), Dowling and Werblin have studied the retinal organization of the mudpuppy in great detail. They observed that neurons in the outer plexiform layer (receptor, horizontal, and bipolar cells) respond to light stimulation by production of slow, graded, sustained potentials. Receptor and horizontal cells respond by hyperpolarizing while bipolar cells either hyperpolarize or depolarize. The polarization of a bipolar cell produced by light stimulation of the center field is antagonized by illumination of the area surrounding the receptive field. In the inner nuclear layer, the neurons driven by the bipolar cells (amacrine and ganglion cells) respond to illumination by depolarizing. Beyond a certain threshold level, depolarization results in classical regenerative spike potential activity.

It is generally agreed that a "vertical" neural pathway connects the photoreceptor cells, via the bipolar cells, with the ganglion cells. The horizontal cells interact laterally ("the horizontal" neural pathway) with the "vertical" pathway while the amacrine cells appear to be synaptically connected to the bipolar cells (3, 4).

The vertical connection pathway is thought to be responsible for the central reaction of the receptive field, while the surround phenomenon results from horizontal interference by the horizontal cells (180). In addition, reciprocal synaptic interconnections between bipolar and amacrine cells have been observed in the vertebrate retina (181, 183). These observations suggest that stimulation of the amacrine cell by the bipolar cell could result in inhibitory feedback of the bipolar process. This inhibition could function in reduction of the sensitivity of the bipolar cell in proportion to the amount of input signal to that bipolar cell. As proposed, the horizontal cells may function in adaptation by inhibition of ganglion cells (4).

A number of investigators have studied the transmission of neural responses from dark adapted retinas (15, 16, 104, 129). In the dark adapted eye, a small quantity of light reaching the retina does not induce photolysis of a measurable percentage of the accumulated rhodopsin (16), yet numerous studies have established that a single light quantum will be absorbed by a molecule of rhodopsin

and that absorption of 6 or more light quanta will give rise to perception of a flash of light (125). Anatomical considerations require that numerous rods must be connected to a limited number of neural cells and subsequently to the optic nerve fibers. Taken together, these observations suggest the mechanism of adaptation must include "summation pools" (16, 128). Thus, in the fully dark adapted state, the ultimate minimal threshold of a single rod cell remains a single quantum hit, but the threshold for vision requires stimulation of the summation pool where inputs from numerous rods are added together. Rushton (16) has suggested that the threshold of the summation pool changes in adaptation and accounts for the gain of sensitivity in the dark adapted eye. Therefore, when no measurable change in rhodopsin can be observed, the increased sensitivity is associated with a feedback mechanism from the summation pool.

Observations of antagonistic zones in the bipolar receptive field, intersynaptic connections in the outer plexiform and inner nuclear layers, the organization of ganglion cell responses (on, off, and on-off units) and the feedback of amacrine cells to bipolar cells in several vertebrate visual systems (3, 4, 6, 180, 181) support the concept of summation pools in a sensitivity gain mechanism. However, neurophysiological evidence from the human eye that supports this hypothesis is incomplete (15).

(See Section V, Suggested Areas for Future Research, p 120).

H. INFLUENCE OF DRUGS AND SMOKING

1. Drugs

Drugs administered for systemic therapy may cause changes in the visual process. These include blurred vision, disturbances in color vision, scotoma, pigmentary degeneration of the retinal tissues, and morphologic tissue changes in the cornea, retina, and optic nerve. Visual disturbances produced as a side effect of some drugs prescribed for therapeutic reasons may be anticipated, especially after high doses or prolonged therapy. However, in some instances the ocular complications may be the result of unanticipated individual reactions to a particular drug.

A number of therapeutic agents frequently produce serious ocular complications (Table 7) (184, 185, 186, 187, 188, 189, 190, 191). It is unlikely that soldiers on active combat duty will be under intensive therapy with the majority of these drugs. In the case of the antibiotics and the antimalarials the soldier may be returned to duty or, indeed, may routinely receive these agents while in combat status. A recent report summarizes the effects of chloroquine and hydroxychloroquine on vision (184).

Alcohol and tobacco will adversely influence vision. Toxic substances such as ozone have been demonstrated to cause a decrease in visual acuity (192), and the oxides of nitrogen, partially oxidized hydrocarbons, and similar toxic elements of the battlefield may cause a deleterious effect on vision. The effects of these substances on vision of man have not been adequately studied. The visual disturbances produced by the hallucinogenic agents including marihuana presumably do not affect the visual process in the eye but elicit a reaction in the visual cortex. Few reports on the enhancement of night vision following the administration of chemical substances were found (184). A deleterious influence on vision is the more common effect.

Perhaps the best known and most obvious drug effect on vision is the pupil-dilating action of atropine and the accompanying cycloplegia. Atropine mydriasis is caused by the relaxation of the sphincter muscle of the iris; the accompanying relaxation of the ciliary muscle tightens the suspensory ligament and the eye is fixed for distant vision (cycloplegia) because the lens becomes less convex.

TABLE 7

DRUGS REPORTED TO FREQUENTLY PRODUCE OCULAR COMPLICATIONS IN MAN

4-Aminoquinoline derivatives (184)
Chloroquine phosphate
Hydroxychloroquine sulfate
Cardiac glycosides (185)
Chloramphenicol (186)
Corticosteroids (187)
Dihydrostreptomycin sulfate (188)
Ethambutol (189)
Phenothiazine derivatives (190)
Chlorpromazine hydrochloride
Thioridazine hydrochloride
Quinine sulfate (187)
Streptomycin sulfate (188)

There appears to be no report on the effect of atropine on night vision or dark adaptation; however, pupil dilation is a normal part of the physiology of night vision. By contrast, pupil constricting drugs (miotics) and those antagonizing the cycloplegia of atropine, e. g. physostigmine, isoflurophate (di-isopropylfluorophosphate, DFP), have not been studied extensively for their influence on dark adaptation or night vision. It may be assumed that these effects would be detrimental (193). In ten normal volunteers miosis caused by the cholinesterase inhibitor isopropyl methylphosphonofluoridate (Sarin) induced a decrease in night vision approximately in proportion to the reduction of the area of the pupil aperture (193). Similar findings were reported for volunteers exposed to DFP vapor (194). The miotic effect of DFP presumably accounted for the rise in threshold of night vision. The congestive iritis and conjunctival hyperemia were the most dangerous eye effects; changes in accommodation were not marked.

Sympathomimetic drugs applied locally to the eye produce pupillary dilation and ischemia of the conjunctiva. Mydriasis is a direct stimulant action of epinephrine on sympathetic fibers to the radial muscle of the iris. Because the dilation is not mediated through the ciliary nerve, concomitant cycloplegia does not occur as with atropine mydriasis. Epinephrine and its congeners are used locally in conjunctivitis and blepharitis. Levo-epinephrine is used in the treatment of chronic glaucoma but the mechanism of its action in reducing ocular pressure is not clear (195). A topically applied 2% levo-epinephrine solution was reported effective in lowering intraocular pressure without interference with visual functions. There was no impairment of visual acuity or night vision in four Air Force pilots tested by this treatment (196). In general, the sympathomimetic mydriatic drugs have not been studied in man for their effects on night vision.

Drugs influencing the autonomic nervous system such as the antimotion sickness drugs, the antihistaminic agents, the decongestants, and the phenothiazine derivatives may cause visual changes by eliciting parasympathetic nervous system stimulant or depressant effects. The classical pupil-constricting actions of the opiates are well recognized.

In recent years, the ability of some drugs to sensitize cells of the body to light has been recognized. Chlorpromazine and related phenothiazines administered therapeutically may induce oculocutaneous effects (197). Uptake of these drugs by pigment granules from the choroid, iris, ciliary body, and retinal pigment epithelium

in vitro has been demonstrated (198). Exposure of the individual to light of a suitable wavelength induces or enhances the abnormal reactions and produces clinical symptoms (190). The localization of chloroquine in melanin pigmented areas of the body has been established. The drug is concentrated in the eyes of pigmented rats, mice, or rabbits in relation to the degree of melanin pigmentation of the skin (199, 200, 201). The pigmented tissues bind chloroquine faster and retain it longer than the tissues of albino animals. These drugs are electron donors and the molecules are light-excited to the chemically reactive singlet state. These reactions presumably involve melanin because it is an electron acceptor.

Prolonged administration of chloroquine in the high doses used in lupus erythematosus and rheumatoid arthritis increases the incidence of retinopathy produced by this drug in human subjects. Chloroquine accumulates in the melanin-rich structures of the cat eye suggesting a possible relationship to retinal damage (202). Histochemically, the primary toxic action of chloroquine in the cat appears to be in the pigment epithelium with subsequent extensive cellular enlargement, and eventual detachment of the retina. Finally atrophy of the rods and cones ensues. The grayish-blue granular substance observed in tissue sections may be the result of binding between the electron-donor drug molecule and the electron-acceptor melanin. Chloroquine, chlorpromazine, and thioridazine initially activated and then inhibited ocular alcohol dehydrogenase-catalyzed retinol oxidation (203). Because these drugs are known to inhibit or activate many enzymes, an explanation of untoward visual effects is difficult on this basis alone.

The early detection of retinopathies in subjects receiving chloroquine therapy has been difficult. However, patients exhibiting scotoma to red light may be effectively treated by withdrawing the drug. Improved methods for the early detection of retinal changes induced by drug therapy are urgently required (184).

2. Smoking

The voluminous literature on tobacco and its effects has been reviewed by Larson et al. (204) and by Larson and Silvette (205). Of the several hundred compounds isolated from the tobacco leaf, two groups, (a) nicotine and related substances, and (b) the isoprenoids (related to isoprene) are of major biological significance.

The former group of alkaloids is believed to be responsible for the pharmacologic effects of tobacco on vision.

Nicotine has central nervous system actions and blocks selectively autonomic ganglia. As a result, the effects of nicotine are manifest on various organ systems after absorption of an extremely small amount during smoking. In addition, other toxic products of tobacco smoke may influence the smoker.

Tobacco smoke is a dense aerosol consisting of millions of semisolid particles. When a cigarette is smoked, according to a standard procedure, the cigarette yields about 33 mg of particulate smoke and about 15 times this amount as gaseous phase smoke. When tobacco is burned the smoke contains nicotine, pyridine bases, hydrocyanic acid, ammonia, carbon dioxide, carbon monoxide, organic acids, aldehydes, hydrocarbons, so-called "tobacco tar and resin," and other constituents. Smoke entering the mouth is distinctly acid, owing to the presence of organic acids. In contrast, the smoke which escapes into the atmosphere from the burning tip is alkaline, owing to greater completeness of combustion and the presence of larger quantities of ammonia. The characteristics of tobacco smoke have been summarized recently by Wynder and Hoffman (206). The chief pharmacologic effects of smoking are believed to be caused by absorption of nicotine.

Smoking one cigarette will produce a measurable increase in blood pressure (10-21 mm), an acceleration of the pulse (5 to 20 beats per min), and a drop in skin temperature (2° to 5°C of the finger; 3° to 7°C of the toe) in the habitual smoker. Tobacco smoke irritates mucous membranes of the respiratory tract and the eye (207, 208).

The concept has been advanced that hydrocyanic acid (HCN) present in tobacco smoke may cause a type of cyanide toxicity (209, 210, 211, 212). Thus, chronic smoking stimulates formation of the readily excreted form of vitamin B_{12} and may precipitate a deficiency state. However, the evidence for chronic cyanide toxicity of this type is not impressive (212, 213, 214).

Attempts have been made to correlate the serum level of cyanocobalamin (vitamin B_{12}) in individuals suffering from "tobacco amblyopia" with the symptoms, but without marked success. There appears to be an abnormality of vitamin B_{12} metabolism; the

serum level is changed and patients respond to parenteral cyanocobalamin although they continue smoking. Other reports have implicated riboflavin and thiamine as well as vitamin B_{12} in this poorly identified clinical state.

The literature on tobacco amblyopia and tobacco-alcohol amblyopia is extremely difficult to review because the syndrome has not been considered objectively (204, 205). Cause-effect relationships are often impossible to establish and "impressionistic" diagnoses are given. Visual defects with diminution of visual acuity, central scotoma for colors, and difficulty in accommodation are prominent features of tobacco amblyopia. The majority of the older literature reported the vision of subjects is better in the evening or in dim or subdued light than in bright light (204). However, recent studies do not confirm this opinion that photopic vision is adversely influenced by the chronic user of tobacco (205). Current investigations on smoking are directed to an understanding of the toxic effects in terms of biochemical changes and this information may resolve the controversy.

Foulds (215) summarized the syndrome of tobacco amblyopia as follows: (1) B_{12} deficiency may be expected in cases of tobacco amblyopia with the symptoms of pernicious anemia; (2) free gastric acid does not rule out the possibility of B_{12} deficiency; (3) the condition of B_{12} deficiency should be suspected in cases of macular degeneration where the visual loss is greater than the degree of macular disturbance would suggest; and (4) treatment with B_{12} should not be administered until the diagnosis has been made, for even a small dose of B_{12} will rapidly convert a megaloblastic marrow to the normoblastic marrow state.

Patients with tobacco amblyopia often consume considerable quantities of alcohol, hence the origin of the term "tobacco-alcohol amblyopia." Victor (216) prefers this term and states that it is really a nutritional amblyopia and should be so described. He concluded that despite dogmatic statements to the contrary, there is no fundamental clinical or pathological distinction between the amblyopia observed in smokers and the amblyopia found in chronic alcoholics. Carroll (217) suggested the term "nutritional retrobulbar neuritis" and believed the condition a toxic amblyopia rather than a nutritional deficiency that precipitates a pathologic process involving vision.

The reports on smoking and dark adaptation are not extensive and it is difficult to make a conclusive summary. Relatively low blood carbon monoxide levels, such as follows the smoking of 3 cigarettes, produces a significant deterioration of night vision (218). One study involved cigarette smoking and the determination of the level of light sensitivity in both rods and cones that persists for 15 to 30 minutes after inhaling smoke from 2 cigarettes. Control subjects smoked non-nicotine cigarettes or breathed pure oxygen. The conclusions were that smoking acts "adversely" on the dark adaptation levels of both rods and cones, and the effect is attributed largely, if not entirely, to nicotine (219). However, studies involving tobacco smoking and the ability to detect objects at night have not been carried out under diverse experimental conditions and the data are inconclusive.

Numerous studies on smoking in military populations have generally revealed that about 78 to 80% of the men smoke cigarettes (205, p 414). If these estimates are accurate and if there is a deleterious effect on vision as a result of smoking, serious consideration should be given to this fact in assigning night military tasks. This is particularly true of the demanding physical requirements of Army aviators. The low carbon monoxide blood levels produced by smoking have been correlated with the effects of oxygen deficits of high altitude (218). A similar example of carbon monoxide exposure from smoking in the sealed environment of submarines has been cited (205, p 434). It is remarkable that, with the potential deterioration in vision produced by cigarette smoking under the critical demands of military operations, more extensive definitive research has not been conducted.

(See Section V, Suggested Areas for Future Research, p 121).

I. ENVIRONMENTAL EFFECTS

Hypoxia will produce a decrement in the visual ability of man as a result of impairment of the cerebral processes, a loss of retinal function, or both. The rapid onset of ocular responses as measured by the ERG and optic tract potentials indicates that retinal functioning is nearly as sensitive to hypoxia as the cerebral processes of consciousness (220). The sensitivity of the visual threshold and acuity to noxious agents or oxygen deprivation requires further investigation (220, 221, 222). The operator of motor vehicles and aircraft is required to perform exacting tasks at low levels of illumination and his environment in these machines could produce a mild hypoxia that would adversely influence his night vision (223, 224, 225). The low oxygen deprivation tolerance of the retina makes this structure uniquely sensitive to mild hypoxia and is recognized in the selection of aviators (226).

The effects of hypoxia on vision have been reviewed by Ohlbaum (227). His study included 19 men, age 20 to 39, with aviation hypobaric experience who volunteered for visual tests before and after exposure to mild and acute hypoxia in a hypobaric chamber. The tests involved the following visual functions: stereopsis, accommodation, convergence, phorias, refractive change, the near phoria, and plus-acceptance for near vision. Normal, healthy young men demonstrate considerable resistance to the stress of moderate hypoxia (123 mm/Hg partial pressure 0_2) and, depending upon the severity of oxygen deficit, loss of accommodation, convergence, and stereopsis follows. Ohlbaum's study quantified these changes as a direct function of altitude (hypoxia). Unfortunately, more investigations of this character have not been reported, especially, studies related to low levels of hypoxia for long time periods using objective visual studies.

Effects of hypoxia on vision are of interest for several reasons. For example, measurement of dark adaptation threshold may provide a sensitive test for hypoxia or environmental noxious chemical agents that may or may not produce hypoxia. From the available evidence, changes produced by reduced oxygen tension are not concerned with the visual pigment cycle alone, but with the neural elements of both the retina and the central nervous system. Any drug or chemical that decreases oxygen availability to the retina by reducing blood flow or oxygen tension, or modifies the nature of the photochemical

substances of the eye, would likely produce some change in night vision and dark adaptation.

Hyperoxygenation produced by breathing pure oxygen has been investigated for its effects on dark adaptation (228). Dark adaptation was selected as a sensitive, easily scored measure. Breathing oxygen at one atmosphere caused decreased rod and cone sensitivity at threshold illumination in only one of five subjects. More information is needed on the effects of breathing oxygen at normal atmospheric pressure on night vision and dark adaptation under military environmental conditions.

Cyanide, carbon monoxide, and ozone cause changes in visual acuity in very low concentrations. Ozone in the respired air in concentrations from 0.05 to 0.20 parts per million has been reported to cause a decrease in visual acuity and may constitute a hazard for men confined in aircraft, submarines, or spacecraft (192). Chemical contaminants of this type are found in industrial smog and localized areas of military support and supply where the equipment generates these potentially toxic elements. The combined effects of hypoxia and environmental toxic substances on dark adaptation and night vision may be greater than previously anticipated. A careful study of these influences on the vision of the soldier should be made as encountered under all military situations. Such a study requires analytical data on concentrations of environmental contaminants and reliable, quantifiable measures of the vision of the soldier.

(See Section V, Suggested Areas for Future Research, p 122).

J. INDIVIDUAL VARIATION

Night vision ability varies among individuals. However, no comprehensive study has been made of individual variation as it relates to night vision and dark adaptation. Such factors as age, physiological state, blood sugar level, and the nutritional status of the individual have been identified as significant. Studies on oxygen deprivation and carbon monoxide poisoning in World War II pilots served to highlight the problem of individual variability. In these investigations, differences in visual capability and dark adaptive capacity were observed among the normal control subjects. In addition, individual metabolic differences, genetic background, and even anatomic differences may be important factors controlling the individual's night vision capability.

The adaptation rate to changing light intensity is significant for the soldier. Fundamental differences exist between experimental laboratory studies that measure light threshold of the fully dark adapted eye under controlled conditions and life situations that require efficient vision in an environment with changing levels of illumination. Normally, the eye must continually accommodate to the visual demands of changing environmental luminance levels (229). For these reasons, an important distinction can be made between the night vision efficiency of the soldier, as measured in test situations, and his rate of adaptation under the more realistic demands of fluctuating light intensities in combat.

In an early study of normal subjects, Sheard (230) observed that approximately 2% showed abnormally high dark adaptation thresholds. Analysis of the dark adaptation thresholds of a group of 45 pilots revealed the normal variation in final threshold was $\pm$ 0.5 to 0.7 log unit. Similar observations have been made in populations of school children (230) and adults (138). With a well trained subject and adequate control of both the environment and the test procedures, Sheard (230) was able to reproduce dark adaptation threshold values on the same subject from day to day within 0.1 log unit. Unfortunately, current studies are difficult to correlate with these older figures. Most investigators comment on the influence of the cooperation of the subject in spite of the objective nature of the test. Thus, the night vision sensitivity tested during prolonged restriction from sunlight in 24 submariners during a 3-month continuous submerged

cruise revealed that 7 individuals exhibited relatively poor scores during the latter portion of the cruise, possibly correlating with low morale, cooperation, and attitude (231). It was assumed that the diet of the test subjects contained an adequate supply of vitamins and other essential nutritional elements.

Individual night vision sensitivity varies with the amount of prior exposure of the person to sunlight and a seasonal variability is recognized. The influence of light spectrum and illumination level on night vision appears reasonably well understood and can be standardized (230). Individual depth perception is an important factor in night vision that has not been studied adequately under controlled conditions. The glare phenomenon or a sudden bright illumination followed by a decreased illumination is difficult to standardize in dark adaptation tests. This effect may be similar to light "shock" on night vision. It is extremely difficult to study the effects of rapid changes in illumination under controlled conditions. In the "photostress test" or "macular dazzle test" (232), noxious agents and drugs were shown to increase the time required for recovery of visual acuity of the subject after exposure to a standardized light flash.

One of the better understood aspects of dark adaptation and night vision is the effect of aging. Average dark adaptation proficiency declines with increasing age. This decrease becomes significant in most persons over 55 to 60 years of age (233). These changes in visual acuity and dark adaptive capability are believed to be related to progressive aging of the lens, retina, optic tract, and higher central nervous system. McFarland et al. (234) concluded that age is highly correlated with dark adaptation thresholds. On the other hand, the progressive rise in dark adaptive thresholds may be more closely related to senescence of the lens and formation of cataracts.

The range of dark adaptation thresholds was reported by Sloan (138) in a group of 101 normal individuals. The change of dark adaptation thresholds was followed over a 40-minute period. The distribution of the individual thresholds at each determination showed close agreement with the theoretical normal distribution curve; sixty-eight percent fell within 1 standard deviation of the normal curve, 95% within 2 standard deviations, and 99.7% within 3 standard deviations. Dark adaptation thresholds of individuals beyond ± 2 standard deviations were considered beyond the normal

range; only 5% of the subjects were in this category. As expected, increase in threshold occurred with increasing age. Measurement of the normal deviation of an individual's variation in dark adaptation threshold requires rigidly standardized methodology and experienced test subjects. Because there is a relatively wide range of individual variation in threshold, it is possible for a person whose final visual threshold is close to the lower limit of "normal" to have an increase in threshold of as much as 1.0 log unit above his own normal level, and still be within the group "normal" range. Cases of this kind could be classified as retinol deficient and might unnecessarily receive vitamin A therapy (138).

Individuals with congenital complete color blindness and bilateral macular degeneration are known; presumably, cone function is completely lost but normal rod function is retained. This dysfunction of the visual process may occur to some degree in a relatively large but unknown number of individuals (138, 139, 230).

Metabolic differences may be reflected in changes in the visual process or dark adaptation thresholds. Wilson (235) reported that the thiocyanate present in body fluids may originate from the diet or from the detoxification of cyanide. The plasma concentration and urinary excretion of thiocyanate in smokers, as compared with nonsmokers, could be interpreted as related to cyanide exposure from tobacco smoke. If a patient had an inborn error of cyanide metabolism and were unable to detoxify cyanide to thiocyanate, such a metabolic abnormality might exhibit itself as a neurological syndrome consistent with symptoms commonly associated with chronic cyanide exposure. This type of metabolic abnormality is illustrative of individual physiologic or genetic variations that may influence such an exquisitely sensitive process as vision. The impairment in dark adaptation in mongols (236) may be considered the result of an abnormal metabolic process. "Normal" subjects may have similar latent metabolic diseases that could produce visual modifications (237).

Visual light thresholds have been studied in neuropsychiatric patients as an objective measure of the perceptual distortions that these individuals experience. Few studies report significant differences in thresholds between psychotic patients and normal controls, but workers in this field have observed repeatedly that these individuals experience autonomic nervous system imbalance (238). In a study of dark adaptation in psychotics, Rubin and Stein (239) found

higher thresholds in psychotics than in normal individuals. Pupillary responses alone, which vary significantly in these individuals, have been considered a diagnostic criterion, and may explain some of the visual differences observed. These findings correlate with those of Kinney (231) in men undergoing prolonged restriction from sunlight.

It is clear from this review that there is need to determine the individual night vision and dark adaptation capability of the soldier assigned to a particular task. This information might prove to be sufficiently dependable to warrant the assignment of key individuals for specific tasks and exclusion of others who should not be assigned responsibilities that require critical night vision. Recognition and identification of the physiological, behavioral, and biochemical variations in men will materially assist in the enhancement of the quality of the Army's night vision and night operations capability.

(See Section V, Suggested Areas for Future Research, p 123).

IV. SYNOPSIS OF REVIEW DISCUSSIONS

VITAMIN A

The relation of night blindness to a nutritional deficiency has been known since antiquity, but the relationships of vitamin A with the provitamin carotenoids and their role in the visual pigments has been established only recently. In man, vitamin A deficiency in the adult usually results in night blindness. Pathology of vitamin A deficiency is probably complicated by other nutritional deficiencies as well as infectious diseases. The occurrence of endemic night blindness is normally associated with dietary inadequacies, individual susceptibility, and environmental circumstances. The ability to absorb retinol and its carotenoid precursors, or store and transport retinol to the eye, involves several complex and interrelated physiological mechanisms.

Although vitamin A is recognized as an essential component of the human diet, minimal and optimal daily requirements are not known precisely. In general, vitamin A influences growth and maturation by affecting vision, bone growth, reproduction, and keratinization of mucous membranes. In the human diet, vitamin A is supplied by absorption of preformed retinol and from carotenoids which are converted to retinol in the gastrointestinal tract.

In an effort to establish human requirements for vitamin A activity, deficiency studies have led to conflicting results. Recent studies suggest that recommended daily dietary allowances and actual vitamin A stores are not closely related. One study (44% age 6 or below) reported that 33% have serum retinol levels below 19.0 μg/100 ml. A study of Canadians revealed 32% had liver retinol levels of 0-40 μg/g. The acceptable average vitamin A liver content is 100-300 μg/g. The quantitative significance of these data can not be established at this time.

Retinyl esters are converted to retinol in the gastrointestinal tract where retinol is absorbed. Carotenoids are converted to retinol, mostly in the small intestine, and absorbed through the intestine wall. In normal adult individuals, retinol and retinyl

esters are absorbed in either aqueous or lipid dispersion; however, absorption is more rapid from aqueous solutions. In man, retinol is esterified as it passes through the intestinal mucosa. The predominant saturated fatty acid esters are retinyl palmitate and stearate. The fatty acid composition of the retinyl esters in the lymph is fairly uniform and is not related to alterations in the composition of the fatty acids ingested. The retinyl esters are transported via the intestinal lymphatics in chylomicrons. Approximately 90% of the absorbed vitamin A occurs as retinyl esters.

The human intestine has a limited capacity to absorb dietary β-carotene directly into the lymph. While carotenoids have been known as precursors of retinol for many years, recent studies have demonstrated that the site of conversion in vivo is apparently the intestinal mucosal wall. Beta-carotene is cleaved centrally (15-15' bond) to form two moieties of retinal. The action is mediated by a dioxygenase enzyme system that requires molecular oxygen. Following cleavage of β-carotene to retinal, reduction to retinol takes place in the mucosal wall. This reaction is mediated by a second soluble protein enzyme which requires as a cofactor either reduced nicotinamide adenine dinucleotide or reduced nicotinamide adenine dinucleotide phosphate. The reduction reaction is stimulated by glutathione and hindered by thiol inhibitors.

The classical concept of retinyl ester transport and storage includes movement of retinyl esters in chylomicrons through the lymphatic system, via the thoracic duct to the blood stream, and finally to the liver where storage occurs. Liver reserves of retinyl esters are hydrolyzed and the retinol is carried to various body tissues. It has been established that the major portion of vitamin A activity in the blood is transported as retinol bound to a specific protein. The retinol-binding protein circulates in the plasma bound to a prealbumin protein that is identical to the "thyroxine-binding" prealbumin of human plasma. The retinol-binding protein-prealbumin complex contains one molecule of each component.

Onset of reduced visual sensitivity without apparent cause is justification for analyses of vitamin A levels in the blood and liver. Meaningful analyses of vitamin A in various tissues require detailed analytical methodology.

OCULAR METABOLISM OF VITAMIN A

The retina and related ocular tissues receive a rich supply of blood from the internal carotid and ophthalmic arteries. The total quantity of vitamin A within the eye is quite limited and presumably the retinol-binding protein-prealbumin complex delivers retinol to the sclera, choroid, and retina. The mechanisms of retinol release are not known. An enzyme is present in bovine pigment epithelium that esterifies retinol. Rapid and selective esterification of retinol in the pigment epithelium would allow subsequent diffusion to photoreceptor cells where hydrolysis occurs. The stereoisomerization of trans-retinal to 11-cis-retinal is thought to be enzymically mediated. In a study of retinol and retinal distribution in the retina and pigment epithelium of the albino rat, the total vitamin A activity in the two tissues was observed to remain relatively constant. The retinol content of the pigment epithelium decreased in dark adaptation while a concomitant increase of retinal occurred in the retina. In the light adapted state, less total vitamin A activity is present in the retina.

Retinal reduction in the visual cycle is dependent on glucose metabolism primarily by way of the pentose cycle. In the light adapted eye, the presence of trans-retinal results in reoxidation of nicotinamide adenine dinucleotide phosphate. Thus, pentose cycle activity and ultimately the requirement for both oxygen and glucose are stimulated. Because glycogen storage in the human eye is limited, ocular tissues are almost entirely dependent on an uninterrupted supply of blood glucose.

Subsequent to events in the visual cycle, the microsomal fraction of the retina is active in esterification of the trans-retinol. Preparations from outer segments are unable to induce esterification, suggesting that the reduced retinal diffuses out of the outer segment and into the microsomes of the photoreceptive or related neural cells. The esterification mechanism does not require adenosine triphosphate, coenzyme A, or other factors. Retinyl palmitate, stearate, and oleate esters comprise about 85% of the total retinyl esters formed. The ratio produced is quite similar in retinal preparations from several animals and man. The fatty acid composition of esters synthesized in the retina is similar to that of liver retinyl esters.

OTHER NUTRITIONAL FACTORS

Dietary protein influences absorption, transport, and storage of vitamin A. The vitamin affects synthesis of muscle and serum proteins. Protein and vitamin A deficiencies often occur simultaneously. Protein supplementation in the diet of protein-deficient individuals increases serum vitamin A, presumably through mobilization of liver stores, and also increased the overall retinol requirement. When low vitamin A reserves are depleted, protein supplementation may stimulate overall growth and thus bring about vitamin A deficiency. These observations emphasize the importance of vitamin A supplementation when protein malnourished individuals receive additional dietary protein.

Recent nutrition surveys suggest that prolonged voluntary or economically produced dietary insufficiency exists within certain population groups. Observations of low serum vitamin A levels indicate that a complete assessment of the dietary adequacy and vitamin A status of normal individuals is urgently required.

Dietary fat intake is another closely related factor in production of vitamin A deficiency and night blindness. While dietary lipid appears to be essential for absorption of carotenoids and perhaps retinol, the quantitative and qualitative aspects are not completely understood.

The obvious importance of vitamin A in the visual process has overshadowed the role of other vitamins and nutritional factors. Deficiency of several other vitamins and minerals produces clinically evident syndromes that include ocular symptoms.

In general, the B-vitamins function catalytically in various steps in intermediary metabolism and thus are important in oxidative metabolic processes critical to the normal functioning of the retina. While deficiencies of biotin, pyridoxine, and pantothenic acid are known to induce ocular disturbances, their effects on the visual process and the metabolism of the dark adapted eye are essentially unknown. Study of an abnormality in vitamin B_{12} metabolism in patients with diabetic retinopathy did not report any effect of vitamin B_{12} deficiency on dark adaptation and night vision. Investigations on the role of vitamin C suggest numerous effects

on various ocular processes and structures; however, the literature is contradictory. Vitamin E is known to reverse or block the lysis of the rat liver lysosomal membrane that can be precipitated by retinol deficiency. There is a paucity of information concerning the effects of vitamin D and vitamin K, if any, on dark adaptation and night vision.

The direct effects of mineral elements on night vision are obscure. Calcium, phosphorus, potassium, and sodium are ubiquitous in body tissues. The deficiency of any one of these minerals could lead to visual impairment as well as other clinical manifestations. Both zinc and selenium are known to be present in relatively high concentrations in certain parts of the vertebrate eye. Since zinc is an essential portion of the enzyme alcohol dehydrogenase, oxidizing trans-retinol to trans-retinal, it is conceivable that zinc deficiency might reduce the rate of rhodopsin regeneration during dark adaptation. A role for selenium in visual excitation has been suggested, but has not been studied.

PHOTOCHEMISTRY OF VISION

Rhodopsin contains the chromophore, 11-cis-retinal and the insoluble protein, opsin. The absorption of light by rhodopsin produces photoisomerization of the chromophore and an apparently spontaneous series of thermic transformations. Photoisomerization produces a series of unstable intermediates, but each contains trans-retinal attached to opsin. Hydrolysis of the final intermediate, N-retinylidene opsin, yields the two final products, trans-retinal and opsin. In addition to inducing stereoisomerization of 11-cis-retinal in rhodopsin, light isomerizes the trans-retinal of the photoproducts back to the 11-cis-retinal isomer. Although the half-life of these intermediates is brief, the concentrations of the metarhodopsins may be involved in controlling visual sensitivity.

The visual pigment is held in multiple double membrane discs within the outer segment of the photoreceptor cells. The discs are stacked and enclosed in the plasma membrane. There is some question as to the exact location of rhodopsin in the disc structure. Recent studies have clarified the processes of rhodopsin synthesis and incorporation of the visual pigment into the disc. Protein is synthesized in the inner segment, moves through the ciliary region, and is incorporated in the lipoprotein discs at the base of the rod outer segment. Continual disc synthesis moves previously synthesized discs to the distal portion of the outer segment. Disintegration of discs occurs in the pigment epithelium, although the mechanisms of movement across the plasma membrane and proteolysis are not entirely understood.

There is more information available concerning the chromophore, 11-cis-retinal, than the protein moiety, opsin. The exact nature of the chemical bonding between the two moieties is under active investigation. The prevailing opinion is that retinal is bound to a free amino group on a lipoprotein; and that the resulting Schiff-base may be either protonated or unprotonated. However, other types of linkage can not be ruled out. Opsin may be a glycoprotein with 11-cis-retinal linked to lysine and cysteine. Similarly, retinal may be held by phosphatidal ethanolamine of the phospholipid-protein prior to photolysis and to the lysine residue of opsin following photolysis. The exact nature of the primary binding between 11-cis-retinal and opsin in the several visual pigments including rhodopsin has not been completely defined.

DARK ADAPTATION

While regeneration of rhodopsin appears to be critical to dark adaptation, other biochemical and neurophysiological factors are involved. Photosensitive pigments regenerate in the dark, but the increase in pigment is insufficient to account for the total decrease in threshold of sensitivity to light. Even in the predominantly rod retina of the rat, dark adaptation is not simply the reversal of light adaptation; two distinct phases in sensitivity gain can be observed. The rapid phase has been termed, the neural adaptation phase; the slower phase, photochemical dark adaptation. The rapid phase is thought to be the reverse of the swift loss of sensitivity which occurs during light adaptation. Dark adaptation is rapid until the rods are adapted to luminance levels where significant photolysis of rhodopsin has occurred. At this point, rhodopsin concentration has a significant effect upon dark adaptation. Thus, the slower phase of dark adaptation is closely related to the regeneration of rhodopsin. Since only the slow phase of dark adaptation appears to be directly related to the concentration of rhodopsin, a signal, or feedback mechanism that indicates the amount of rhodopsin present, may originate in the retina.

The necessity for accurate assessment of visual sensitivity has led to the development of various quantitative and qualitative methods for measuring dark adaptation. Historically, the psychophysical methods were developed first; electrical and optical methods were developed later. Considerable confusion has resulted from attempts at direct comparison of the changes in visual sensitivity with these different methods because the sensitivity of the eye to light depends upon several interrelated critical factors used as experimental variables. Psychophysical measurement is valuable in determining the presence of visual defects. Since dark adaptation involves the entire eye, including both the rod and cone systems, the psychophysical methods are affected by individual differences in ocular as well as retinal morphology and physiology.

The electrical responses of the eye are of value in studying rod function. The method most widely used is the electroretinogram. The electroretinogram measures the gross response of the retina rather than the electrical activity of individual cells. The surface of the living retina can be observed with the ophthalmoscope and, when connected to a suitable recorder, a quantitative measure can

be made of the reflected light (reflection densitometry). Utilizing both the electroretinogram and reflection densitometry, both visual pigment changes and adaptation can be determined accurately.

Extensive studies of visual pigment regeneration rates demonstrated the regeneration rate of in vitro rhodopsin preparations and dark adaptation in vivo are nearly identical. Dark adaptation of the cones occurs initially, followed by increased sensitivity of rod cells in the lowered luminance. The logarithm of the threshold, not the threshold itself, depends upon the concentration of the visual pigment. Study of the frog eye suggests the relatively rapid phase of dark adaptation may be linearly related to the logarithm of the threshold value. It may be also quantitatively dependent upon the concentrations of visual cycle intermediate, metarhodopsin II. These observations have not been confirmed in other vertebrate visual systems.

INITIATION OF NEURAL RESPONSE

Absorption of a light quantum by the rhodopsin molecule results in molecular rearrangement of the absorbing pigment and initiation of the neural phase of the visual process. The mechanisms of generation of the neural impulse in the rod cell following absorption of a photon remains the most intriguing question in visual neurophysiology. Several hypotheses have been proposed to explain the mechanism whereby neural stimulation results from absorption of one light quantum by one molecule of visual pigment.

Photochemical stimulation initiates changes in electrical potential within the retina and between retinal cells and adjacent cells. These measurable electrical phenomena are associated with initiation of the neural signal. However, most evidence suggests that these changes of electrical potential within the retina are only indirectly related to the actual initiation of the neural signal evoked by light stimulation of the photoreceptor cells. Another electrophysiological response, the slow (S)-potential has been observed in intracellular recordings of receptor and horizontal cells of lower vertebrate retinas. The luminosity (L)-type S-potentials are sustained, vary with illumination over a limited range of luminance, and are always hyperpolarizing. L-type S-potentials have been related to dark adaptation. Visual excitation may involve either a hyperpolarizing (L-type S-potential) or depolarizing signal arising in the horizontal and receptor cells.

It is generally agreed that a "vertical" neural pathway connects the photoreceptor cells, via the bipolar cells, with the ganglion cells. The horizontal cells interact laterally with this pathway while the amacrine cells appear to be synaptically connected to the bipolar cells. The vertical connection pathway is thought to be responsible for the central reaction of the receptive field, while the "surround phenomenon" results from horizontal interference by the horizontal cells. It has been proposed that the horizontal cells may function in adaptation by inhibition of ganglion cells. Anatomical considerations require that numerous rods must be connected to a limited number of neural cells and subsequently to the optic nerve fibers. Taken together, these observations suggest the mechanism of adaptation must include "summation pools." Evidence from studies of several vertebrate visual systems supports

the concept of summation pools in a sensitivity gain mechanism. However, neurophysiological evidence from the human eye supporting this hypothesis is incomplete.

INFLUENCE OF DRUGS AND SMOKING

Drugs administered for systemic therapy may cause changes in the visual process, including blurred vision, disturbances in color vision, scotoma, pigmentary degeneration of the retinal tissues, and morphologic tissue changes in the cornea, retina, and optic nerve. Visual disturbances produced as a side effect of certain drugs prescribed for specific therapeutic reasons may be anticipated especially after high doses or prolonged therapy.

There are reports of adverse effects of many drugs on vision, e. g. cardiac glycosides, 4-aminoquinoline derivatives, phenothiazines, corticosteroids, and certain antibiotics. It is unlikely that soldiers on active combat duty will be under therapy with most of these drugs.

In recent years, the ability of some drugs to sensitize cells of the body to light has been recognized. Chlorpromazine and related phenothiazines administered therapeutically may induce oculocutaneous effects. The pigmented tissues bind chloroquine faster and retain it longer than the tissues of albino animals. These reactions may involve melanin within the pigment epithelium.

Several agents, such as alcohol and tobacco, adversely influence vision. Nicotine has central nervous system actions and blocks selectively autonomic ganglia. As a result, the effects of nicotine are manifested on many organ systems after absorption of even an extremely small amount of nicotine during smoking. In addition, other toxic products of tobacco smoke may influence the smoker. The literature on tobacco amblyopia and tobacco-alcohol amblyopia is extremely difficult to review because the syndrome has not been considered objectively. Cause-effect relationships are often impossible to establish and "impressionistic" diagnoses are reported. Visual defects with diminution of visual acuity, central scotoma for colors, and difficulty in accommodation are prominent features of tobacco amblyopia.

Patients with tobacco amblyopia often consume considerable quanti' es of alcohol, hence the origin of the term "tobacco-alcohol ambl pia." Numerous studies on smoking in military populations have evealed that about 78-80% of the men smoke cigarettes. If these timates are accurate and if there is a deleterious effect on

vision as a result of smoking, serious consideration should be given to this fact in assigning night military tasks. The low carbon monoxide levels in the blood produced by smoking have been correlated with the effects of oxygen deficits of high altitude.

ENVIRONMENTAL EFFECTS

Hypoxia will produce a decrement in the visual ability of man as a result of impairment of the cerebral processes, a loss of retinal function, or both. Any noxious material or chemical contaminant that either decreases oxygen availability to the retina by reducing blood oxygen tension, or modifies the nature of the photochemical substances of the eye, will likely produce some change in night vision and dark adaptation.

Environmental contaminants such as ozone, carbon monoxide, and cyanide have been demonstrated to cause a decrease in visual acuity. The oxides of nitrogen, partially oxidized hydrocarbons, and similar toxic elements of the battlefield may cause a deleterious effect on vision but the effects of these substances have not been adequately studied.

INDIVIDUAL VARIATION

Night vision ability varies among individuals. Factors such as age, physiological state, blood sugar level, and the nutritional status of the individual have been identified as significant. An important distinction can be made between the night vision efficiency of the man, as measured in test situations, and his rate of adaptation under the realistic demands of fluctuating light intensities in the combat situation.

Analysis of the dark adaptation thresholds revealed that the normal variation in final threshold was $\pm$ 0.5 to 0.7 log unit. It was assumed that the diet of the test subjects contained an adequate supply of vitamins and other essential nutritional elements.

Individual night vision sensitivity varies with the amount of prior exposure of the person to sunlight. Moreover, there is seasonal variability. Average dark adaptation proficiency declines with increasing age. Changes in visual acuity and dark adaptive capability are believed to be related to progressive aging of the lens, retina, optic tract, and higher central nervous system. The progressive rise in dark adaptive thresholds may be related to senescence of the lens and formation of cataracts.

V. SUGGESTED AREAS FOR FUTURE RESEARCH

VITAMIN A

Although vitamin A is recognized as an essential nutrient of the human diet, the daily minimal requirement and optimal intake levels are not known precisely. The currently used estimates of the dietary requirements are based upon visual tests in a limited number of individuals. The recommended allowances were increased arbitrarily to insure an additional supply for body requirements over and above those of vision. Recent studies suggest that recommended daily allowances and actual vitamin A stores are not closely related. The significance of these findings remains to be established; however, it highlights the urgent need for more data on several aspects of vitamin A metabolism in man. The following topics should receive research emphasis:

- Vitamin A requirements at various growth stages;
- Determination of the precise relationships between dietary intake, body tissue levels, and scotopic capacity in man; and
- Establishment of the daily minimal and optimal dietary intakes for maintenance of maximal scotopic vision.

Recent investigations have clarified the mechanisms of retinol absorption and the conversion of β-carotene to retinol in the intestinal mucosa. Additional studies on the conversion of provitamins would provide useful information on the relationships between dietary intake, absorption, and utilization. These processes are modified by disease states, infection, and dietary deficiencies. Areas for future research to elucidate these factors should include:

- The relationships between vitamin A levels in various tissues, excretion pathways, and such pathologic states as gastrointestinal disease, acute or chronic infections, and metabolic diseases; and

- The study of vitamin A metabolism in patients with various disease states to correlate any deviations from normal values with the patient's dark adaptation threshold and night vision capability.

The discovery of retinol-binding protein bound to a plasma prealbumin as a carrier mechanism selective for retinol is a significant advance in the study of vitamin A transport and metabolism. The observation of the retinol carrier system affords a reasonable hypothesis why excessive dietary supplementation with retinol alone will not enhance scotopic vision. The ocular supply of retinol may be dependent upon the carrier system. This hypothesis should be studied further. At present, the relationship between the level of retinol in the blood and the level of retinyl esters in the liver is obscure except when liver vitamin A levels are reduced. Developments in this field suggest the following areas for future research:

- The interrelationships between binding of retinol and thyroid hormone by retinol-binding protein-prealbumin complex, retinol transport, and metabolism of thyroid hormone;

- Further study of the role of retinol-binding protein and prealbumin binding as related to transport of 11-cis-retinal precursors to the eye;

- Study of the mechanisms that maintain blood plasma retinol levels; for example, regulation of retinol-binding protein synthesis and release of retinol from retinyl esters;

- A comprehensive study of liver storage of retinol, especially the factors that control the hepatic distribution as well as the maximum amount stored; including,

- An investigation of the relationship between liver reserves of retinol serving a protective role in the absence of dietary intake and storing of excessive retinol leading to hypervitaminosis A or retinol toxicity.

There is a paucity of knowledge concerning the mechanisms and significance of retinol catabolism and excretion in man. Areas for future research should include:

- The study of effects of increased urinary excretion of retinol in severe infectious diseases and stress conditions as related to night vision capability; and

- The study of the influence of retinol deficiency states, decreased serum levels, and increased urinary excretion on ocular retinol metabolism, dark adaptation, and night vision.

There is a pressing need for acceptable, standardized techniques for the analysis of retinol and retinyl derivatives in body fluids and tissues. It is often difficult to correlate data on retinol analyses from several laboratories because of minor differences in analytical methodology. Future research should include continued emphasis on:

- Development of acceptable, accurate analytical methods that apply to the wide range of vitamin concentrations found in foodstuffs and body tissues of various population groups; and

- Analytical methodology that permits rapid separation and accurate identification of carotene, retinol, and their derivatives.

(See Section III B, p 26).

OCULAR METABOLISM OF VITAMIN A

Vitamin A metabolism within the eye and the metabolic functions of the pigment epithelium in the visual process warrant additional study. Of particular interest is the relationship of these biochemical processes to dark adaptation and night vision. Consideration should be given to future investigation on:

- Localization and mechanism of retinol release from retinol-binding protein-prealbumin carrier system, and the oxidation and isomerization to 11-cis-retinal prior to synthesis of visual pigments;

- The study of the synthesis and possible hydrolysis of retinyl esters in the pigment epithelium, and oxidation of retinol and subsequent isomerization to 11-cis-retinal in the rod outer segment; and

- Functions of the pigment epithelium in addition to absorption of spurious reflected light, with emphasis on metabolism of vitamin A derivatives following absorption and degradation of visual pigment discs.

Because a limited vitamin A supply would influence rod cells adversely and thereby reduce the capacity for dark adaptation and night vision, the study of rod-cone rivalry for vitamin A derivatives should be investigated more thoroughly. Research should include:

- A thorough study of stereoisomerization of both retinol and retinal within the outer segment of the photoreceptive cells and pigment epithelium;

- A study of the interconversion of retinol and retinyl esters within the pigment epithelium and adjacent tissues should be studied in several vertebrate systems; and

- Investigation of ocular retinol metabolism and scotopic vision in various diseases that have military significance, e.g. diarrhea, pneumonia.

(See Section III C, p 46).

OTHER NUTRITIONAL FACTORS

The interrelationships of vitamin A and other nutritional factors affecting dark adaptation and night vision are incompletely understood. In spite of a long recognized need for controlled studies involving manipulation of intakes of all nutrients, relatively few comprehensive reports are available. Suggested areas for future research include:

- Controlled studies of daily vitamin A requirements including treatment regimens that provide several levels of other nutrients;
- Elucidation of ocular metabolism of proteins in all age groups as evidence suggests that protein synthesis and turnover may be of greater significance in ocular vitamin A metabolism than previously realized;
- Investigation of the effects of the commonly encountered nutrient deficiencies on retinol transport in the body; and
- Investigation of the role of nutritional factors such as ascorbic acid, riboflavin, zinc, and selenium in ocular metabolism.

(See Section III D, p 53).

PHOTOCHEMISTRY OF VISION

The subcellular architecture of the photoreceptor cells, the synthesis of the proteins in the visual process, the arrangement of rhodopsin molecules within the outer segment, and the transformational details of the process of rhodopsin photolysis are prominent aspects of current vision studies. Continued elucidation of the precise details of these processes will augment the understanding of photochemical processes involved in dark adaptation and night vision. Research in this field should include:

- Investigations on the phenomenon of light-induced reverse photolysis to rhodopsin as it relates to visual pigment synthesis in night vision;
- Studies of photoproduct transformations, concentrations, and equilibria as these may regulate or otherwise influence visual pigment synthesis and the processes of dark adaptation;
- Study of the resynthesis of rhodopsin following hydrolysis and release of the retinal moiety;
- Investigation of the binding phenomena between opsin and the retinal moiety throughout the rhodopsin cycle;
- Elucidation of the structure and composition of the visual pigment protein in photoreceptor cells of human and other vertebrate retinas;
- Investigations on how photochemically induced molecular rearrangement of retinol isomers may induce the conformational changes in the visual pigment protein; and
- Continued study of subcellular architecture within the rod cells to clarify the relationships of histological structure and biochemical function in night vision.

(See Section III E, p 59).

DARK ADAPTATION

The specific biochemical and neurological events that control and regulate dark adaptation remain unclear. The relation of "after-images" and "retinal noise" to the dark adaptation processes requires additional clarification. Future research should include:

- The study of the origin of the "retinal noise" and its relation to dark adaptation and photoisomerization of the visual pigments;
- An investigation of the experimental variables per se, such as light flashes of varied time and intensity that influence, but often have little direct effect on dark adaptation rates and rhodopsin photolysis; and
- Correlation of knowledge of the processes of dark adaptation with the requirements of night vision devices to more efficiently prepare the soldier for night operations.

Methodology for testing dark adaptation rate and the absolute threshold in man has reached a high state of technical development, e.g. retinal densitometry and recording of evoked potentials. However, these sensitive methods require complex equipment and experienced, technically trained scientists for their operation. Simplified devices for clinical, investigative, or military use have been made. Additional consideration should be given to:

- An analysis of the requirements for night vision in specific military tasks of all types and the methods of selection of soldiers for these tasks; and
- Review of procedures currently employed for testing dark adaptation and night vision in meeting military requirements for night vision capability.

(See Section III F, p 66).

INITIATION OF NEURAL RESPONSE

The generation of neural impulses in the photoreceptive cells of the eye following light stimulation continues to be the dominant topic of visual neurophysiology. The biochemical transfor nations of the visual pigments that are initiated by absorption of light quanta are reasonably well establishe , but the mechanisms that link rhodopsin transformations to neural excitation are incompletely understood.

Elucidation of the mechanisms of visual excitation of the neural response is central to the understanding of the process of night vision. Current research investigations have established the detailed histological character of the vertical and horizontal neural channels within the vertebrate retina. Recent studies have correlated histological observations with neurophysiological functions and have revealed the origin, role, and relationships between graded and spiked pote ials as well as the synaptic interconnections within the neural channels. Future research should include the following:

- Clarification of the anatomical process and physiological bases of "gain control" mechanisms, summation pools, and the surround effect in dark adaptation;

- Additional studies on the subcellular electrophysiological phenomena associated with the visual process including ion migration within the photoreceptor cells in the process of neural response following photolysis;

- Application of the concepts of charge transfer at the inter- or intra-molecular level within the photoreceptive and adjacent neural cells; and

- Further study of the visually evoked hyperpolarization and depolarization within the receptor and horizontal cells as well as the other graded and spiked potentials within the retina including receptor potentials and initial components of the electroretinogram.

(See Section III G, p 81).

INFLUENCE OF DRUGS AND SMOKING

Relatively little is known about the specific limitations on the vision of man imposed by therapuetic agents, tobacco smoking, or alcohol ingestion. Proper use of optical aids for night vision enhancement should include a consideration of these potentially deleterious influences. Future research should include:

- Study of the visual effects of drugs commonly administered to the soldier under combat conditions;
- Further examination of the suggested relationships between the use of tobacco and alcohol and the occurrence of amblyopia, decreased visual acuity, central scotoma for color, and loss of accommodation. The significance of frequency of smoking and temporal relationships of smoking to dark adaptation measurements require further study as these relate to the military requirements of the soldier;
- The development of improved methods to detect early ophthalmologic changes in the soldier, that may be applied to a large number of men, to rapidly screen for potentially hazardous visual injury; and
- Comprehensive review of the effects of many classes of drugs, smoking, and alcohol on the visual capability of the soldier.

(See Section III H, p 86).

ENVIRONMENTAL EFFECTS

Relatively little research has been conducted on the effects on vision, especially night vision, of chemical environmental contaminants on the battlefield, in rest and supply areas, or in military aircraft and vehicles. These toxic substances may adversely affect photopic and scotopic vision. Future research should include:

- Analysis of the toxic elements, including carbon monoxide and dioxide, ozone, the various hydrocarbons, and oxides of nitrogen, to ascertain the usual and maximal amount of exposure and the study of the combined effects of these substances on dark adaptation and night vision;

- Study of the potential effects of interaction of noxious environmental contaminants with military prophylactic or therapeutic drug regimens on dark adaptation and night vision;

- The influence of toxic environmental contaminants or therapeutic drugs on the effective use of optical aids by the soldier under reduced illumination; and

- The effects of climatic extremes and mild hypoxia on night vision and dark adaptation as these relate to military tasks of the soldier.

(See Section III I, p 93).

INDIVIDUAL VARIATION

There is a paucity of information on the normal variations in dark adaptation and night vision in individual soldiers. Future research should include:

- More extensive examination of the range of individual variation in dark adaptation and night vision;
- Study of normal variations in dark adaptation and night vision in soldiers, especially those with combat and field command responsibilities, or special tasks;
- Investigation of the incidence and influence of astigmatism, accommodation defects, and other ophthalmologic deficiencies on the night vision capability of individual soldiers; and
- Analysis of the value of training individuals for night vision capability, recognition of individuals with inadequate or superior night vision capabilities, and assignment of military duties to the best qualified men would lead to more efficient use of night vision devices.

(See Section III J, p 95).

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VII. AUTHOR INDEX

VIII. GLOSSARY

Accommodation	Adjustment of the eye for various distances; specifically, alteration of the convexity of the crystalline lens in order to bring light rays from an external object to a focus on the retina.
Adaptometer	A device for determining the course of dark adaptation and for measuring the minimum light threshold perceived.
After-image	The subjective sensation image of an object that persists after the object has disappeared or the eyes are closed. See retinal noise.
Amblyopia	Dimness of vision; partial loss of visual acuity or "sight," in the absence of correctable defects or organic lesions in the eye structure and optic nerve.
Bleaching	Refers to the change in color of the retinal surface that occurs when light photolyzes rhodopsin to photoproducts. Although chemically ambiguous, bleaching generally refers to the photolysis of rhodopsin to N-retinylidene + opsin.
Cycloplegia	Paralysis of the ciliary muscle of the eye; loss of ability to accommodate.
Dark adaptation	Adjustment of the eye occurring under reduced illumination in which sensitivity to light is increased.
Ergastoplasm	Cytoplasmic area of the inner segment of the photoreceptive cell where protein synthesis occurs.

Fovea centralis	Central pit; a central depression in the macula lutea of the retina.
Golgi apparatus	Intracellular membrane-limited vesicles that are thought to function in synthesis, secretion, or storage of cellular products.
Luminance (B)	= 0.3142 millilambert. The luminous intensity of a surface in a given direction per unit of projected area; luminance refers to the "effectiveness" of a given light on the eye, regardless of its origin.
Mesopic vision	Vision with both rod and cone cells functioning.
Micelle	Super-molecular colloidal particle, usually a packet of chain molecules in parallel arrangement.
Millilambert	A unit of brightness; 1/1000 of the value of 1 lambert; 1 lambert is equal to $1/\pi$ candela per cm^2 or lumens/cm^2.
Miosis	Excessive contraction of the pupil.
Mydriasis	Dilation of the pupil.
Opsin	The protein moiety of the visual pigment.
Phagosomes	Distinct inclusion bodies within cells of the pigment epithelium that destroy photoreceptive discs; cf. Ref. 88.
Phoria	The direction of one eye, its line of sight, or some other reference axis, in relation to the other eye; manifested in the absence of an adequate fusion of visual stimuli.
Photochemical	Pertaining to a chemical reaction induced or markedly accelerated by reception of radiation energy, usually ultraviolet, visible, or rarely, infrared.

Photoconduction	Light-induced excitation of electrons which results in a change in electric potential.
Photon	One quantum of light energy.
Photopic vision	Vision in bright light with light adapted eyes believed to be mediated by the cones of the retina.
Plus-acceptance	The acceptability of a dioptric correction (in a lens prescription or during a visual task) based on criteria related to "blur-redness," discomfort, or other clinical symptoms.
Psychophysical vision test	Test that requires a subjective recognition and response to quantitative changes in luminance.
Quantum	Any emission or absorption of radiant energy in a number of individual discrete quantum events. Each is one single quantum of energy (light frequency x 6.624×10^{-27} erg. sec.). Light is absorbed by pigments in single quanta, each quantum is absorbed by one molecule of visual pigment.
Receptive field	Portion of the retina that produces a response in a ganglion cell.
Retinal noise	Spontaneous excitation of the visual pigment molecules that produces the same effects as light excitation. Related to "dark light" of the retina.
Rhodopsin	Visual pigment of the vertebrate rod cell, composed of 11-cis-retinal and opsin.
Scotoma	A blind or partially blind area within the visual field.

Scotopic Vision	Vision in bright light with light adapted eyes believed to be mediated by the cones of the retina.
Singlet state	A transient excited state where energy absorption has elevated a molecule or atom to a higher level of energy; characterized by electron spin equal to zero.
Summation pool	The concept of a site within the neural layer of the retina where spatial and temporal summation occur as the eye dark adapts; the increased sensitivity or "gain control" inherent in the process of dark adaptation, i.e. neural adaptation, is a consequence of summation of rod signals in the pool.
Surround phenomenon . .	Experimental observation that the light-induced response in the center of a visual field is modified by the photoreceptive response of cells peripheral to that central area.
Threshold	The least light intensity value that will elicit a response or a measurable difference in response. Normally used in reference to:
a) absolute threshold. .	Least light intensity detectable when background is absolutely dark. Also referred to as minimal, minimum, or final threshold.
b) contrast threshold. .	Minimal difference in luminance which can be perceived between two adjacent luminous fields, e.g. stimulus and background lights in a dark adaptation test.
c) increment threshold.	The contrast threshold value determined by presentation of a luminous field in

	which the luminance of both stimulus and background lights are altered by standardized increments.
Triplet state	A transition state in which the electron pairs in the atoms of a molecule are no longer paired as in the singlet state. A molecule can absorb energy and be excited to an upper electronic state - the excited state process. It may return to the ground state in a radiative process (phosphorescence), or without emitting radiation. Excitation energy may be transferred to other chromophores or by participation in photochemical reactions.
Visual acuity	Ability of the eye to focus clearly and sharply on and interpret the shape, size, and relative distance of objects.
Visual threshold	The minimum amount of light that elicits a sensation of light (not to be confused with visual acuity).
Wernicke-Korsakoff Syndrome	Central nervous system disorder resulting from vitamin B_1 (thiamine) deficiency, characterized by disturbed ocular mobility, ataxia, impaired mentality, and occasionally polyneuropathy.

IX. AD HOC STUDY GROUP AGENDA

The agenda for the ad hoc study group meeting held at Beaumont, Federation of American Societies for Experimental Biology, Bethesda, Maryland, on October 8 and 9, included the following topics:

- The physiology and biochemistry of vision
- Theoretical aspects of dark adaptation
- Photochemistry of the dark adapted eye
- Excitation and initiation of neural response
- Vitamin A metabolism in the retina
- Absorption, transport, and storage of Vitamin A
- Problems in methodology and measurement
- Other nutritional factors in dark adaptation and night vision
- Drug effects on dark adaptation and night vision
- Individuality and range of human variation.

X. LIST OF ATTENDEES

AD HOC STUDY GROUP MEETING, OCTOBER 8 AND 9, 1968

ON

A STUDY OF VISION AS RELATED TO DARK ADAPTATION AND NIGHT VISION IN THE SOLDIER

CHAIRMAN

C. Jelleff Carr, Ph.D.
Director, Life Sciences Research Office
Federation of American Societies for Experimental Biology
9650 Rockville Pike
Bethesda, Maryland 20014

CO-CHAIRMEN

Robert E. Hodges, M.D.
Department of Internal Medicine
University Hospitals
University of Iowa
Iowa City, Iowa 52240

Robert E. Olson, M.D.
Professor and Chairman
Department of Biochemistry
School of Medicine
Saint Louis University
1402 S. Grand Avenue
Saint Louis, Missouri 63104

PARTICIPANTS

LTC Robert W. Bailey, MSC
Commanding Officer
U.S. Army Aeromedical
Research Unit
Department of the Army
Fort Rucker, Alabama 36360

George H. Beaton, Ph.D.
Professor and Head
Department of Nutrition
School of Hygiene
University of Toronto
Toronto 5, Ontario, Canada

J. William Boehne
Chief, Special Dietary Foods Branch
Division of Nutrition
Food and Drug Administration
Department of Health, Education, and Welfare
Washington, D.C. 20204

Colonel John E. Canham, MC
Commanding Officer
U.S. Army Medical Research and Nutrition Laboratory
Fitzsimons General Hospital
Denver, Colorado 80240

John E. Dowling, Ph.D.
Department of Ophthalmology
School of Medicine
Johns Hopkins University
Baltimore, Maryland 20018

Kenneth D. Fisher, Ph.D.
Research Associate
Life Sciences Research Office
Federation of American Societies for Experimental Biology
9650 Rockville Pike
Bethesda, Maryland 20014

John C. Forbes, Ph.D.
Professor Emeritus
Medical College of Virginia
3304 Chiswick Court
Silver Spring, Maryland 20906

Lt. Donald E. Furry, MSC
Bureau of Naval Medicine and Surgery
Office of the Assistant Chief for Aerospace Medicine
Aerospace Physiology Training Branch
Potomac Annex
Department of the Navy
23rd and E Streets, N.W.
Washington, D.C. 20390

Sidney Futterman, Ph.D.
Associate Professor
Department of Ophthalmology
School of Medicine
University of Washington
Seattle, Washington 98105

DeWitt S. Goodman, M.D.
Associate Professor
Department of Medicine
College of Physicians and Surgeons
Columbia University
New York, New York 10032

Peter Gouras, M.D.
Head, Section on Ophthalmology Physiology
Ophthalmology Branch
National Institute of Neurological Diseases and Stroke
National Institutes of Health
Bethesda, Maryland 20014

Philip L. Harris, Ph.D.*
Director, Division of Nutrition
Food and Drug Administration
Department of Health, Education, and Welfare
Washington, D.C. 20204

* Present address:
Nutritional Consultant
3122 Buch Street, N.W.
Washington, D.C. 20015

Tyron E. Huber, M. D.
Director, Office of Biomedical Studies
Federation of American Societies for Experimental Biology
9650 Rockville Pike
Bethesda, Maryland 20014

James Edward Huff, Ph. D.
Research Associate
Life Sciences Research Office
Federation of American Societies for Experimental Biology
9650 Rockville Pike
Bethesda, Maryland 20014

LTC Benjamin Kislin, MC
U.S. Air Force School of Aerospace Medicine
Department of the Air Force
Brooks Air Force Base, Texas 78235

Leland J. Kitchen, Ph. D.
Second Vice President
The Chase Manhattan Bank
National Association
1 Chase Manhattan Plaza
New York, New York 10015

Major Leonard Kowalski
Education Division
U.S. Air Force School of Aerospace Medicine
Department of the Air Force
Brooks Air Force Base, Texas 78235

Edward F. MacNichol, Jr., Ph. D.
Director
National Institute of Neurological Diseases and Stroke
National Institutes of Health
Bethesda, Maryland 20014

LTC John T. Miller
Combat Materiel Division
Office of the Chief of Research and Development
Department of the Army
The Pentagon
Washington, D. C. 20310

Colonel Robert W. Neidlinger, MC
Chief, Laser Section
Surgical Research Branch
U.S. Army Medical Research and Development Command
Office of The Surgeon General
Washington, D. C. 20315

W. E. J. Phillips, Ph. D.
Food and Drug Directorate
Department of National Health and Welfare
Tunney's Pasture
Ottawa 3, Ontario, Canada

Oswald A. Roels, Ph. D.
Associate Chairman
Marine Biology
Lamont Geological Observatory
Columbia University
Palisades, New York 10964

William A. H. Rushton, Sc. D.
Institute of Molecular Biophysics
Florida State University
Tallahassee, Florida 32306

W. Mitchell Sams, Jr., M. D.
Section of Dermatology
Mayo Clinic
Rochester, Minnesota 55901

Howerde E. Sauberlich, Ph. D.
Chief, Chemical Division
U. S. Army Medical Research and
Nutrition Laboratory
Fitzsimons General Hospital
Denver, Colorado 80240

George Wolf, D. Phil.
Associate Professor of Physiological
Chemistry
Department of Nutrition and Food
Science
Massachusetts Institute of Technology
Cambridge, Massachusetts 02139

Stephen Yeandle, Ph. D.
Deputy Head
Biophysics Division
Naval Medical Research Institute
National Naval Medical Center
Bethesda, Maryland 20014

EX OFFICIO PARTICIPANTS

Allan L. Forbes, M. D.
Chief, Scientific Analysis Branch
Life Sciences Division
Army Research Office
Office of the Chief of Research and Development
3045 Columbia Pike
Arlington, Virginia 22204

Arthur J. Emery, Ph. D.
Scientific Analysis Branch
Life Sciences Division
Army Research Office
Office of the Chief of Research and Development
3045 Columbia Pike
Arlington, Virginia 22204

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13. ABSTRACT

This technical report was prepared to provide the Life Sciences Division, Army Research Office with a succinct summarization of recent advances in the understanding of dark adaptation and night vision capability.

The scope of the study included: current knowledge of the biochemical and physiological aspects of dark adaptation and night vision, the role of nutrition as it affects dark adaptation, pharmacologically induced alterations of night vision, the effects of smoking and noxious environmental agents on night vision, and individual variability in dark adaptation and night vision capacity.

A synopsis of the review discussions is given. Suggestions are made for future research in these areas.

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Drugs						
Environmental Contaminants						
Individual Variation						
Nutrition						
Retinol (Vitamin A)						
Other Nutrients						
Night Vision						
Photochemistry of						
Neural Excitation in						
Retinol (Vitamin A)						
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MEMORANDUM

TO: Recipients of Life Sciences Research Office Report, "A Study of Vision as Related to Dark Adaptation and Night Vision in the Soldier"

FROM: Kenneth D. Fisher, Research Associate, LSRO

SUBJECT: Error in the Report

There is an error in the glossary on page 160. A definition of "photopic vision" was inadvertently substituted for that of "scotopic vision." The attached gummed label containing the corrected definition should be attached to the top of page 160.

Vision under reduced illumination by the dark adapted eye in which the rod cells of the retina are the photoreceptors.

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