ing therapy, the conjunctival lesions have markedly receded, in many to the point of near disappearance. Those not receiving therapy have shown no improvement.

Description of Group and Procedures

One hundred and sixty-six adults, 17 to 65 years of age were examined for grossly elevated spots. Forty-five were white females; seven, colored females; 107, white males; and seven, colored males. The white individuals were from various racial stock. None regarded themselves as sick, and all attended work regularly. All except three received incomes ranging from $52-95 a month.

Their eyes were examined prior to therapy. Twenty-three persons permitted only gross examination, but are included in the total for calculation of the proportion of gross spot cases. The others were examined with the biomicroscope as well as in the gross. Both types of examination were limited to the area of the bulbus exposed upon extreme rotation in many directions. In addition, the inside of the lower lid of some individuals was examined grossly, but the upper lid was not everted.

Inasmuch as specific skin lesions have been reported as an early manifestation of avitaminosis A, the skin was examined in forty-seven persons with all grades of severity of ocular lesions prior to vitamin therapy. Solely for convenience, the skin examination was restricted to males among those listed for therapy. A brief history of ocular symptoms was likewise taken from these same individuals.

For ascertaining the dietary requirements of vitamin A, dietary records were taken from a selected number representative of the various stages of the conjunctival lesion, as well as those not showing it. On most of the persons with lesions, adaptometer tests were conducted before, at various intervals during, and upon completion of therapy. The results on requirements and the correlation of conjunctival lesions with dark adaptation will appear in subsequent papers.

Because of the gravity of advanced conjunctival changes, all persons with fully developed, elevated Bitot's spots were offered, even urged, to take therapy. A few refused for various reasons; they thus formed a control group for the advanced cases with spots.

Of those individuals showing gross conjunctival changes without spots and those showing only microscopic changes, only a part received therapy. Cases were graded by severity into groups from which individuals to whom therapy was offered were selected at random so that twenty-three of seventy-eight persons received therapy.

Therapy was instituted in one group on September 23 and in a second group on November 1, 1940, and consisted of 100,000 U.S.P. (International) units of pure vitamin A in four capsules of 25,000 units each during the day. For the most part, the therapy was taken in the presence of the dispenser, during the five work days; for over the week-end a supply was given to be taken home. None of the individuals were advised of the nature of their ocular condition and its probable dietary basis. No change in diet was advised, in order that there would be no suggestion or encouragement to take other or additional supplements *ex cathedra,* or to modify dietary habits.

A very few among those receiving therapy, as well as those not receiving therapy, have since become unavailable through departure and could not be further followed. Through some whim, one or two stopped therapy. In all, sixty-one persons are still receiving vitamin A capsules; treatment has been discontinued on the nine now completely restored. Eye examinations have been conducted at intervals on the groups receiving and not receiving treatment; for the former these examinations have formed the basis for terminating therapy.

Ocular Signs and Lesions in Gross "Spot" Cases

Of the one hundred and sixty-six persons examined, sixty-five (39 per cent) had one or more manifest spots.

For the most part, the manifest spot cases include the most advanced cases. By manifest spots is meant grossly perceptible elevated conjunctival spots of distinctive color and characteristic location. Since these patients exhibited different phases of the advanced stage, the observations, both gross and microscopic, are most lucidly and succinctly presented by a composite description. (Figures 1 and 2. These are described on pages 239 and 240.)

Facing bright daylight but not sunlight, most "spot" cases showed definite photophobia and lacrimation most readily elicited, however, upon examination with the slit lamp. Almost all of these patients had previously been aware of these disturbances, but it is striking that so few had noticed the spots until called to their attention.

The caruncle and plica semilunaris were usually swollen and engorged. In many instances the eyelids were swollen. The inferior fornix conjunctivae showed looseness, additional folds, and some congestion.

The vascular network in the conjunctiva was conspicuous; vessels converged radially from the canthus and fornices towards the limbus. These are large, prominent, superficial vessels from which, by close inspection, numerous lesser branches may be seen to ramify and form a fine network. This vascular pattern is distinct, but what at first seems paradoxical, the vascular plexus appears less pronounced and extensive in the eyes with most severe conjunctival involvement. Often in these instances the large vessels seem to reach only half way to the limbus.

Generalized changes varying with severity occurred in the bulbar conjunctiva. In bold outline one part may be elevated in bandlike form above the remaining conjunctiva. There is usually wrinkling or folds, frequently along the line of apposition of the bulbar with the upper margin of the lower palpebrum, although vertical crescentic folds are sometimes seen near the inner canthus. In detail the surface shows further unevenness because the conjunctiva is raised

slightly over the vessels, leaving small shallow depressions in honeycomb pattern within the vascular outlines.

In texture the conjunctival surface may be smooth or rough; invariably it has diminished luster. Its color may be creamy, ivory, white, greenish-white, whitish-green, or bluish-milky, according to severity. Very frequently it is a yellowish orange, taupe, or gray brown with underlying whitish green, due to association with vascularization. In appropriate light the conjunctiva of the partially advanced cases showed opalescence; sometimes it was greenish yellow, sometimes amethyst, but most often it had a silvery or galena hue.

Moreover, in seven cases pigmentation was seen as sharply localized deposits or as a narrow rim following the boundary of the limbus. This occurred only in the colored individuals, never in the white.

Depending on the stage of severity, the conjunctiva showed changes in its transmission of light. In the most advanced cases, it was opaque. The color of the choroid shining through the sclera, indeed most of the vascular network, was completely obscured. Where there was opalescence, the conjunctiva was usually translucent. Frequently the superficial strata of an elevated area appeared as a transparent film, much as if a sheet of cellophane were superimposed on an opaque conjunctiva. Less advanced cases showed various degrees of translucence or diminished transparency.

That the conjunctiva is thickened may be inferred from the following gross manifestations: The irregular surface with its bandlike elevations; the very great depth to which light penetrates in the opalescent cases; the thick superficial transparent film.

Uneven contour, diminished smoothness, lackluster, and wrinkling of the surface, opalescence, localized pigmentation, thickness, changed color, and decreased transmission of light all characterize manifest xerosis conjunctivae.

The large series of "spot" cases with lesions in various gradations

of development presented many intermediate stages of xerosis up to fully developed. In one zone of an eye, the changes may occasionally, in advanced stages, be of a similar degree over the entire area, but for the most part they do not occur uniformly. Because of what appears to be predilection in the site of progression, there are various topical patterns of color, thickness, and transmissibility. Frequently in the nasal zone the conjunctival thickening and opacity is limited to the third adjacent to the canthus. At the equator this may converge to a band which runs to the limbus. Thus, in the less advanced cases, the changes may be limited to a localized segment or band, but later they may extend over the entire zone with the band forming a superstructure. The most marked involvement is near both the canthus and limbus.

The Bitot's spot occurred as part of the same process of conjunctival change. It is a small localized area where the tissue change is most advanced. In the first classification of individuals the criterion was arbitrarily adopted that the area must be elevated above its surrounding tissue in order to be regarded as a Bitot's spot. Its more pronounced color and opacity, as well as its elevation, gives it a rather well-defined border and makes it grossly distinguishable from the remaining altered conjunctiva.

Almost always the spot was located at the junction of the equator and limbus. It was most frequently triangular with the base adjacent to the limbus; but other shapes, such as oval, occasionally occurred. Its surface contour was various; flat, undulatory, ridge, and dome forms occurred about equally. In color the spot was usually white, creamy, yellow, or orange, and almost always it was opaque. It varied in the extent to which it was elevated above the rest of the conjunctiva.

Among the large number of persons the spot was observed in various stages of formation; hence, the variability in size, elevation, and color. In general, the white spots were in the earlier stage of development, while the yellow or orange were in the advanced

stage. Just as the spot occurred in various stages of development, it was associated with various stages of change in the rest of the conjunctiva, but the latter was always less advanced. In the spot cases there was no gross opacity in the cornea.

Considering both the entire conjunctival lesion and the spot jointly, the degree and extent of change were usually not the same in the two zones of the same eye. In eleven persons, one spot occurred; in nine persons, three spots occurred. When two eyes were involved, each with one spot in corresponding zones, nasal lesions were more frequent than temporal. Where spots occurred in all four zones, the nasal lesions were usually more advanced than the temporal. Here the similar zones of the individual's two eyes, e.g., the nasal zones of both eyes, often but not invariably showed a like degree and extent of change. The distribution of cases according to number of spots was as follows: one spot, 11 persons; two spots, 31; three spots, 9; and four spots, 14.

Biomicroscopic Examination. Illumination of the eye with the slit lamp brings out clearly any photophobia and lacrimation.

Upon biomicroscopic examination the large superficial conjunctival vessels were seen to ramify into medium-sized vessels which in turn branched into fine vessels; these medium and fine branches of one vessel anastomosed among themselves and with those of another to form the network. If the conjunctiva is translucent, the vessels can be seen at several levels. Furthermore, the superficial vessels anastomose with deep vessels at various points besides the limbus. The superficial network is more extensive than the deep network. If the conjunctiva is opaque, the several strata of the superficial vessels, as well as the deep vessels, are completely obscured. The greater the impenetrability of the conjunctiva to light, the less prominent the vascular network; thus, paradoxically the more advanced stages of the process appear to have less vascular involvement. All the superficial vessels are dilated and engorged, even in the early stages; this accounts for their gross prominence. Such

deep vessels as may be seen are usually likewise dilated and engorged.

In avitaminosis A the vascular reaction at the limbus, while somewhat similar in tendency to that in ariboflavinosis, shows distinct differences. In the "spot" cases the process instead of occurring all around the limbic circumference is limited to two arcs from 8 to 10 and 2 to 4 o'clock. There is no plexiform tiering; the arcades, failing proliferation, do not extend beyond one layer. This single tier of arcades is not continuous, for here and there anastomosis has failed so that there is an interrupted pattern. Thus it appears as a vascular serration with missing teeth. Furthermore, invasion of cornea by the capillaries was slight, negligible, or absent. Corneal opacity was relatively infrequent. This is not to say that in still more severe cases the vascular reaction at limbus might not be more pronounced. In present cases, however, it was less developed and extensive there than that seen in early ariboflavinosis. Although the avitaminosis A was in an advanced stage with its most pronounced conjunctival change adjacent to the limbus, the vascular reaction there was not of the same order. Unlike that in ariboflavinosis, it was most pronounced in the superficial vessels over the conjunctiva.

Besides the vascular reaction in the grossly elevated "spot" cases, the biomicroscope reveals details of changes seen grossly, as well as those not seen grossly. The topography of the conjunctiva (surface contour) is seen to have areas of localized elevation in the form of a band, spot, or both. Wrinkling, observed grossly, is especially prominent under the biomicroscope, and is located at the line of apposition of the superior border of the lower lid with the conjunctiva bulbi. Small conjunctival cysts when situated superficially may produce a bulge, but more often they are situated deeper. Localized pigment deposits as granules or powder may be seen in some cases.

It is convenient to consider the observations on thickness and light transmission in an entire zone, and then in the spot. When part of the conjunctiva is seen to be elevated, increased thickness is

inferred. Elsewhere thickness may be determined through orientation with deep vessels. Where there are several layers of superficial vessels and opacity obscures the deeper superficial as well as the deep vessels, this may be misleading. Then some of the superficial vessels are apt to be mistaken for the deep, and increased thickness may not be recognized. In almost all instances where a spot was present, there was increased thickness of the conjunctiva over most of that zone.

In the biomicroscopic examination of the conjunctiva it is possible to recognize with slit-lamp illumination three main degrees of transmission of light: transparency, translucency, and opacity. Since the conjunctiva was always examined under tension from rotation of the eye, any diminution of transmission was minimized rather than exaggerated. A transparent conjunctiva illuminated diffusely permitted the scleral landmarks and deep vessels to be seen distinctly. Under focal illumination the conjunctiva itself appeared as a moderate suspension of fine flakes in a clear medium. When translucence prevailed, by diffuse illumination the scleral landmarks and deep vessels were seen indistinctly as through frosted glass, or were almost completely obscured. By focal illumination the conjunctiva presented a uniformly dense suspension of opaque flakes in a turbid medium; with the gradations in translucence there was considerable variability in the size of the flakes, the turbidity of the medium, and the density of the suspension. With opacity, the conjunctiva by diffuse illumination was impervious to light and deep vessels were not visible. Here focal illumination added little to recognition.

Transmission of light was frequently not uniform for the entire area of a zone. For example, on the equator at the midpoint there may be punctate opacities which under indirect illumination are shown to be isolated flocculent clumps. Nor was transmission always uniform throughout the depth of the conjunctiva. The superficial layers of the conjunctiva were often more transmissive than

the deep. By diffuse illumination the larger deep vessels were palel outlined as though frost-covered. Thus, the translucence appears t be mainly in the deep conjunctival layer, or, with the upper laye transparent or translucent, the deep vessels—and probably also th deeper rami of the superficial vessels—may be entirely obscurec Here the opacity is restricted to the deep layers with their surfac having a cottony appearance.

Accordingly, in classifying the transmissiveness of the conjunc tiva with reference to these two strata, the following categories wer used: Tr Tl, Tl Tl, Tr O, Tl O, OO. As may be readily recognized Tr, Tl, and O are abbreviations for transparent, translucent, anc opaque, respectively. The first character of the symbol for eacl category refers to the superficial conjunctival strata; the secon character to the deep. It should be cautioned that where the deej conjunctival layers are less transmissive than the superficial—as ir TrTl, Tr O, or Tl O—an extensive superficial vascular networl may be mistaken for the deep, increased conjunctival thickness ma be overlooked, and an erroneous conclusion reached.

In a zone with a spot, all degrees of transmission were observec in the rest of the conjunctiva. As might be expected, when the spo is in the earliest stage of development, there is least change in th remaining area; when the spot is more fully developed, there i general zonal opacity.

The spot itself, as seen microscopically, shows changes more pro nounced than elsewhere in the conjunctiva. Viewed by diffuse illu mination, it may exhibit scattered dots of opacity; by either foca or indirect illumination these are seen to be due to isolated clump of flocculent material. When farther advanced, the opaque mas may comprise a dense coalescence of flakes with loose aggregate around its border. Developed still more, the spot may appear eithe gelatinous or horny.

In a few instances where gross examination revealed a spot char acteristic in all respects except that it did not project above th

adjacent surface, it was possible by microscope to confirm its identity and to determine whether it was at all elevated. Then, too, in some zones the microscope detected very early opaque spots which were not grossly perceptible. Actually, both these types are true spots in the very early stages, but they are not included in the foregoing data on the number of persons with spots or on the zonal distribution of spots.

Individuals Without Manifest Spots

The conjunctivae of seventy-eight individuals without manifest spots were also examined grossly and microscopically. Presenting many gradations, the observed changes extended over a wide range. Profound gross alterations were seen throughout some zones, never as advanced as in most severe "spot" cases but definitely more pronounced than in early "spot" cases. The most advanced showed extensively the characteristic color changes, lackluster, and opacity. Gross nonelevated spots were observed occasionally at the junction of the equator and limbus. Some persons exhibited only the characteristic superficial vascular network in the conjunctiva. On the whole, the "nonspot" group showed less intensively any of the characteristic conjunctival changes than did the manifest spot group. Indeed, in the mildest stage little or nothing may be seen grossly; the initial changes may be revealed definitely only by biomicroscopic examination.

In practice it was convenient to classify all the "nonspot" cases according to the severity and extent of involvement on the basis of microscopic findings. Severity was judged by the degree of light transmission with transparency, translucency, and opacity representing progressively advancing stages. Where transmission differed in the superficial and deep conjunctival layers, that in the latter was regarded as decisive. Classification into the three main groups was determined by the most severe state predominating in any one zone. Then subgrouping according to extent was based on

the number of zones showing preponderantly the same condition.

Certain manifestations were noted in association with particular stages. Usually light transmission was in inverse proportion to the thickness of the conjunctiva. The vascular network, as seen microscopically, is least extensive and complex in pattern in the transparent conjunctiva. It appears to be more extensive and elaborate in translucent conjunctivae than in opaque. In opaque conjunctivae the network may seem to be as inconsiderable as in transparent conjunctivae. This is because the opacity obscures most of the network which in actuality is most extensive and elaborate.

In the seventy-eight "nonspot" persons, the microscopic observations on light transmission through the conjunctivae revealed all stages over a broad range. Seventy-seven of them had diminished transmission in one or more zones. Thus, 99 per cent of the "nonspot" group showed definite signs of avitaminosis A. Twelve persons showed only marked translucence in one or two zones. Judged by less strict criteria, which excludes these twelve persons, sixty-five (83 per cent) of the "nonspot" group had marked translucence in three or four zones, or opacity in one or more zones.

Of the 143 persons examined with the biomicroscope, 45 per cent had manifest spots (gross) and another 54 per cent had distinct characteristic microscopic changes. By the method of classification which includes grouping of the "nonspot" cases according to the degree of light transmission, 45 per cent of the persons had one or more spots, 31 per cent had one or more opaque zones, and 23 per cent had one or more markedly translucent zones as determined by microscopic examination. It should be noted that Bitot's spot is merely one stage in manifest xerosis conjunctivae. In some of the "nonspot" group, among a number of those presenting opaque zones upon microscopic examination, the xerosis was of such severity that it was also grossly perceptible.

Changes on Therapy

Upon administration of 100,000 I.U. vitamin A daily to both

"spot" and "nonspot" cases, regardless of severity, the initial changes detectible by microscope were the same. There was diminution of engorgement in the superficial network with vessels still dilated. The circulatory stream did not fill the vessel and its flow was slow; then there was granular circulation followed by beaded or empty vessels. The latter were seen as shadow vessels. With this retardation in flow or disappearance of the stream, the vessels diminished in size. In most instances these vascular changes took place first in that half of the conjunctiva which borders on the cornea. Soon thereafter the entire conjunctiva, which may have been translucent or opaque, became gradually thinner and more transparent. With diminution in thickness of the conjunctiva, cysts and superficial wrinkling are not infrequently seen as transient manifestations. The clearing in the medium advances while recessive changes in vessels are continuing, yet vessels may seem more numerous because many previously obscured by opaque medium now become visible. Gradually the spot diminishes in size, becomes perceptible as an opacity only by microscope, and finally disappears. If the treatment is complete, the conjunctiva becomes smooth, thin, lustrous, much less vascularized, and highly transparent or very slightly translucent.

In persons with gross lesions, several weeks after beginning repair had been followed by microscopic examination, signs could also be recognized by simple inspection. Perhaps the earliest improvement grossly perceptible was in lessened photophobia and lacrimation. Later it was noted that the conjunctiva had changed from opaque white to translucently bluish; at first slight and only in a small area, then gradually increasing in extent and completeness. The decreasing thickness and increasing clarity of the conjunctiva permit the choroid shining through the sclera to be seen. For a time Bitot's spot may appear more prominent because its borders are more sharply outlined and its opacity is cast into sharper contrast by the clearing in the adjacent, somewhat less severely affected conjunctiva. Gradually the spot diminishes in size and disappears. The swelling in the

caruncle and lids recedes. Finally, upon complete recovery, the co junctiva has a bluish-milk shade and has taken on a noticeable lust and sparkle which enliven the eyes and impart an animated expre sion to the face.

It should be noted that the criteria of complete recovery are rigo ous since they are based on microscopic observations: slight tran lucency and thinness of the conjunctiva with inactivity in or absenc of an excess vascularity. After receiving therapy for eight month one person with spots has been completely restored and discharge In all others with spots, the conjunctiva has become less vascula thinner, clearer, and more lustrous. The spots are much diminishe in size; in many no longer grossly elevated; in some detectible onl by microscope. Of the persons with "nonspot" lesions, eight hav been fully restored and discharged. Naturally, since the "nonspot lesions are usually less severe, more in this group were among th first to show complete recovery. Nevertheless, they have require not less than six months' intensive therapy.

In both groups those who have not received therapy have show no improvement.

Following the full recovery of those still receiving therapy, ther will be a more complete report.

The results of the adaptometer tests, under rigid conditions of tes and with specially calibrated instruments, will be published soo in a preliminary report. At this time it may be said that only a fe very high values were found in the total range for the entire grou Not all persons with most advanced xerosis showed high levels, no were high levels restricted to those with most pronounced xerosi

Discussion

The ocular manifestations of avitaminosis A are xerosis conjunc tiva, including Bitot's spot, and xerosis corneae with subsequen corneal turbidity, ulcer, and keratomalacia. There is a very extensiv bibliography dating back over one hundred years on the nomencl ture, etiology, and pathogenesis of the conjunctival and corne

changes, as well as their interrelation, but its presentation will be reserved for a later paper. Yet it is worth while to mention here that all these manifestations in the order enumerated are regarded as successive stages of one process.

Since the present study pertains only to the initial stages, it is appropriate to cite briefly some of the original observations on the conjunctival lesions. Although the first description is usually attributed to Bitot (4) in 1863, Cohn (5) cites sixty prior references to the condition dating back to 1803.

During this time it was known by various names. Some of these, such as xerophthalmos (6), xeroma (7), conjunctiva arida (8), and dry conjunctiva (9), expressed the dryness so often present in the pronounced stage.

Several authors preferred to stress the primary nature of the lesion. Accordingly, from its histogenic character, they denoted it under the descriptive names of cuticular conjunctiva (10), Ueberhäutung der Conjunctiva (11), Hautbildung der Bindehaut (12), skinning over the conjunctiva (9). These terms are highly expressive of its histogenic nature and gross appearance, what is today called the metaplastic character of the epithelium.

Then von Ammon (13), more concerned with differentiating its etiological independence of an inflammatory process than in denoting its essential character, proposed the name of xerosis conjunctivae. In a footnote, he explained: "Xerosis (η ξηρωσῖς), das Trocknen, Austrocknen. Der Herausgeber hofft, dass dieser Name durch die Beschreibung und Charakterisirung der Krankheit sich rechtfertigen wird. Er hat die bekannteren Wörter, Xerophthalmos oder Xeromma (v. ξηρος und ὄμμα), deshalb nicht gewählt, weil die Grichen, da, wo sie dieses Wort gebrauchen, hiermit die in Folge der Entzündung der Bindehaut oder anderer Theile des Auges entstehende Trockenheit dieses Organs bezeichneten." But the choice was not fortunate inasmuch as it was still vague and misleading.

Later Bitot (4) described the conjunctival lesions as epithelial strata or plaques assuming various shapes, but he gave them no name. Subsequent to his publications, several of his contemporaries referred to them as Bitot's spots, a name which has since gained some currency.

At the present time there is no satisfactory nomenclature expressing the true nature of the lesion. Unfortunately, it still retains the designations xerophthalmia and xerosis conjunctivae which are open to misconception because dryness is not its primary or most significant characteristic and is recognizable only in pronounced cases. Moreover, xerophthalmia is not specific for the conjunctival stage since it includes xerosis corneae as well as xerosis conjunctivae.

To some extent Bitot's spots are mentioned in the literature, but such an eponymic designation is not to be recommended. Besides, it applies only to a very particular stage of the conjunctival lesion. Of the three terms still in vogue, xerosis conjunctivae is perhaps the least objectionable to denote the conjunctival lesion, but it should carry a connotation of the fundamental nature of the lesion.

Xerosis conjunctiva, and the more advanced stage xerosis corneae, were reported in association with a series of diseases and were attributed to numerous causes. Within two years of Bitot's observation, Gama Lobo (14) asserted that xerosis occurring in Brazilian slaves resulted from lack of suitable and sufficient food. In the next year Blessig (15) noted that the xerosis appeared preponderantly during the seven-week Lenten fast and receded thereafter. He insisted that it was the consequence of a nutritional disturbance which was not simple inanition, and suggested lack of nitrogenous substances. Calling attention to the severe disturbance of the general nutritive condition so frequently observed with the eye lesions, Förster (16) in 1877 inclined to the view that "nutritive deficiency" was responsible for the ocular changes, comparable to such trophic disturbances as decubitus and diabetic gangrene. Shortly thereafter de Gouvêa (17) declared that xerophthalmia is a natural conse-

quence of the general nutritional disturbance caused by chronic progressive anemia which resulted in part from heavy labor and an insufficient and deficient diet. In the same year Thalberg (18) reported the occurrence of keratomalacia in infants nursed by mothers who gave sufficient milk but were anemic or debilitated by prolonged fasting. Likewise, Schoeler (19) in 1887 observed the ocular lesions in adults who were on restricted or unbalanced diets.

From 1866 to 1904, twelve reports appeared on the successful use of liver or cod-liver oil internally for xerophthalmia (20). In treating more than 1,500 infants with xerosis conjunctivae, Mori (1904) (21) found immediate and specific response to cod-liver oil. Since their diets contained little fat, and they responded to liver oil, he attributed the ocular lesions to inadequate fat. He advanced this hypothesis despite his lack of success with sesame or olive oil.

In 1906 Falta and Noeggerath (22), feeding rats on a "purified" diet, noted the development of a conjunctivitis in the course of their general nutritive decline. Reproducing these results in a further investigation of this possible relationship between the conjunctival disease and diet, Knapp (23) in 1909 drew the interesting conclusion that the eye disorder was due to a specific dietary deficiency of an unknown substance. Then came McCollum and Davis' (24) demonstration that growth was not possible in rats restricted to a standard ration unless a substance contained only in certain fats (fat-soluble A) was included. Shortly, Osborne and Mendel (25, 26) pointed out that inflamed and purulent eyes appeared in animals on diets deficient in the fat-soluble vitamin, one source being cod-liver oil, and disappeared upon administration of it.

Whereas the preceding observations revealed a deficiency of fat-soluble A as the cause of an eye disease, but did not identify the latter with xerophthalmia; other investigations next showed that the ocular disease induced experimentally by a deficient diet was really xerophthalmia, but did not recognize and identify the missing dietary factor as fat-soluble A. Using a diet complete in calories and

known constituents but deficient, as they knew, in certain other unidentified indispensable substances, Freise, Goldschmidt, and Frank (27, 28) asserted that they had experimentally produced keratomalacia. They placed it among the deficiency diseases, but their experiments did not permit them to characterize the deficiency.

Impressed by the low fat content in the diets of his xerophthalmic patients and the striking efficacy of cod-liver oil in an epidemic in Denmark during World War I, Bloch (29), though cognizant of McCollum's results, subscribed to Mori's theory of fat deficiency as the cause of the eye disorder. McCollum and Simmonds (30) thereupon enunciated the view that xerophthalmia in human beings and in rats was analogous, representing a deficiency in vitamin A. They said: "We feel confident that these cases of xerophthalmia reported by Mori and Bloch should be looked upon as a 'deficiency disease' not hitherto recognized in its true relation to diet. It is not, as these authors believe, a 'fat starvation' which produced the condition, but a lack of the unidentified dietary factor, fat-soluble A, which occurs in just those foodstuffs which they observed to possess curative properties."

Night blindness is another ocular manifestation reported as appearing in avitaminosis A. Literally it is failure or imperfection of vision at night or in dim light. There is an older and more extensive recorded history for night blindness than for xerosis. Among the views on its etiology, the nutritional was based on dietary inquiries or observations on effective therapeutic agents.

In old Chinese medicine, chicken or sheep liver was highly recommended as a specific for night blindness; and among the home remedies, chicken-liver extract in honey was popular (31, 32). In 1859 Graefe (33) designated insufficient and poor food as a contributory factor in its causation. Following Bitot's contention that xerosis and night blindness were associated as parts of the same process, it might be expected that both would be attributed to the same cause and that therapy found effective for one would be used

for the other. But, in the main, developments in views on their cause did not proceed in parallel.

Some of the early investigators who put forward the hypothesis of a nutritional etiology of xerosis did not mention any associated night blindness, nor even suggest that the same cause might be responsible for both (16, 18, 19). On the other hand, several of their contemporaries reporting that night blindness appeared under conditions of poor nutrition, as in prisons (34, 35) and after long fasts (36), presented it as an independent entity. From 1863 to 1910 there appeared a series of reports on the beneficial effects of cod-liver oil or liver for night blindness: in one or two xerosis was mentioned but with skepticism or uncertainty over any relationship to night blindness; in most, xerosis was not mentioned; in some, scurvy was cited as a significant associated manifestation (37, 20). Epidemic night blindness was stated by a few to be a consequence of faulty diet, particularly an imbalance (37); one specified fat deficiency (38).

It is true that Blessig (15) in 1866 charged both xerosis and night blindness to a nutritional disturbance occasioned perhaps by a deficiency of nitrogenous substances. Krienes (37) in 1896 attributed concurrent essential night blindness and xerosis to the same causes, of which one was nutritional disturbance. Groenouw (39) in 1904 mentioned the simultaneous occurrence of the two signs on long voyages where the diet was unsatisfactory. Furthermore, de Gouvêa (17) in 1883 and Mori (21) in 1904 reported that both conditions responded to cod-liver oil. Accordingly they stated that the two manifestations had a common cause; the former suggested improper and insufficient food; the latter specified a fat deficiency. These were clear exceptions to the trend to consider night blindness apart from xerosis.

Even during the period from 1913 to 1917 when vitamin A was discovered, when the occurrence of xerophthalmia in A-deficient animals was observed, and when xerosis in persons was found to be

a manifestation of avitaminosis A, any relationship of night blindness to these developments was not at once demonstrated. Perhaps the reason lies in the course of events peculiar to night blindness. Very early it was reported as occurring alone and also in association with numerous diseases. In classifying its appearance under many circumstances the earliest distinction was between idiopathic or epidemic and symptomatic. In 1881 Parinaud (40) suggested that night blindness is dependent on a disturbance of the visual purple in the retina. Treitel (41) in 1885 concluded that it is characterized essentially by a disturbance in dark adaptation. In turn, this was attributed to involvement of the visual purple in the rods.

With the development of several instruments, dysadaptation was found to result from many circumstances; and all the while the classifications of night blindness increased in number and kind. Commenting on the unsuccessful attempts to unify the concepts of night blindness, Birch-Hirschfeld (42) summed up the status in 1917: "The chief difficulty in explaining the nature of night blindness rests on the fact that we are dealing with a symptom rather than a uniform disease produced by a particular etiology." He presented a classification based on eleven causes, each with a different mechanism affecting visual purple. Thus it came to be believed that there were several kinds of night blindness. Acute epidemic or essential night blindness was regarded as due to dietary deficiency. During World War I, however, there were epidemics attributed to nondietary factors. Furthermore, it was pointed out that night blindness and dysadaptation were not synonymous, that disturbance in the transmissive mechanism, apart from the receptive tissue, could bring about night blindness by preventing effective operation of the visual purple.

In 1915 Wietfeld (43) suggested that essential or epidemic night blindness might be due to a lack of vitamins. Upon curing this form with carrot juice or liver, Zak (44) in 1917 stated that it was a manifestation of avitaminosis, although his studies did not permit him to

decide whether it was an independent disease or a symptom of scurvy. Hift (45) laid great emphasis on the concurrence of night blindness and scurvy. At the same time Birch-Hirschfeld (42) likewise specified vitamin deficiency as one of the primary influences in the pathogenesis of night blindness, citing scurvy, beriberi, and keratomalacia as examples without identifying the relation of night blindness. In 1923 Popovitch (46) suggested that it resulted from a deficiency in the fat-soluble vitamin since therapeutically active substances were rich in it. By testing the ability of rats to jump off a table in a dim light, after previous exposure to bright sunlight, Holm (47) demonstrated that vitamin A deficient rats had developed a well-defined night blindness. The administration of vitamin A to them resulted in a disappearance of symptoms. At the same time Fridericia and Holm (48) reported that vitamin A deficient rats placed in the dark after exposure to light showed a retarded regeneration of visual purple. Thus one form of night blindness, with dysadaptation due to impaired regeneration of visual purple, was linked with avitaminosis A.

Very largely on the basis of the latter studies (47, 48), night blindness came to be regarded also as the earliest sign of avitaminosis A. Of the delay in regeneration of visual purple, Fridericia and Holm said: "This symptom is an early one, being manifested as soon as the growth of the young rat stops and earlier than the onset of pronounced xerophthalmic symptoms." Even more emphatic was Holm: "The hemeralopia in the experimental-rats could be detected soon after the alimentation on food without fat-soluble A had begun, ... *at a stage where it was impossible to perceive any other sure signs of avitaminosis* except a slight failure to increase normally in weight."

This view that night blindness is the earliest sign of avitaminosis A gained ready acceptance in clinical medicine. In a text-book (49) on the clinical manifestations of avitaminoses, it is said: " . . . . . bilden sie eine besondere Trias, die allerdings beim gleichen Indivi-

duum nicht immer gleichzeitig, sondern meist in einer bestimmten zeitlichen Reihenfolge: Hemeralopie- Xerophthalmie-Keratomalacie, angetroffen wird." Several reasons probably contributed to this acceptance. Although originally the simultaneous presence of two or all three of the signs in the same person finally came to be noted, there was no common agreement at that time on the sequence of events. Subsequently knowledge concerning night blindness developed separately. Within the past 25 years there have been numerous recorded epidemics of night blindness. In that time there have been few or no reports on any high incidences of xerosis conjunctivae, although there have been recorded outbreaks of xerosis corneae and keratomalacia in which xerosis conjunctivae, alone, as the initial change, must certainly have been present earlier. Emphasis, however, was placed on the more severe stage, keratomalacia; indeed xerophthalmia more and more came to connote more strictly the corneal stage. As an advanced stage, its subsequence to night blindness was not questioned. Furthermore, night blindness was detected because of patient's complaint; but in xerosis conjunctivae, since visual acuity is not markedly affected, the patients are usually not concerned over the symptoms until inquiry directs attention to them.

When night blindness was said to be the earliest sign, it came to mean that it is a manifestation of mild avitaminosis A, either too short in duration or insufficiently severe in degree to produce xerophthalmia (50). This view gave fresh impetus to tests for dark adaptation as a means of detecting avitaminosis A, particularly the subclinical stage. With technical improvements it became possible to measure small deviations in dark adaptation. Since manifest night blindness was regarded as the earliest ocular sign of avitaminosis A, these small changes were understandably interpreted as a still earlier stage of the disturbance. All this has strengthened the notion that night blindness, or dysadaptation, is the earliest change.

Nevertheless, when the entire record of events is carefully con-

sulted, it is proper to raise three questions: Is night blindness a specific manifestation of avitaminosis A? Can night blindness result from vitamin A deficiency alone? Is night blindness the earliest sign of avitaminosis A? Each has a bearing on the usefulness of the adaptometer as a means of detecting subclinical avitaminosis A. The first two questions, however, may be considered jointly.

By almost every investigator of epidemic night blindness, from the very earliest to the more recent, its onset has been attributed to overexposure to bright light (4, 17, 33, 35-40, 42, 47, 48). Its occurrence predominantly among workers exposed to the sunlight for long hours, day after day, as in the fields and at sea, was at once suggestive and convincing. In accord with it were the observations that night-blind patients experienced no difficulty in seeing in early morning although it was much darker than in the evening (17, 48). Throughout the course of expanding and shifting views on the etiology of night blindness, investigators continued to lay stress on light; most of them designated it as the determining or precipitating influence. Deficient diet was regarded until recently only as a contributory factor. Other evidence added support to the view that light was a significant influence. For many years the standard treatment for night blindness was confinement in a dark room for 48 hours, or the use of dark glasses. The prompt efficacy of this treatment gave substance to the views about the influence of light in the causation of night blindness.

On the experimental side, it should be recalled that Fridericia and Holm succeeded in inducing night blindness and dysadaptation in vitamin A deficient rats only after exposing them to intense sunlight for several hours daily over a period of several weeks and then to artificial light for 20 minutes prior to the test (47, 48). Holm declared (47): "Hemeralopia does not develop through lack of fat-soluble-A-vitamin alone; *it is necessary also that the individuals be much exposed to light.*" It may well be that actinic rays have an aggravating effect on avitaminosis A; it should be borne in mind

that such a reaction has been noted in ariboflavinosis and pellagra. In any event, all these observations are pertinent to any consideration of the prevalent view that vitamin A deficiency alone produces night blindness as a specific manifestation. They also raise the question whether the present procedure in the tests for dysadaptation would permit detection of it in the subclinical stage.

The place of night blindness in the sequence of ocular manifestations is a matter fundamental to the early detection of avitaminosis A. When all circumstances are taken into account, it is quite possible that night blindness may not be the earliest ocular change. Reexamination of the very early records brings out the uncertainty in the matter and at the same time indicates the advisability of giving fuller consideration to xerosis conjunctivae. It is well to recall that one hundred years ago clinicians seeking signs for early detection of the syndrome debated this very question of whether night blindness or xerosis conjunctivae is earlier. There was marked divergence of opinion, but the evidence supported equally well, if not preponderantly, the priority of xerosis. For one thing, in Bitot's series of cases, the conjunctival spots occurred without night blindness. Besides, in some cases night blindness appeared only after the xerosis was far advanced. Bitot regarded xerosis as the herald of night blindness.

Although the recorded epidemics of night blindness in which xerosis was not mentioned have doubtless favored acceptance of night blindness as the earliest manifestation of avitaminosis A, the view really hinges on the animal experiments of Fridericia and Holm (47, 48). It should be noted that when they stated (48) that dysadaptation preceded pronounced xerophthalmic symptoms, they meant that dysadaptation preceded corneal involvement, which is an advanced or late stage. Furthermore, when Holm (47) stated that night blindness developed in the rats before any perceptible signs of avitaminosis except retardation in growth, he was judging by three signs not recorded for man: enophthalmus, loss

of ciliary hair, and a peculiar lacrimal secretion. He did not mention looking for xerotic changes in the conjunctivae other than to state that because of physical conditions it is impossible to produce Bitot's spots in rats. Certainly on the basis of neither study can it be said that night blindness precedes xerosis conjunctivae. In fact, the observations, both clinical and experimental, would seem to cast some doubt on the validity of the prevalent view that night blindness is the first ocular sign of avitaminosis A.

Present-day work does not dispel this doubt. In studies on adaptation with sensitive equipment, often the validity of the data on avitaminosis A has not been supported by therapeutic evidence. In other instances it has been shown that small differences supposedly representing improvement from vitamin A therapy were probably learning responses or instrumental artefacts (51, 52, 53).

This background would seem to warrant reopening the question whether xerosis or night blindness is the earlier manifestation. While the old observations serve to revive the issue, they cannot settle it. Then both conditions were diagnosed only in their advanced stages and in a way—xerosis by gross examination and night blindness by history—which is inconclusive on the point of priority. For this it is necessary to have observations with sensitive instruments on early dysadaptation and xerosis, noting their concurrence or order of appearance. With the calibrated adaptometer and the biomicroscope, this became possible. In the present study dysadaptation did not precede the xerosis conjunctivae. Indeed, dysadaptation was not specifically correlated with the degree of conjunctival change.

It is generally accepted that characteristic lesions in the eye are not the only changes in avitaminosis A, nor are they regarded as the first. However, the intimation that skin lesions, under such varied names as follicular hyperkeratosis, phrynoderma, and xeroderma, represent the initial manifestation (54), finds no support from histopathological studies on experimental animals. In the

"spot" cases of the present study, only occasionally were possible dermal lesions noted; then they were so indefinite as to be questionable. None were seen in persons with less severe eye lesions. In the entire series, therefore, gross cutaneous did not precede ocular changes.

In suggesting biomicroscopic examination of the eye as a means of detecting early avitaminosis A, it is not meant to imply that the ocular lesion is the sole, the first, or the most important change. Xerophthalmia is not synonymous with avitaminosis A. Histopathological examinations on both humans and animals have shown that avitaminosis A is characterized by widespread epithelial changes throughout the body, for example, the respiratory, paraocular, and renal, as well as the ocular organs (55, 56, 57). Wolbach and Howe (56) have stated that xerophthalmia is not the earliest manifestation of avitaminosis A in the rat. For human beings there is very little evidence on what is the initial site and the sequence of sites undergoing change.

Nevertheless, among the organs showing early change, the eyes are a favorable site for detecting vitamin A involvement, for they are accessible to observation or test. There is another point of advantage: the initial lesion in the eye occurs in the conjunctiva. Inspection for gross changes, including Bitot's spots, may be used in screening advanced cases, which may be subgrouped, if desired, according to the number of zones affected. Biomicroscopic examination detects subgross changes of all gradations which may be classified according to severity and extent. Hence, by combined gross and microscopic examinations, it is possible to determine all stages of xerosis and thus to grade the avitaminosis A.

Especially does the biomicroscopic examination of the bulbar surface present several additional advantages: (1) it shows the early changes in the conjunctiva—site of the initial ocular lesion in avitaminosis A—that are not visible grossly; (2) it is a rapid, convenient, and objective method for detecting the very early avita-

minosis A; (3) it permits a simultaneous examination of the limbus and cornea for early ariboflavinosis, from which avitaminosis A is easily differentiated; (4) it provides a much-needed means for ascertaining the dietary requirements for both vitamin A and riboflavin.

In the present study, the examination of conjunctivae both grossly and biomicroscopically shows a high prevalence of avitaminosis A in this low-income group. It is so high as to seem at first glance almost incredible, but it is substantiated on several grounds.

In reporting on a national dietary survey Stiebeling and Phipard stated (58): "Taking 6,000 International Units per day as the allowance for the adult man, . . . it is estimated that the lowest 25 per cent of the diets [for all of the white families represented by the study] furnished 2,000 or less International Units a requirement unit a day, and the lowest 75 per cent, less than 4,500 International Units a day." In the cities of the North Atlantic region, including New York City, they found that in the group with a weekly per-capita expenditure for food between $1.25 and $1.87, 67 per cent had less than 2,000 International Units, 20 per cent had between 2,000 and 3,999 Units, and 9 per cent between 4,000 and 5,999 Units. At least 90 per cent were thus receiving less than the estimated required amount of vitamin A. In the present study, the prevalence of avitaminosis A in the comparably low-income group was more than 90 per cent.[2] These figures strikingly bear out the dietary data while the latter, in turn, account for the high prevalence, suggesting that dietary deficiency was largely responsible.

In addition, it is not at all unlikely that in some instances other factors contributed to the prevalence. For example, it is conceivable that certain acute illnesses disturbing the vitamin A economy may have brought on the avitaminosis or accentuated existing lesions so

[2] A lower prevalence would be expected in higher income groups. Upon examination of 25 adults in a medium income group, 16 showed definite conjunctival changes. Five persons in the group had gross spots. It is more than likely that avitaminosis A is one of the more commonly occurring deficiency diseases and is present in a considerable proportion of the population.

that in convalescence even an abundant amount of the essential in the diet would not be sufficient for rapid restoration. With a slightly inferior diet recovery would not be complete for an indefinite period.

Furthermore, with manifest conjunctival lesions in 45 per cent of the persons, a sizeable number with less pronounced changes visible only with the biomicroscope would be expected. But above all, the response of the affected persons to the specific therapy attests to the actuality of avitaminosis A in so large a proportion of the group.

Upon administration of therapy, recession is similar in type to that in ariboflavinosis: obliteration of vessels and dissipation of opacities. The striking feature, however, is the very long period required for complete recovery, a matter of months even with therapy of high potency. This is reasonable considering that when the eyes show such profound change, many epithelial structures throughout the body are known to be simultaneously affected. Restoration of all this epithelium takes time.

These results indicate that complete recovery from this deficiency disease is not so rapid as it is popularly reported. This protracted recovery, even with high dosage of vitamin A, also casts a significant light on therapeutic practice in avitaminoses. Currently it is often asserted that adequate diet corrects deficiency diseases. In a sense this is true if time is no consideration. But if therapy of high potency brings about complete recovery only after an extended period, an optimum diet might be expected to require a very much longer time. It seems necessary to take the view that persons affected with deficiency diseases need intensive specific therapy for most rapid recovery. Obviously, an optimum diet should be instituted for its supplementary nutritive value, its protection against outbreak of other deficiencies, and for establishment of satisfactory dietary practice by the patient. Then when therapy is withdrawn upon recovery, the satisfactory dietary habits suffice for maintenance.

The use here of 100,000 I.U. of vitamin A daily is not to be construed as a recommendation or precedent that this amount is necessary for maximum rapid therapeutic results. In the present study it was essential to administer an amount that would ensure maximum response. It is certain that tissues have critical rates of response and that doses in excess of the amounts satisfying those rates have no further effect. It is common experience that effective therapeutic dosage for an avitaminosis is at least five to six times the maintenance requirement. Actually, therefore, it may be that daily levels of vitamin A between 25,000 and 50,000 I.U., for example, will be found sufficient to produce maximum therapeutic response. That is to be determined.

Summary

Of 143 persons in a low-income group, 45 per cent had gross and another 54 per cent had microscopic ocular lesions characteristic of avitaminosis A. The ocular condition was xerosis conjunctivae.

Following administration of vitamin A as specific therapy to a part of the group, the conjunctival lesions in nine persons have now completely disappeared, as judged in all instances by biomicroscopic examination. In all others receiving therapy, the conjunctival lesions have markedly receded to the point of near disappearance.

In all cases the striking feature is the very long period of time required for complete recovery, a matter of months even with therapy of high potency.

Those persons not receiving therapy have shown no improvement.

It is suggested that xerosis probably precedes night blindness as an early sign of avitaminosis A.

For detection of early avitaminosis A in surveys, the biomicroscopic examination is recommended as a simple, convenient, objective method. When it is combined with gross examination, all degrees of xerosis may be graded according to severity and extent.

The marked prevalence of avitaminosis A in this low-income group, objectifying and validating previous dietary data, suggests its relatively frequent occurrence in the population at large.

References

1. Kruse, H. D.; Palmer, C. E.; Schmidt, W.; and Wiehl, Dorothy G.: Medical Evaluation of Nutritional Status. I. Methods Used in a Survey of High School Students. The Milbank Memorial Fund *Quarterly*, July, 1940, xviii, No. 3, pp. 257-283.

2. Kruse, H. D.; Sydenstricker, V. P.; Sebrell, W. H.; and Cleckley, H. M.: Ocular Manifestations of Ariboflavinosis. *Public Health Reports*, January 26, 1940, 55, pp. 157-169.

3. Sydenstricker, V. P.; Sebrell, W. H.; Cleckley, H. M.; and Kruse, H. D.: The Ocular Manifestations of Ariboflavinosis. A Progress Note. *The Journal of the American Medical Association*, June 22, 1940, 114, pp. 2437-2445.

4. Bitot: Mémoire sur une lésion conjonctivale non encore décrite, coïncidant avec l'héméralopie. *Gazette Hebdomadaire de Médecine et de Chirurgie*, May 1, 1863, 10, No. 18, pp. 284-288. Also *Gazette Médicale de Paris*, July 4, 1863, 18, No. 27, pp. 435-438.

5. Cohn, H.: Ueber Xerosis Conjunctivae. Breslau. Habilitations-schrift. 1868, 43 pp.

6. Schmidt, Joh. Adam: Ueber die Krankheiten des Thränenorgans. Wien, Joseph Geistinger. 1803, 350 pp.

7. Benedict, T. W. G.: Handbuch der praktischen Augenheilkunde. III: Von den chronischen Krankheiten der Augenlieder, der Bindehaut, Kornea, Sklerotika und Regenbogenhaut. Leipzig, Dyk'schen Buchhandlung. 1824, 159 pp.

8. Mackenzie, William: A Practical Treatise on the Diseases of the Eye. From the last London edition, Boston, Carter, Hendee and Company, 1833, 703 pp.

9. Lawrence, W.: A Treatise on the Diseases of the Eye. London, John Churchill, 1833, 364 pp.

10. Travers, Benjamin: A Synopsis of the Diseases of the Eye, and their Treatment: To Which are Prefixed a Short Anatomical Description and a Sketch of the Physiology of that Organ. 2nd edition, London, Longman, Hurst, Rees, Orme and Brown. 1821, 462 pp.

11. Jäger: Uebersicht der in der chirurgischaugenärztlichen Klinik des königl. Universitätskrankenhauses zu Erlangen vom 1. October 1828 bis zum I. October 1829 behandelten Krankheitsfälle und verrichteten Operationen. *Medicinisch-chirurgische Zeitung*, 1830, 1, pp. 28-32.

12. Klingsohr, E.: Die Ueberhautung der Bindehaut. Inaugural-Abhandlung, Erlangen, Kunstmann'schen Schriften. 1830, 36 pp.

13. v. Ammon: Beobachtungen, Ansichten und Zweifel über die Entstehung der Xerosis conjunctivae. *Zeitschrift für die Ophthalmologie*, 1831, 1, pp. 65-79.

14. Gama Lobo: *Gazeta Medica de Lisboa*, August 28, 1865, No. 16, p. 430; September 13, 1865, No. 17, p. 466. Cited by Ullersperger, B.: Brasilianische Augenentzündung. *Klinische Monatsblätter für Augenheilkunde*, 1866, 4, pp. 65-75.

15. Blessig: Ueber Xerose des Bindehautepithels und deren Beziehung zur Hemeralopie. *St. Petersburger Medicinische Zeitschrift*, 1866, 11, pp. 343-354.

16. Förster: Beziehungen der Allgemein-Leiden und Organ-Erkrankungen zu Veränderungen und Krankheiten des Sehorgans. Handbuch der gesammten Augenheilkunde, redigirt von A. Graefe und T. Saemisch, 7; *Pathologie und Therapie* (Theil 5, Capitel XIII), pp. 59-234. Leipzig, Verlag von Wilhelm Engelmann, 1877.

17. de Gouvêa, H.: Beiträge zur Kenntniss der Hemeralopie und Xerophthalmie aus Ernährungsstörungen. *Graefe's Archiv für Ophthalmologie,* 1883, 29 (Abtheilung I), pp. 167-200.

18. Thalberg, J.: Zur Casuistik der durch Inanitionszustände bedingten Hornhautgangrän. *Archiv für Augenheilkunde,* 1883, 12, pp. 315-332.

19. Schoeler: Beitrag zu den xerotischen Hornhautleiden unter Aufführung einer neuen, bisher von mir nicht beobachteten Form dieses Leidens nach Entziehungsdiät. *Berliner Klinische Wochenschrift,* 1887, 24, pp. 979-982.

20. Blegvad, O.: Xerophthalmia, Keratomalacia and Xerosis Conjunctivae. *American Journal of Ophthalmology,* February, 1924, 7 (Series 3), No. 2, pp. 89-117.

21. Mori, M.: Ueber den sog. Hikan (Xerosis conjunctivae infantum ev. Keratomalacie). *Jahrbuch für Kinderheilkunde und Physische Erziehung,* 1904, 59, (9. Band der dritten Folge): pp. 175-195.

22. Falta, W. and Noeggerath, C. T.: Fütterungsversuche mit künstlicher Nahrung. *Beiträge zur Chemischen Physiologie und Pathologie,* 1906, 7, pp. 313-322.

23. Knapp, P.: Experimenteller Beitrag zur Ernährung von Ratten mit künstlicher Nahrung und zum Zusammenhang von Ernährungsstörungen mit Erkrankungen der Conjunctiva. *Zeitschrift für Experimentelle Pathologie und Therapie,* 1909, 5, pp. 147-169.

24. McCollum, E. V. and Davis, M.: The Necessity of Certain Lipins in the Diet During Growth. *The Journal of Biological Chemistry,* 1913, 15, pp. 167-175.

25. Osborne, T. B. and Mendel, L. B.: The Influence of Butter-fat on Growth. *The Journal of Biological Chemistry,* 1913-14, 16, pp. 423-437.

26. Osborne, T. B. and Mendel, L. B.: The Influence of Cod-liver Oil and Some Other Fats on Growth. *The Journal of Biological Chemistry,* 1914, 17, pp. 401-408.

27. Goldschmidt, M.: Experimenteller Beitrag zur Aetiologie der Keratomalacie. *Archiv für Ophthalmologie,* 1915, 90, pp. 354-403.

28. Freise, E.; Goldschmidt, M.; and Frank, A.: Experimentelle Beiträge zur Aetiologie der Keratomalazie. *Monatsschrift für Kinderheilkunde,* 1916, 13, pp. 424-430.

29. Bloch, C. E.: Lidelser hos Smaaborn opstaaet paa Grund af Fedtmangel. Xerophthalmia et Dystrophia alipogenetica. *Ugeskrift for Laeger,* March 1, 1917, 79, pp. 309-325; March 8, 1917, 79, pp. 349-370.

30. McCollum, E. V. and Simmonds, N.: A Biological Analysis of Pellagra-Producing Diets. II. The Minimum Requirements of the Two Unidentified Dietary Factors for Maintenance as Contrasted with Growth. *The Journal of Biological Chemistry,* 1917, 32, pp. 181-193.

31. Lee, T'ao: Historical Notes on Some Vitamin Deficiency Diseases in China. *The Chinese Medical Journal,* September, 1940, 58, No. 3, pp. 314-323.

32. Ishihara, S.: Zur Aetiologie der idiopathischen Hemeralopie bzw. Xerosis conjunctivae. *Klinische Monatsblätter für Augenheilkunde,* 1913, 51, (Neu Folge *15*), pp. 596-603.

33. Graefe, Alfred: Beiträge zum Wesen der Hemeralopie. *Archiv für Ophthalmologie,* 1859, 5, (Abth. I), pp. 112-127.

34. Cless, G.: Die Gesundheitsverhältnisse der höheren Civilstrafanstalten des Königreichs Württemberg. *Deutsche Vierteljahrsschrift für öffentliche Gesundheitspflege,* 1879, 11, pp. 393-407.

35. Dumas, A.-J.-A.: Contribution a l'étude de l'héméralopie essentielle et de son traitement. Thèse pour le doctorat en médecine. Paris, 41 pp. (1889).

36. Kubli, T.: Zur Lehre von der epidemischen Hemeralopie. *Archiv für Augenheilkunde,* 1887, 17, pp. 409-411.

37. Krienes, Hans: Ueber Hemeralopie, speziell akute idiopathische Hemeralopie. Wiesbaden, J. F. Bergmann, 1896, 185 pp.

38. Toporoff, A.: Po voprosu ob etiologii povalnoi kurinoi sliepoti v voiskakh. (On the Question of Epidemic Night Blindness in the Army.) *Voyenno-Meditsinskiy Jurnal,* 1886, 156, (Part 2, Section 3), pp. 27-42.

39. Groenouw, A.: Beziehungen der Allgemeinleiden und Organerkrankungen zu Veränderungen und Krankheiten des Sehorganes: Erkrankungen der Atmungs-, Kreislauf-, Verdauungs-, Harn-, und Geschlechtsorgane, der Haut und der Bewegungsorgane, Konstitutionsanomalien, erblichs Augenkrankheiten und Infektionskrankheiten. *Graefe-Saemisch Handbuch der gesamten Augenheilkunde* (herausgegeben von T. Saemisch), 11, Abteilung 1, Teil I, Seite 1-823. Zweite neubearbeitete Auflage. Leipzig, Wilhelm Engelmann, 1904.

40. Parinaud: L'héméralopie et les fonctions du pourpre visuel. *Comptes Rendus Hebdomadaires des Séances de L'Académie des Sciences,* 93, pp. 286-287. Also *Gazette Médicale de Paris,* 1881, 52, (6. série, tome III), p. 484.

41. Treitel, Th.: Ueber Hemeralopie und Untersuchung des Lichtsinnes. *Graefe's Archiv für Ophthalmologie,* 1885, 31, (Abth. I), pp. 139-176.

42. Birch-Hirschfeld, A.: Ueber Nachtblindheit im Kriege. *Archiv für Ophthalmologie,* 1917, 92, pp. 273-340.

43. Wietfeldt: Avitaminose als Ursache der Nachtblindheit im Felde. *Münchener Medizinische Wochenschrift* (Feldärztliche Beilage), December 14, 1915, 62, (II. Hälfte), p. 1743.

44. Zak, E.: Beobachtungen an Hemeralopie- und Skorbutkranken. *Wiener Klinische Wochenschrift,* 1917, 30, pp. 592-595.

45. Hift, R.: Beobachtungen über Skorbut und Hemeralopie. *Wiener Klinische Wochenschrift,* 1918, 31, pp. 939-942.

46. Popovitch, A.: L'héméralopie de cause alimentaire. *Archives D'Ophtalmologie,* 1923, 40, p. 315.

47. Holm, E.: Demonstration of Hemeralopia in Rats Nourished on Food Devoid of Fat-Soluble-A-Vitamin. *The American Journal of Physiology,* 1925, 73, pp. 79-84.

48. Fridericia, L. S. and Holm, E.: Experimental Contribution to the Study of the Relation between Night Blindness and Malnutrition. Influence of Deficiency of Fat-Soluble A-Vitamin in the Diet on the Visual Purple in the Eyes of Rats. *The American Journal of Physiology,* 1925, 73, pp. 63-78.

49. György, P.: Xerophthalmie und Keratomalacie. Kapitel in: Avitaminosen und verwandte Krankheitszustände. Herausgegeben von W. Stepp und P. György. Berlin, Julius Springer. 1927, 817 pp. (172).

50. Medical Research Council: Vitamins: A Survey of Present Knowledge. Special Report Series, No. 167. London, His Majesty's Stationery Office, 1932, 332 pp.

51. Palmer, C. E. and Blumberg, H.: The Use of a Dark Adaptation Technique (Biophotometer) in the Measurement of Vitamin-A Deficiency in Children. *Public Health Reports,* 1937, 52, pp. 1403-1419.

52. Palmer, C. E.: The Dark Adaptation Test for Vitamin-A Deficiency. *American Journal of Public Health,* 1938, 28, pp. 309-315.

53. Hunt, E. P. and Palmer, C. E.: Medical Evaluation of Nutritional Status. II. Measurement of Visual Dark Adaptation with the Adaptometer. The Milbank Memorial Fund *Quarterly,* October, 1940, 18, No. 4, pp. 403-424.

54. Lehman, E. and Rapaport, H. G.: Cutaneous Manifestations of Vitamin A Deficiency in Children. *The Journal of the American Medical Association,* February 3, 1940, 114, No. 5, pp. 386-393.

55. Leber, Th.: Ueber die Xerosis der Bindehaut und die infantile Hornhautverschwärung nebst Bemerkungen über die Entstehung des Xerophthalmus. *Graefe's Archiv für Ophthalmologie,* 1883, 29, (Abtheilung III), pp. 225-290.

56. Wolbach, S. B. and Howe, P. R.: Tissue Changes Following Deprivation of Fat-Soluble A Vitamin. *The Journal of Experimental Medicine,* 1925, 42, pp. 753-777.

57. Van Leersum, E. C.: Vitamin A Deficiency and Urolithiasis. *British Medical Journal,* November 12, 1927, ii, pp. 873-874.

58. Stiebeling, H. K. and Phipard, E. F.: Diets of Families of Employed Wage Earners and Clerical Workers in Cities. United States Department of Agriculture, Circular No. 507, Washington, D. C., U. S. Government Printing Office, 1939, 140 pp.

Explanation of Figures

Fig. 1. 1st Row, Person A; 2nd Row, Person B. On each row from left to right, the zones are presented in the following order: right temporal, right nasal, left nasal, and left temporal. In each instance the eye has been rotated to expose more completely the particular zone under discussion.

3rd Row, the first two illustrations are the right and left eye, respectively, of Person B. The third and fourth illustrations are the right and left nasal zone, respectively, of Person C, with the eyes rotated temporally. Persons A and B have a spot in each zone, i.e., the nasal and temporal zones of both eyes; C only in each of the nasal zones. They also form a descending series in severity.

Fig. 2. 1st Row, Person D; 2nd Row, Person E; 3rd Row, Person F. On each row from left to right, the first two pictures show the right and left eye, respectively. The third and fourth illustra-

tions are of the right and left nasal zone, respectively, with the eyes rotated temporally.

Spots may be seen in all of the nasal zones of each eye in this series: the rows form a descending series in severity.

The entire series, including both Figures 1 and 2, shows a diminution in the pigmentation of the lesions from Person A to Person F.

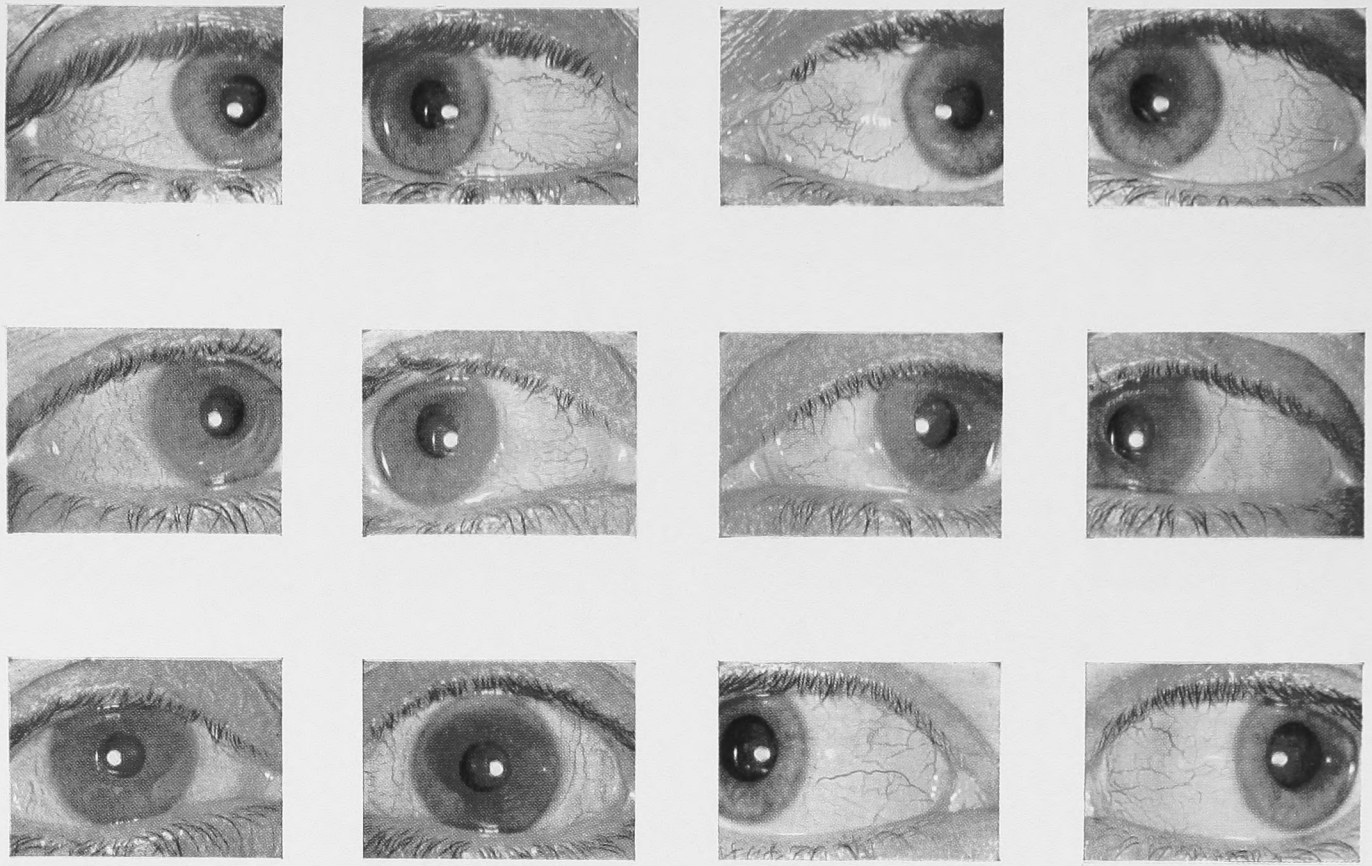

Fig. 1. See explanation on page 239.

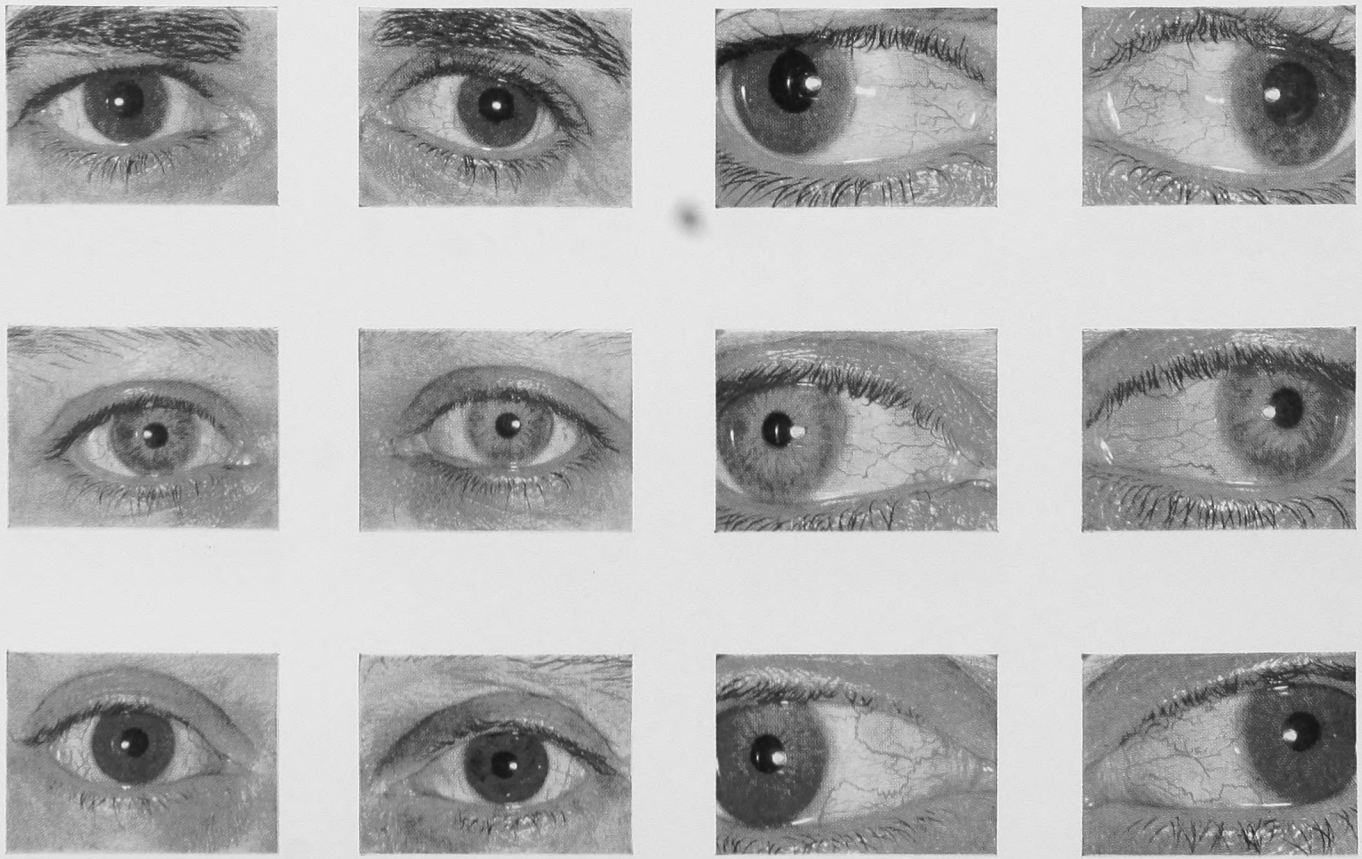

Fig. 2. See explanation on pages 239 and 240.