THE RELATION BETWEEN DARK ADAPTATION AND THE LEVEL
OF VITAMIN A IN THE BLOOD

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The purpose of the present study is to determine
if a relation exists between dark adaptation mea-
surements and the level of vitamin A and total
carotenoids in the blood plasma, in normal subjects
and in patients with cirrhosis of the liver.

It has been established that the retina's ability
to adapt to the dark depends upon an adequate
supply of vitamin A from the diet. The evidence
has been reviewed by Wald and his co-workers
(1), and by Hecht and Mandelbaum (2). Al-
though failures to observe any influence of vita-
m in A intake upon dark adaptation have been
recorded (3 to 5), other studies of experimental
vitamin A deficiency (1, 2, 6 to 10) have shown
that the visual threshold at complete dark adapta-
tion can be elevated greatly by reduced vitamin A
intake. In the latter studies the rate of dark
adaptation remained unaltered.

It has been shown previously (11 to 15) that
patients with cirrhosis of the liver may have
greatly delayed dark adaptation, with or without
elevation of the final threshold. Since in these
patients the response to vitamin A therapy was
characterized by an increase in the rate of dark
adaptation and a decrease in the final threshold
(when originally high), it was concluded that
there exists in cirrhosis of the liver a disturbance
of vitamin A metabolism which differs from ordi-
nary vitamin A deficiency.

It also has been shown that low values for
vitamin A are found in the plasma and liver of
experimental animals with vitamin A deficiency
(16, 17). Moreover, the livers of rats with carbon
tetrachloride cirrhosis have been shown to contain
only half the amount of vitamin A present in the
livers of normal animals fed the same quantity of
food and of vitamin A (18). Likewise, in pa-

tients with cirrhosis of the liver, low values for
vitamin A are found in both the circulating plasma
(19 to 22) and in the liver tissue at autopsy (22
to 26). Since both dark adaptation and the
level of plasma vitamin A are related directly to
the state of nutrition with reference to vitamin
A, it seemed reasonable to expect a degree of
correlation between the two types of measure-
ment.

METHODS

The apparatus and the technique here employed for
measuring the dark adaptation function have been de-
scribed elsewhere (12, 27, 28). The intensity of the
white pre-adapting light was 6,000 millilamberts, and was
viewed by the subject with the right eye for 3 minutes.
The test light, a flash of 0.2 second duration, passed
through a violet filter (Corning No. 511). The retinal
region tested was a circular area whose diameter sub-
tended a 2° visual angle and was located 5° nasally to the
fovea of the right eye of the subject. Both the pre-
adapting light and the test flash were viewed through a
2 mm. artificial pupil placed at a distance of 3 mm. before
the cornea of the subject.

The plasma level of vitamin A and total carotenoids
were determined by a modification of the method de-
scribed by Kimble (29). It was found that shaking the
plasma sample for 15 minutes with the ethanol before
adding petroleum ether insured more complete precipita-
tion of the proteins and more thorough extraction of the
vitamin A and carotenoids. It was also discovered that
using the chloroform and the antimony trichloride solu-
tion at a low temperature (circa 10° C.) delays the
development and fading of the blue color of the vitamin
A-SbCl₅ reaction sufficiently to permit several readings
before the maximum density is attained and passed, thus
making possible a more exact estimate of the maximum
value. The densities were measured in a Bausch and
Lomb spectrophotometer. The vitamin A and carotenoid
levels were expressed as international units (I.U.) and
micrograms (µgm.), respectively, per 100 ml. of plasma.
Whenever a sufficient quantity of plasma was available,
duplicate determinations were made.

All of the patients received highly nutritious diets
which were estimated from food tables (30) to provide
at least 13,000 I.U. of vitamin A daily. None had fever,
jaundice, or diarrhea at the time the tests were made.
The observed abnormal values, therefore, are not attrib-
utable to low intake of the vitamin, to fever, nor to faulty
gastrointestinal absorption due to jaundice or diarrhea.
RESULTS

In Figure 1 are plotted the upper and lower limits of the data of 60 individual dark adaptation tests made on 37 normal persons between the ages of 20 and 45 years. The abscissae are minutes in the dark after cessation of light adaptation, and the ordinates are the logarithms of the threshold intensities expressed in micromicrolamberts (\( \mu \)L). The final threshold is the lowest threshold reading obtained during a stay in the dark sufficiently long to define the entire rod function. The adaptation time is defined as the number of minutes in the dark required for the dark adaptation function to attain a threshold level of 5.50. This parameter obviously possesses both velocity and threshold-level dimensions, and thus serves as an over-all index of the subject's dark adaptation status.

Values for the adaptation time and for the final threshold of the 37 normal persons are given in Table I. When more than one observation was made on an individual, the mean value is given, and the number of observations indicated in parentheses. The adaptation time ranges in value from an average of 9.5 minutes to 15.0 minutes, with a mean of 13.1 minutes. The final threshold values range from an average of 3.95 to 4.42, with a mean of 4.20. For unexplained reasons the values for a single individual may vary in exceptional cases by as much as 3 minutes and 0.4 log unit over a period of several months. However, the usual limits of change over a period of 2 or 3 weeks are approximately \( \pm 0.5 \) minute and \( \pm 0.2 \) log unit.

Within the age limits studied, neither sex nor age appear to exert a significant influence upon either the adaptation time or the final threshold.

The plasma vitamin A values found in Table I are based upon 74 measurements on 44 normal persons between the ages of 20 and 45 years. The values range from 109 to 309 I.U. per cent and have a mean value of 198 I.U. per cent. The amount of variation in single individuals over a period of months may be almost as great as the individual differences shown in the table. Changes as great as 50 per cent have been observed within a period of only one week. This instability of the vitamin A blood level presents a striking contrast to the relative constancy of the dark adaptation function. It is accounted for in part

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**FIG. 1.** THE LIMITS OF 60 DARK ADAPTATION MEASUREMENTS IN 37 NORMAL SUBJECTS

Average values of the parameters designated adaptation time and final threshold for each subject are recorded in Table I.
by a seasonal variation, possibly correlated with diet (31). However, so many departures from the seasonal trend have been noted, that, almost certainly, one or more additional unknown factors must exert an influence upon the level of vitamin A in the blood.

The difference of 30 I.U. per cent between the mean values for men and for women in the plasma vitamin A data of Table I is found to have statistical significance. This confirms similar findings by Kimble (29) and by Murrill and his co-workers (32). On the other hand, the mean plasma carotenoid levels of the two sexes are practically identical, which contrasts with the findings of Kimble and of Murrill et al. of slightly higher values for women than for men.

Within the age limits studied, no significant influence of age upon the plasma vitamin A and carotenoid levels was observed.¹

¹ In another study (33), by a procedure which was calibrated against the present technique, the mean level of vitamin A in the blood of infants between 3 weeks and 6 months of age was found to be 74 I.U. per cent, that for infants between 6 and 18 months of age 110 I.U. per cent, and that for children from 6 to 12 years of age 117 I.U. per cent. When the mean of 198 I.U. per cent here obtained on adult subjects is added to this series, it is apparent that the level of plasma vitamin A rises significantly with increasing age up to the adult level.
TABLE II—Continued

<table>
<thead>
<tr>
<th>Subject</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>Plasma vitamin A</th>
<th>Plasma carotenoids</th>
<th>Adaptation time</th>
<th>Final threshold</th>
</tr>
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<tr>
<td>15C</td>
<td>F</td>
<td>Cirrhosis of the liver</td>
<td>47</td>
<td>133</td>
<td>26.5</td>
<td>4.20</td>
</tr>
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<td>16C</td>
<td>F</td>
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<td>62</td>
<td>291</td>
<td>21.8</td>
<td>4.25</td>
</tr>
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<td>F</td>
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<td>100</td>
<td>179</td>
<td>19.8</td>
<td>4.40</td>
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<td>16F</td>
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<td>63</td>
<td>270</td>
<td>17.0</td>
<td>4.40</td>
</tr>
<tr>
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<td>Cirrhosis of the liver</td>
<td>161</td>
<td>66</td>
<td>12.5</td>
<td>4.00</td>
</tr>
<tr>
<td>36C</td>
<td>M</td>
<td>Cirrhosis of the liver</td>
<td>47</td>
<td>135</td>
<td>19.0</td>
<td>4.10</td>
</tr>
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<td>17.5</td>
<td>4.20</td>
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<tr>
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<td>93</td>
<td>166</td>
<td>14.5</td>
<td>4.80</td>
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<td>Cirrhosis of the liver</td>
<td>27</td>
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<td>14.0</td>
<td>5.00</td>
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<tr>
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<td>58</td>
<td>18.0</td>
<td>4.30</td>
</tr>
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<td>60</td>
<td>57</td>
<td>19.4</td>
<td>4.50</td>
</tr>
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<td>55C</td>
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<td>44</td>
<td>15.1</td>
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</tr>
<tr>
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<td>Cirrhosis of the liver</td>
<td>116</td>
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<td>4.90</td>
</tr>
<tr>
<td>57C</td>
<td>M</td>
<td>Cirrhosis of the liver</td>
<td>164</td>
<td>79</td>
<td>10.4</td>
<td>4.50</td>
</tr>
<tr>
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<td>85</td>
<td>42</td>
<td>18.8</td>
<td>4.24</td>
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<td>36</td>
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<tr>
<td>61C</td>
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<td>Cirrhosis of the liver</td>
<td>98</td>
<td>40</td>
<td>24.0</td>
<td>4.90</td>
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<td>Cirrhosis of the liver</td>
<td>89</td>
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<td>12.5</td>
<td>4.40</td>
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<tr>
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<td>Cirrhosis of the liver</td>
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<td>28</td>
<td>13.1</td>
<td>4.30</td>
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<td>Nephrasis</td>
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<td>9.0</td>
<td>3.95</td>
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<td>4.05</td>
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<tr>
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<td>F</td>
<td>Diabetes mellitus</td>
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<td>16.7</td>
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</tr>
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<td>97</td>
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<td>Urolithiasis</td>
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<td>56</td>
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<td>4.35</td>
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<tr>
<td>27H</td>
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<td>Urolithiasis</td>
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<td>4.35</td>
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<td>75</td>
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</tr>
<tr>
<td>52H</td>
<td>F</td>
<td>Hyperthyroidism</td>
<td>173</td>
<td>58</td>
<td>15.5</td>
<td>4.10</td>
</tr>
<tr>
<td>52H</td>
<td>F</td>
<td>Hyperthyroidism</td>
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<td>37</td>
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<td>3.67</td>
</tr>
<tr>
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<td>F</td>
<td>Hyperthyroidism</td>
<td>162</td>
<td>50</td>
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<td>4.10</td>
</tr>
<tr>
<td>53H</td>
<td>F</td>
<td>Myxedema</td>
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<td>145</td>
<td>13.0</td>
<td>4.16</td>
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<tr>
<td>54H</td>
<td>F</td>
<td>Myxedema</td>
<td>170</td>
<td>133</td>
<td>16.1</td>
<td>4.50</td>
</tr>
<tr>
<td>71H</td>
<td>M</td>
<td>Anomalous portal vein</td>
<td>166</td>
<td>179</td>
<td>14.8</td>
<td>4.50</td>
</tr>
</tbody>
</table>

shows the relation of the plasma vitamin A values to (A) the dark adaptation time, and to (B) the final threshold.

DISCUSSION

When the several groups of subjects are regarded as a single population, the data of Figure 2 show that the higher dark adaptation values
Since the data of the several groups are not randomly distributed over the same range of values, it is apparent that the correlations arise from a tendency of the data to group themselves according to the separate clinical categories, the cirrhotics being at one end of a series and the normals at the other. This tendency for patients with cirrhosis of the liver to have higher dark adaptation and lower plasma vitamin A values than normal controls has been previously observed (22). However, in the previous study the dark adaptation and vitamin A values were not measured simultaneously.

Similar correlations between dark adaptation measurements and the plasma vitamin A level have been reported previously by others. It is possible that these correlations, like those of the present data, are attributable to other factors rather than to a direct dependence of the retina upon the level of vitamin A in the blood. In the studies by Lindqvist (20), Pett and LePage (34), and Lewis et al. (33), heterogeneous groups of patients (miscellaneous diseases) were also employed. In that by Josephs and his co-workers (35), the subjects were drawn from four different nutritional categories as determined by questionnaires and by economic status.

Evidence that the retinal supply of vitamin A may be largely independent of the level of the vitamin in the blood is provided by the observations of Lewis and his co-workers (36), who found that the retinas of rats on a diet of low vitamin A content retained a maximal quantity of vitamin A, although the plasma level had dropped to an extremely low value. Even more striking is the finding that thyroid extract or α-dinitrophenol administered to patients with delayed dark adaptation, not only lowered the plasma vitamin A and carotenoid levels, but simultaneously increased the speed and extent of dark adaptation (37). Still other factors, enumerated in an earlier report (22), have been shown to influence independently either the dark adaptation or the blood vitamin A level. It nevertheless appears reasonable, when known complicating factors are excluded, to regard dark adaptation values as measures of the utilization of vitamin A by the retina. The level of vitamin A in the blood, on the other hand, has been shown ex-
experimentally to be an index of the amount of the vitamin stored in the liver (16, 17). Thus, the two types of measurement probably record quantitative variations in two quite different aspects of vitamin A metabolism.

**SUMMARY**

Measurements of dark adaptation upon 37 normal persons revealed no sex differential. In determinations of the plasma vitamin A and total carotenoid levels in 44 normal persons, the mean vitamin A level for the women was found to be 14 per cent lower than that for the men, while the mean carotenoid levels were the same in the two sexes.

Sixty-seven simultaneous dark adaptation and plasma vitamin A and carotenoid measurements were obtained in 14 normal persons, 18 persons with cirrhosis of the liver, and 7 persons with various other chronic diseases. Within the cirrhotic and normal groups, separately considered, no significant correlations were observed between the plasma vitamin A or the plasma carotenoid levels and the dark adaptation values. When all of the normal and abnormal subjects were grouped together as a single population, however, a degree of correlation between the dark adaptation measurements and the vitamin A values became apparent. This relation was interpreted as arising from differences peculiar to the several diagnostic groups studied, rather than from a causal relation between the level of vitamin A in the blood and the rate and extent of dark adaptation.

**BIBLIOGRAPHY**


