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A STUDY OF DIET IN RELATION TO HEALTH. DARK ADAPTATION AS AN INDEX OF ADEQUATE VITAMIN A INTAKE

III.—The Relation of Diet to Rate and Extent of Dark Adaptation

BY

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WHEN this investigation was started (March, 1938), there were three main methods in use for studying dark adaptation as an index of vitamin A intake. The modification of Edmund and Clemmesen's method described by Mutch and Griffith (1937) was being used at the Rowett Research Institute as part of the scheme for an extensive dietary and clinical survey. Meanwhile studies of dark adaptation with the Birch-Hirschfeld photometer had been published by Maitra and Harris (1937) with an estimate of frequency of subnormal dark vision in groups of school children. From America reports had appeared of investigations with the new patented modification of the latter photometer, the biophotometer (Jeans, Blanchard and Zentmire, 1937; Jehgers, 1937) and this method was also being used to assess the incidence of vitamin A deficiency in groups of the population. It appeared desirable, therefore, to determine whether the different methods

already in use, applied to the same subjects, would assess similarly their powers of dark adaptation. Dr. L. J. Harris kindly agreed to co-operate and a series of comparative tests was therefore made. In these, Dr. M. A. Abbasy, from Dr. Harris' laboratory, used the Birch-Hirschfeld photometer and biophotometer, with the assistance of members of the staff of the Rowett Research Institute. Members of the present team used the Mutch-Griffith apparatus and the Rowett adaptometer, described in the second paper of this series (Thomson et al., 1939). It should be noted that the new instrument was then being used simply to estimate the threshold attained by the subject after 15 minutes' dark adaptation, five minutes thereafter being allowed for the test.

Assessments were made on 12 adults (members of staff), 12 adolescent boys from an industrial school and 24 school children from a poor quarter in Aberdeen. After 15 minutes in darkness, each subject was tested on the four instruments in the following order:—Rowett adaptometer; Mutch-Griffith photometer; biophotometer; Birch-Hirschfeld photometer. Tests were made on three consecutive days without vitamin A supplementation and again after an interval (one to 11 days in different cases) during which vitamin A was given as two capsules of halibut liver oil daily.* One of the children was not retested after taking vitamin A, on account of illness.

It is not proposed to present the results in detail. They may be briefly summarised as follows:—of the original 48 cases, 19 were assessed normal and 7 subnormal by all methods. Of 47 retested after taking vitamin A, 38 were assessed normal by all methods. The remaining 22 in the first test, and 9 in the second, were each assessed abnormal by one or more methods, but none of them by all four methods.

The two tests coming first in the series selected many more subjects as "deficient" than did the Birch-Hirschfeld photometer and biophotometer. This suggested that the length of the period in darkness, or dim light, prior to the test might be affecting the results. It was, therefore, decided to investigate the matter more fully on the Rowett adaptometer. A few preliminary tests showed that not all subjects were completely dark adapted in 20 minutes, and that the time required for complete adaptation depended on the antecedent illumination in which the subject had been working. For further clarification of the relationship between previous light conditions and the subsequent rate of dark adaptation, we began to time the course of dark adaptation down the light scale on the adaptometer, following

* We have to thank the Crookes' Laboratories, Ltd., for the gift of ample supplies of halibut liver oil capsules.

various antecedent lights. The development of this work, and a description of the final technique, which gives a result independent of previous light conditions, was given in our second paper (Thomson et al., 1939).

Technical difficulties having been overcome, we investigated the relationship between rate of dark adaptation and vitamin A intake. All the work now to be described was done with the full technique, using the E test object.

Determination of Normal Standards of Dark Adaptation.—At the beginning of this work it was tentatively assumed (a) that the vast majority of cases of clinical and subclinical hemeralopia are due to varying degrees of vitamin A deficiency, (b) that there is a quantitative correlation between degree of hemeralopia and vitamin A intake and (c) that all except a few anomalous and pathological cases of hemeralopia can be cured rapidly by administration of a vitamin A concentrate. These assumptions were founded on much previous work on the subject by many workers, e.g., Jeans, Blanchard and Zentmire (1937), Jehgers (1937), Maitra and Harris (1937), Edmund and Clemmesen (1936), Mutch and Griffith (1937). At this time Palmer and Blumberg (1937), using the biophotometer, and Snelling (1936), using the Birch-Hirschfeld photometer, had shown that results were not reliable nor responses to vitamin A administration consistent, but as the methods were open to criticism on grounds of technique, the physiological concepts behind them were not necessarily invalidated.

With these ideas in mind, we carried out tests on a number of subjects to determine the standards of dark adaptation to be expected in normal subjects, i.e., subjects who habitually took a diet such as is considered not to be deficient in vitamin A. This was done on 53 adults (mainly workers in the Rowett Institute), who were all on a good normal diet, some of whom had been taking halibut liver over long periods and all of whom received one week's supplementation of two capsules of halibut liver oil (17,000 I.U. of vitamin A) daily prior to testing. The average curve obtained and the frequency distribution are presented in Tables I and II. The frequency distribution is based on the "time to aperture 2," which was chosen because, firstly, it represents practically complete adaptation and, secondly, most of those who experienced delay in seeing the test object at aperture 2 gave readings to aperture 4 within the same time range as those who completed adaptation in 14 minutes or less. Repeat tests showed that this delay was not due to lack of practice or of concentration. It should be noted, therefore, that it is inadequate to record only the upper portion of the curve, as the slope of this part seems to bear no constant relation to the form

of the remainder. This point is stressed by Tansley (1939) and has already been discussed in our last paper.

As regards sex differentiation, the above group consisted of 32 males and 21 females. The average for the sexes separately, and the deviations from these averages, are very similar, so that we do not think it necessary to present the data separately.

From the above results, we concluded that subjects who were not deficient in vitamin A might be divided into two groups on the basis of "time to aperture 2"; the larger of the groups, 80 per cent. of the subjects, reached that aperture in from 7 to 14 minutes and the distribution about the mean was roughly symmetrical. The other group took longer than 14 minutes, and from the differences in the shape of their curves could be considered as being "anomalous" in some way.

As will be seen, further work made this tentative division difficult to retain. It is, however, roughly the basis on which we distinguish between "normal" and "delayed" adaptation. Over 60 per cent. of all subjects fell within the period of 7 to 14 minutes.

Rates of Dark Adaptation in Children on Different Diets.—Following on this, the method was applied in five areas where the Carnegie United Kingdom Trust Dietary Survey was being carried out. Food surveys had been conducted in these areas, so that the vitamin A consumption of the subjects tested could be roughly assessed. The vitamin A figures given in Table I are calculated as the intake per head per day. In three of these areas, an experimental group of children had been given a general dietary supplement for one year previous to the test, the remainder of the surveyed population acting as controls. In the dietary supplements, the main source of vitamin A was halibut liver oil. Milk, cheese, eggs and vegetables also provided part of the supplement of vitamin A. However inaccurate, therefore, the estimates of dietary vitamin A intake from the unsupplemented diets may be, there is no doubt that the vitamin A intake of the experimental children was much higher than that of the controls. Nor is there any doubt that the vitamin A intake of the Rowett adults and public school boys was much above that of the other unsupplemented groups.

Precautions were taken throughout this survey work that the workers did not know whether the subject being tested was from the "fed" or control group. Thus any possibility of influencing the results through preconceived ideas was eliminated.

The first subjects tested were boys in an orphanage whose normal diet contained about 1,000 I.U. of vitamin A per head per day. A proportion of them had received supplements which were calculated to add 5,000 I.U. to this amount daily. Tests

were conducted in July, 1938, when the extra food had been given for six months, and in January, 1939, when it had been given for a year. The average curves obtained and the frequency distributions are shown in Tables I and II. Owing to boys leaving the institution, the groups were not identical at each test, but 24 boys from the fed group and 23 from the control group were tested on both occasions. Table III presents the detailed data for these.

In the interval between these two tests, the method was applied in other areas as follows:—

(1) On 30 children from a community in South Wales, whose average daily intake of vitamin A was approximately 3,000 I.U. per head per day.

(2) On 50 boys from a private boarding school in the North of Scotland. These boys had been maintained for at least a year previously on a first-class diet and in a first-class environment. The vitamin A content of the diet was approximately 6,000 I.U. per head per day, and this was derived chiefly from actual food-stuffs, not from vitamin A concentrates.

(3) On school children in two rural villages in Aberdeenshire, which are five miles apart and similar as regards size of population and type of inhabitant. In one village the children, for a year previously, had received a school meal which contained about 3,500 I.U. of vitamin A per head per day. Their home diet provided about 1,500 I.U. per head per day. The children from the control village had about 2,500 I.U. per head per day, on an average.

(4) In March, 1939, tests were made on 21 "fed" children and 18 "control" children in Dundee. The average home diets of the fed and control groups contained between about 1,000 I.U. and 1,500 I.U. of vitamin A per head per day. The former received a supplement which provided a further 3,500 I.U. or so per head per day.

The data for these tests are presented in Table I as the average curves for each group, and in Table II as the frequency distributions of the "time to aperture 2." All the children tested adapted ultimately to aperture 2 illumination.

It will be seen that it is not the case that slower average curves are associated with lower average vitamin A intakes. Inspection of the data of individuals shows that there is no correspondence between the frequency distributions about the means of the rate of dark adaptation and of vitamin A intake. For reasons of space we are unable to present the detailed data here. In the groups where supplementary feeding was given, no improvement in the standard was obtained. The only exception to this was the summer test in the orphanage, where the "fed" group did significantly better than the control group. This difference was not maintained six months later.

TABLE I—AVERAGE CURVES

GROUP	No. in Group	Average Vit. A intake, per head per day	APERTURE							
			9	8	7	6	5	4	3	2
Rowett Adults - - -	53	Good normal diet (not analysed)	M. S.	M. S.	M. S.	M. S.	M. S.	M. S.	M. S.	M. S.
			0 51	1 10	2 1	2 53	4 11	5 47	8 44	12 33
Public School - - -	50	6000 I.U.	1 20	2 11	3 23	4 36	6 0	7 45	10 24	13 30
Welsh Group - - -	30	3000 I.U.	1 11	1 44	2 55	3 55	5 34	7 9	9 31	12 58
Aberdeenshire Agriculture Group	33	1500 I.U.	2 7	3 9	4 33	5 39	7 13	9 41	13 17	20 4
	24	+3500 I.U.	1 54	2 54	4 1	5 13	6 39	8 35	12 16	19 56
Dundee Group	21	1000-1500 I.U.	1 24	2 18	3 32	4 41	6 11	7 57	10 53	15 54
	18	+3500 I.U.	1 33	2 23	3 49	4 50	6 17	8 21	11 6	16 36
July 1938, Orphanage, January, 1939	45*	1000 I.U.	0 59	1 28	2 5	3 17	4 35	5 53	8 35	11 14
		+5000 I.U.								
	34*	1000 I.U.	1 9	1 48	2 40	3 41	4 59	6 30	10 4	16 6
	31*	1000 I.U.	1 39	2 28	3 48	4 51	6 24	8 6	10 38	13 40
	37*	+5000 I.U.								
		1000 I.U.	1 30	2 24	3 38	4 49	7 19	7 55	10 25	13 31

* 24 common to both fed groups, and 23 to both control groups.

† Excluding two cases where the intake is more than double the average this figure becomes 2000.

TABLE II—FREQUENCY DISTRIBUTIONS

GROUP	No. in Group	MINUTES TO APERTURE 2																				29	30 or more	
		7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26			27
Rowett Adults -	53	1	2	4	7	17	7	2	3	1	1	2	...	...	2	1	2	...	...	1	...	...	...	...
Public School -	50	...	...	4	3	6	6	3	7	6	5	3	3	...	2	1	...	...	1	...	...	...	...	...
Welsh Group -	30	...	...	...	5	6	4	4	1	4	5	...	1	...	...	...	...	...	...	...	...	...	...	...
Aberdeenshire { Fed -	33	...	...	1	1	...	1	3	3	3	1	2	1	3	...	2	2	2	1	...	1	2	...	1
Agriculture { Control	24	...	1	...	...	...	1	...	2	1	3	2	1	1	3	2	1	...	...	1	...	2	1	1
Dundee Group { Fed -	21	...	1	1	...	2	3	...	1	1	3	4	1	...	...	...	2	1	...	...	...	...	...	1
Control	18	...	...	...	...	1	4	1	4	1	...	4	...	2	...	...	...	...	...	...	...	...	...	1
July, 1938, { Fed -	45	...	1	8	9	11	4	7	4	...	...	...	...	...	1	...	...	...	...	...	...	...	...	...
Control { Control	34	...	...	1	3	8	3	3	3	5	1	...	1	...	1	...	...	...	...	...	...	1	1	3
Orphanage, { Fed -	31	...	...	...	3	7	5	3	3	3	1	2	1	...	1	2	...	...	...	...	...	...	...	...
January, 1939 { Control	37	...	...	3	1	2	9	6	6	3	2	2	1	1	...	...	1	...	...	...	...	...	...	...
TOTAL -	376	1	5	22	32	60	47	32	37	28	22	21	10	7	10	8	8	3	2	2	1	5	2	9

TABLE III—DETAILED DATA FOR ORPHANAGE BOYS TESTED TWICE

GROUP	JULY, 1938									JANUARY, 1939								
	9	8	7	6	5	4	3	2		9	8	7	6	5	4	3	2	
CONTROL	M. S.	M. S.	M. S.	M. S.	M. S.	M. S.	M. S.	M. S.		M. S.	M. S.	M. S.	M. S.	M. S.	M. S.	M. S.	M. S.	
W.B.	- 1 10 2 5	3 5	4 0	5 5	6 30	8 30	11 15	1 58	3 35	5 15	6 43	7 13	8 48	14 17	18 42			
A.T.	- 0 35 0 50	1 40	2 25	3 45	5 3	9 5	14 7	1 4	1 44	2 23	3 56	5 8	7 11	10 0	16 56			
P.F.	- 1 35 2 0	4 35	5 10	6 25	7 25	12 10	16 0	2 8	3 30	5 9	5 47	7 10	8 25	10 13	13 5			
H.B.	- 0 55 1 30	2 13	3 30	4 35	7 0	11 35	18 15	1 20	2 16	3 25	4 40	5 17	6 34	7 37	9 10			
J.K.	- 1 30 1 50	3 5	3 40	5 5	7 10	11 20	15 5	0 58	2 50	3 44	3 59	7 23	9 51	14 14	17 40			
R. McQ.	1 0 1 15	1 50	2 20	2 55	6 0	7 30	10 55	1 42	2 14	3 15	4 31	5 40	8 19	9 10	11 21			
T.G.	- 1 0 1 30	1 45	3 45	5 0	5 45	8 15	9 40	1 25	2 25	3 39	4 33	5 44	8 42	10 45	14 30			
A.D.	- 1 35 2 21	2 55	3 30	4 25	5 20	7 0	9 50	1 3	2 10	3 20	5 30	6 44	8 8	9 48	12 15			
G.G.	- 0 50 3 25	4 0	4 45	5 45	7 35	24 0	54 0	2 4	3 43	4 42	5 37	7 34	8 31	9 50	13 5			
J.T.	- 2 30 2 55	3 25	4 0	5 5	8 30	12 0	36 0	1 11	1 55	4 47	5 15	7 32	8 56	10 42	14 45			
S.G.	- 0 30 1 0	1 40	2 25	2 55	4 10	7 45	11 20	0 24	0 47	1 5	1 32	3 7	4 44	5 43	10 0			
I.K.	- 1 2 1 45	2 35	3 30	5 5	6 15	8 5	27 20	1 45	3 0	4 40	5 16	6 3	8 22	9 44	12 49			
J. McK.	- 1 5 2 10	2 50	3 40	5 20	7 25	10 10	14 35	0 40	1 7	2 11	3 38	6 5	7 35	11 20	12 0			
A.S.	- 1 0 1 25	1 45	2 15	3 30	5 55	8 5	12 20	0 45	1 0	2 15	3 23	4 23	6 5	7 48	12 24			
H.F.	- 0 45 1 25	2 5	3 40	5 5	6 10	8 45	19 40	1 25	1 50	2 21	4 16	5 29	7 54	11 39	17 15			
A.W.	- 1 20 2 5	3 30	4 30	6 0	7 20	9 0	14 35	2 7	3 45	5 29	6 29	8 3	9 4	12 40	15 48			
D.D.	- 1 5 1 20	1 50	3 35	4 50	6 45	9 45	14 25	1 17	2 2	4 6	4 56	6 45	8 31	10 55	13 53			
G.P.	- 1 5 1 20	1 55	5 15	5 50	6 30	10 40	12 0	1 35	2 44	4 59	6 0	6 22	7 52	11 9	12 15			
N.G.	- 0 50 1 45	2 15	3 35	4 25	5 30	7 25	15 10	1 45	2 15	3 56	5 6	7 48	8 13	11 7	13 12			
A.C.	- 1 0 1 30	2 30	3 40	5 0	6 5	8 35	10 50	2 15	3 18	4 30	5 28	7 31	9 29	12 15	13 52			
E.B.	- 1 20 1 45	4 0	4 45	5 30	6 55	9 25	11 5	2 32	3 47	4 38	5 8	6 57	9 13	9 48	11 38			
H.R.	- 1 15 1 40	2 15	3 50	6 5	6 45	7 50	11 20	1 11	1 34	2 34	5 21	7 9	7 48	9 0	12 25			
E.W.	- 2 0 4 35	5 30	6 15	7 35	8 20	9 25	12 45	1 2	1 29	2 31	4 32	6 14	7 16	9 55	11 20			

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TABLE III—*contd.*

GROUP	JULY, 1938									JANUARY, 1939								
	9	8	7	6	5	4	3	2		9	8	7	6	5	4	3	2	
	M. S.	M. S.	M. S.	M. S.	M. S.	M. S.	M. S.	M. S.		M. S.	M. S.	M. S.	M. S.	M. S.	M. S.	M. S.	M. S.	
G.V.	- 1 2	1 27	2 27	3 20	4 56	6 20	8 53	11 12		...	3 17	5 10	6 10	7 32	8 43	10 21	11 30	
J.S.	- 1 40	2 5	2 45	4 20	5 15	6 20	8 20	10 35		2 53	2 15	3 41	4 53	6 14	8 33	10 35	14 53	
R.G.	- 1 15	1 45	2 10	3 0	4 40	6 15	7 48	9 45		1 27	2 8	4 0	4 42	6 20	7 6	9 18	12 25	
A.McK.	- 0 45	1 10	1 35	2 30	4 50	5 55	7 55	9 25		1 7	1 9	1 56	2 33	4 10	6 45	8 7	9 44	
M.H.	- 0 45	1 10	1 40	2 10	2 55	5 25	6 30	9 30		0 47	1 22	3 26	4 43	6 7	8 24	12 13	13 15	
J.S.	- 0 45	1 2	1 50	2 45	3 30	5 50	8 30	11 30		1 23	1 57	3 32	4 55	6 58	7 40	11 50	16 40	
C.M.	- 0 45	1 25	2 0	2 30	4 40	5 30	8 30	13 50		1 6	2 30	4 45	5 23	7 43	8 58	10 24	11 43	
J.H.	- 0 55	1 20	1 58	3 10	4 55	5 58	7 50	10 20		1 10	1 38	3 0	3 42	4 33	7 0	10 26	11 13	
D.D.	- 0 55	1 10	1 50	3 15	4 0	5 20	7 15	10 30		1 40	3 6	4 6	5 28	6 48	8 30	13 9	15 0	
J.L.	- 0 55	1 25	2 20	3 10	4 10	5 40	8 15	13 0		1 36	2 21	3 50	4 49	6 58	8 42	12 34	15 40	
W.R.	- 1 2	1 28	2 50	3 27	4 58	6 44	9 32	13 30		1 27	2 35	3 50	4 42	6 26	7 27	9 58	12 17	
J.McD.	- 1 10	1 35	2 20	3 40	4 55	6 35	8 45	14 10		...	...	...	...	...	...	...	10 35	
E.M.	- 0 55	1 25	1 55	2 50	4 30	6 25	10 5	13 55		...	...	...	...	...	...	...	21 15	
J.R.	- 0 55	1 5	2 15	4 25	5 55	7 30	10 20	13 0		...	...	...	...	...	...	...	...	
S.G.	- 0 55	1 58	2 20	3 55	5 0	6 40	8 55	11 30		1 3	1 41	3 10	3 35	5 20	6 43	8 24	10 7	
R.D.	- 0 55	1 20	2 5	3 50	4 50	6 0	9 0	10 50		1 5	2 5	2 21	4 9	5 44	6 56	7 18	11 19	
H.F.	- 0 55	1 15	1 50	2 40	3 17	5 10	8 44	11 20		1 0	2 1	3 7	4 10	6 18	7 1	9 41	11 10	
D.W.	- 1 0	2 0	3 5	3 35	5 45	7 20	11 0	14 5		1 49	2 58	5 3	5 35	7 23	9 50	13 45	14 8	
G.L.	- 1 45	2 30	2 55	3 45	6 10	6 45	10 0	13 20		...	...	...	...	...	...	...	11 20	
F.C.	- 0 55	1 30	2 10	3 50	4 40	5 40	9 35	12 40		1 20	2 33	3 55	5 15	6 45	8 33	10 39	13 7	
R.R.	- 0 55	1 15	2 10	2 40	3 24	4 15	9 5	12 10		...	...	...	...	...	...	...	11 55	
J.W.	- 1 10	1 20	2 0	3 25	4 30	5 20	8 35	10 45		1 48	2 5	3 38	4 45	6 20	6 55	11 12	20 48	
P.S.	- 0 55	1 5	1 30	2 45	4 40	6 55	9 40	11 30		1 16	2 34	3 36	5 18	6 44	8 26	12 40	17 4	
A.B.	- 0 50	1 50	3 10	4 5	5 0	5 40	9 40	11 30		...	...	...	...	...	...	...	17 53	

Inspection of the detailed orphanage results (Table III) shows that the rate of adaptation in certain individuals changed markedly in the six months between the July and January tests, e.g., G.G., J.T., I.K., J.R., J.W. These changes did not correspond to any known change in the diet or environment. It is noteworthy that the greatest changes are for the better. As a number of these cases were tested twice on each occasion, with excellent agreement between the results, the improvement does not appear to have been due to practice.

Effect of Vitamin A Administration in Individual Cases.—Two groups of children at the orphanage who gave slow curves were intensively treated with vitamin A concentrate and retested at intervals. The first group (four boys) had been on the basal diet for at least one year previously. The second group (two girls and one boy) had been on the supplemented diet for a year. A control group of 5 boys was tested at intervals without receiving any medication. In order that the question of the vitamin A potency of the halibut liver oil might not arise, half the children were given halibut liver oil (18,000 I.U. of vitamin A daily) and half avoleum (12,000 I.U. vitamin A daily).

The results are summarised in Graphs 1, 2 and 3, plotted as "time to aperture 2" against the day of test. It will be seen that no consistent improvement was produced by the vitamin A. Of exceptional interest, however, is the dramatic improvement in two cases in group 2 (Graph 2) which occurred after the ninth day of supplementation. If this improvement was due to vitamin A, the question of a critical dose or of cumulative effect arises. This should be considered in connection with questions of absorption of the vitamin (see discussion).

A similar experiment was carried out for three weeks on four children in Aberdeen. These had a preliminary test; then they were given two capsules of halibut liver oil (about 16,000 I.U. of vitamin A) daily and retested at intervals. The data of this experiment are not complete owing to domestic disturbances in the families concerned. The results are shown in Graph 4 and show fluctuations similar to those obtained in the orphanage. One child in this series should receive special mention (curve marked G.K.). He had been tested six months previously, in summer, during the experimental work on technique, and had given very slow curves on several occasions. The improvement which his performance underwent during the next six months is parallel to one or two cases in Table III. Here, also, there was no obvious change in diet or surroundings, other than the treatment with halibut liver oil which he had during the tests six months earlier, which might account for the change in rate of dark adaptation.

In addition to these data, there are the cases of certain workers at the Rowett Institute who have consistently given very slow

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curves in spite of a good diet and vitamin A supplementation. It has been noted and verified that they show marked changes in rate of adaptation from one time to another which we are unable to assign to any dietary or environmental cause. (But see also page 719.)

GRAPH 1

GRAPH 2.

GRAPH 3.

DATA FOR GRAPHS 1, 2 AND 3

Curve No.	GRAPH I "Unfed" Group		GRAPH II "Fed" Group		GRAPH III Control Group	
	Day of test	Time to Ap. 2	Day of test	Time to Ap. 2	Day of test	Time to Ap. 2
1		M. S.		M. S.		M. S.
	1	17 15	1	16 20	1	14 45
	4	12 23	4	18 23	4	16 0
	9	11 17	9	11 43	10	13 15
	14	10 45	13	11 20	14	12 20
	24	13 19	24	10 45	25	14 58
2	31	12 52	30	11 12	...	...
	1	17 40	1	24 55	1	16 23
	4	17 37	5	22 26	5	16 32
	9	14 38	9	28 50	9	13 11
	14	14 47	11	30 47	14	11 52
	24	12 11	18	20 26	23	14 57
3	31	14 0	25	18 34	...	...
	1	21 57	1	18 24	1	21 15
	4	13 48	5	16 7	5	14 10
	9	14 35	9	24 54	9	15 34
	14	12 53	12	19 38	18	12 42
	24	18 34	18	9 10	24	11 20
4	31	19 4	25	10 35	...	...
	1	18 42	...	...	1	16 56
	8	15 3	...	...	8	15 4
	10	13 25	...	...	14	20 35
	15	14 44	...	...	24	11 39
	23	14 46	...	...	30	11 0
5	30	12 35	...	...	...	...
	1	15 48	...	...	...	...
	3	15 15	...	...	...	...
	8	16 35	...	...	...	...
	12	16 30	...	...	...	...
	23	16 18	...	...	...	...

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GRAPH 4.

DATA FOR GRAPH 4

Curve No.	Day of test	Time to Ap. 2	
		M.	S.
1 (G.K.)	1	24	27
	6	32	50
	9	26	32
	14	24	4
2	1	16	3
	6	24	40
	9	16	32
	14	16	54
3	1	18	15
	6	19	25
	9	24	40
4	1	12	37
	6	18	8
	9	15	0

Discussion

Other Recent Work.—While the work was in progress, numerous observations had been made elsewhere on the relation between dark adaptation and the normal diet, or on the effect of adding vitamin A concentrate to the latter. As there is considerable variation in technique and interpretation among these workers, it is not easy to analyse their results from a physiological viewpoint. The majority of them have not been concerned with the physiology of the test, but were working empirically to ascertain whether or not some particular method gave the desired results.

Broadly speaking, however, the following workers obtained a positive correlation between dietary vitamin A and dark adaptation, or improvement on the administration of concentrates: Frandsen (1937), Toverud (1937), Friderichsen and Edmund (1937), Youmans et al. (1937), Booher and Williams (1938), Corlette et al. (1938), Caussade et al. (1938), Gridgeman and Wilkinson (1938), Groth-Petersen (1938), Haines (1938), Juhász-Schäffer (1938), McKenzie (1938, 1939). It should be noted, however, that Juhász-Schäffer found a similar improvement when wheat germ oil was administered.

Other workers (Poulsen (1937), Snelling (1938), Gantzel (1938), Frazier and Li (1938), Isaacs, Jung and Ivy (1938) and Palmer (1938)) found no correlation between dietary vitamin A and dark adaptation, or no consistent improvement on administration of vitamin A.

Staz (1937), Schuck and Miller (1938), Vanzant (1938) and Kentgens (1938) obtained equivocal results. Vanzant stressed the technical difficulties of the method. Staz studied the dark adaptation of 200 Rand miners, about 20 per cent. of whom showed delay in the first test. When these were retested after seven months 20 per cent. were still defective, but only 4 per cent. were defective at both tests.

Booher et al. (1939), Hecht and Mandelbaum (1939), Wald, Jehgers and Arminio (1938), Jehgers (1937), and Pett (1938) have observed the effect on dark adaptation of an experimental diet low in vitamin A, using various techniques. They all report diminished rate of dark adaptation or a raised threshold after a specific time, the first effects being observed after a period on the diet which varied from 1 day (Hecht and Mandelbaum, 1939) to 124 days (Booher et al., 1939).

There is also considerable doubt about the time required for a "cure" by administration of vitamin A. Thus Wald, Jehgers

and Arminio* obtained a response in about 30 minutes by oral administration of 100,000 I.U. in one dose and complete normality within $2\frac{1}{2}$ hours, whereas Hecht and Mandelbaum found that two months were required for a complete cure and that a single injection of 100,000 I.U. during the period of slow adaptation caused very little and very transient change.

The attempt has been made by certain workers to correlate the vitamin A content of the blood and rate of dark adaptation. Lindqvist (1938) and Juhász-Schäffer (1938) obtained positive results, but these were not confirmed by Baum and McCoord (1939) and Pies and Wendt (1939). Kentgens (1938) found a correlation in the majority of his cases, but showed that certain persons have subnormal dark adaptation even when the blood vitamin A is normal.

It should be noted that, of the above workers, those who used the same instruments are in considerable disagreement as to what constitutes a reliable technique. In no case have they tested their techniques adequately in order to determine the extent and effect of variables other than vitamin A administration, especially the effect of antecedent light. It appears to us that all of these methods must have considerable uncontrolled variables, the extent of which has not been accurately compared with that believed to be due to vitamin A intake. For these reasons, we believe that both positive and negative results should be accepted with reserve.

Effect of Colour.—One point in technique has been examined by us since finishing the survey work. Our method is possibly the only one in which white light was used throughout the study. The Edmund and Clemmesen method and its modification used Tscherning "neutral" glasses, which are reported as blue by Vraa-Jensen (1936).† The Birch-Hirschfeld photometer and the method used by Wald, Jehgers and Arminio employ "neutral" wedges to reduce the light; the biophotometer technique, reducing the light by means of a rheostat, may change the quality of the light at low illuminations; and the method described by Hecht and Schlaer (1938) employs deep violet light.

In order to test whether our negative results might be due to the use of white light in the photometer, a violet filter was inserted behind the diaphragm (Wratten filters 35 and 64), providing a

* Since this paper went to press, Wald and Stevens (Proc. Nat. Acad. Sci. (1939), Vol. XXV, p. 344) have reported observations on another subject which confirm those of Wald, Jehgers, and Arminio; but it is also stated that no night-blindness developed in about half of a group of subjects (number not given) who were similarly treated. The authors cannot account for this difference in response, as all subjects were "saturated" with vitamin A before taking the deficient diet, and hence it was not a question of variable reserves.

† An analysis by us showed a low maximum of transmission at 520 $m\mu$; but they are extremely near to true "neutrality."

cut off at $480m\mu$, corresponding to the quality of light employed by Hecht and Schlaer. In order to obtain sufficient light at the test object a 24 watt 6 volt car headlamp bulb was used in place of the standard bulb, and run from an accumulator. There was no voltage control, so the experimental error was wider than with the standard apparatus, but we did not think it large enough to interfere with the purpose of the experiment. The U test object was used.

Five adults on an adequate diet were tested with white light and immediately afterwards with violet. They were then given 17,000 I.U. of vitamin A daily, as halibut liver oil, for seven to 10 days, and retested. The average curves are presented in Graph 5. From these results it was concluded that aperture 5, using the violet light, was roughly equivalent to aperture 2 on

GRAPH 5.—SAME SUBJECTS, TESTED WITH AND WITHOUT VIOLET FILTER.

DATA FOR GRAPH 5
WHITE LIGHT
VIOLET LIGHT

	9	8	7	6	5	4	3	2	9	8	7	6	5		
I.D.	27/6/39 5/7/39	m. s. 0 55 0 57	m. s. 1 48 1 50	m. s. 2 8 3 24	m. s. 2 58 3 50	m. s. 5 5 4 42	m. s. 6 10 6 28	m. s. 8 33 8 48	m. s. 10 22 12 27	m. s. 5 12 4 23	m. s. 6 4 6 5	m. s. 7 47 8 10	m. s. 9 44 10 10	m. s. 1 42 13 15	17,000 I.U. Vitamin A daily since previous test
A.M.T	27/6/39 5/7/39	0 24 0 30	0 58 0 42	1 30 1 17	2 33 1 37	4 7 3 40	5 50 5 27	7 35 8 5	9 53 8 55	1 40 2 0	2 10 4 8	3 55 5 8	7 48 6 45	9 58 9 5	17,000 I.U. Vitamin A daily since previous test
E.C.O.	28/6/39 6/7/39	0 35 0 28	1 7 0 48	1 24 1 3	1 50 2 13	4 14 4 2	5 11 6 21	7 51 8 16	8 48 9 35	3 14 3 2	4 32 4 56	6 55 6 13	8 45 8 8	10 44 11 7	17,000 I.U. Vitamin A daily since previous test
J.L.	30/6/39 10/7/39	1 31 1 40	2 57 2 40	4 55 4 5	5 46 4 35	7 10 6 25	7 55 8 5	10 10 12 45	12 18 13 20	2 25 5 30	7 25 7 00	10 45 7 50	12 15 10 40	12 42 12 50	17,000 I.U. Vitamin A daily since previous test
E.H.	30/6/39 7/7/39	0 44 0 53	1 11 1 18	1 56 1 57	2 31 3 20	3 1 4 28	5 29 6 58	6 46 7 49	9 40 9 12	4 40 4 28	5 55 5 55	7 22 7 30	9 26 9 43	12 50 11 45	17,000 I.U. Vitamin A daily since previous test
Averages		0 51 0 54	1 36 1 28	2 23 2 21	3 8 3 11	4 43 4 39	6 6 6 40	8 5 9 9	10 12 10 42	3 26 3 53	5 13 5 37	7 21 6 57	9 36 9 5	11 59 11 36	Before Vitamin A ad- ministration After Vitamin A ad- ministration

TABLE IV—EFFECT OF HALIBUT LIVER OIL ON CHILDREN, USING VIOLET LIGHT FOR TESTS

	9	8	7	6	5	
	M. S.	M. S.	M. S.	M. S.	M. S.	
C.B. -	12/7/39 4 35 19/7/39 5 12 26/7/39 5 24	6 30 6 55 7 55	7 30 7 50 8 42	12 25 9 30 9 15	19 20 16 50 17 10	17,000 I.U. Vitamin A daily since previous test. " " " " " " " "
M.B. -	12/7/39 4 50 19/7/39 4 35 26/7/39 2 55	7 7 6 33 5 0	9 20 7 50 6 25	10 40 11 0 7 45	14 20 19 30 14 5	" " " " " " " "
J.A. -	12/7/39 7 55 19/7/39 3 20 26/7/39 5 55	10 8 8 40 8 15	12 4 10 55 9 45	16 14 12 30 13 20	18 37 29 5 16 25	" " " " " " " "
M.M. -	13/7/39 5 30 17/7/39 6 20 24/7/39 5 0	7 0 6 55 6 40	8 3 10 0 7 50	8 55 13 25 10 2	11 20 14 17 14 42	" " " " " " " "
W.M. -	13/7/39 6 45 17/7/39 6 12 24/7/39 5 7	7 55 7 18 6 40	8 55 8 30 7 48	11 35 10 30 9 45	19 0 17 58 16 30	" " " " " " " "
C.S. -	14/7/39 2 25 20/7/39 6 50 27/7/39 6 15	6 51 8 15 6 50	8 55 9 25 7 57	12 17 11 35 9 25	17 47 12 40 11 15	" " " " " " " "
G.B. -	14/7/39 6 50 20/7/39 6 15 27/7/39 6 50	7 57 7 22 3 35	9 17 8 30 4 30	13 4 9 55 6 25	14 5 16 10 7 15	" " " " " " " "
S.B. -	14/7/39 3 24 17/7/39 6 25 27/7/39 0 25	6 55 12 20 0 50	10 12 13 35 7 25	12 8 14 20 7 55	13 10 18 20 10 45	" " " " " " " "
M.B. -	18/7/39 2 35 25/7/39 4 24	5 10 5 20	6 55 6 40	7 25 9 35	14 10 16 25	" " " " " " " "
R.M. -	18/7/39 6 45 25/7/39 4 55	7 15 6 12	7 40 8 18	8 20 9 50	17 17 11 15	" " " " " " " "
S.H. -	13/7/39 6 50 17/7/39 5 42	8 45 8 32	10 35 12 10	13 46 20 32	17 57 21 47	" " " " " " " "

the standard apparatus. Direct measurements of illumination were not made.

Following on this, 12 children from a slum clearance area in Aberdeen were tested with violet light, then given two capsules of halibut liver oil daily for varying intervals, and retested twice during the dosage period (in some cases once). The testing of one child had to be abandoned owing to lack of co-operation. The results for the remainder are shown in Table IV.

It will be seen that there seems to be no very significant difference between the results on white light and on violet light.

Sources of Error.—Apart from the technical differences and errors which have confused the study of this problem, many other difficulties arise to complicate the issue.

The estimation of the amount of vitamin A or its precursors in foodstuffs has not yet reached a high degree of precision; published results for any one foodstuff show a wide range of variation, and it is not possible to be certain that published results are valid for the particular foods in any one diet. In experimental studies in which large doses of concentrates are given, this is not of importance, but it is of importance when attempts are made to correlate the vitamin A or carotene content of natural foodstuffs with dark adaptation.

Absorption and Utilisation.—It is generally held that preformed vitamin A and its precursors are absorbed into the portal circulation and that the liver acts as a store in which conversion of precursors to vitamin A takes place. It has been found that preformed vitamin A is almost completely absorbed from the intestine (Wendt (1937), Wilson et al. (1937); De (1937)) but that only half or less than half of the carotenoids may be absorbed (Wilson et al.; De; Van Eekelen and Pannevis, (1938); Clausen and McCoord (1938)). The absorption of carotene depends upon the simultaneous presence in the intestine of a suitable solvent (Van Eekelen and Pannevis, Wilson et al., De) and the loss of both precursors and of vitamin A in the faeces may be increased by the presence of other substances, such as mineral oil (Andersen, 1938).

Storage.—Little is known about the storage of vitamin A in the human subject, but it is a possibility that fluctuations in response to the administration of vitamin A and to diets low in vitamin A may be due to variable stores or storage capacity. Moore (1937) estimated the vitamin A reserves in 1,000 adult livers and found that these varied greatly in various pathological states. Ellison and Moore (1937) estimated the reserves at

autopsy of the livers of children under 15 with similar results. Work on animals does not give much more information about factors influencing storage. However, Davies and Moore (1937) brought forward evidence that vitamin A reserves in the rat are influenced by previous diet. Chevallier, Choron and Espy (1936) found a seasonal fluctuation of liver reserves in guinea pigs. Thorbjarnarson and Drummond (1938) claimed that storage in the rat was maximal when the diet contained much fat and that choline depleted these stores. Their results, however, were not substantiated by Lease and Steenbock (1939).

Rôle of Vitamin A in Light Perception.—Since the experiments of Fridericia and Holm (1925) who showed that dark adaptation is accompanied by regeneration of visual purple in the retina, it has usually been considered that retinal sensitivity is a simple function of visual purple concentration in the retina. Hecht had shown (1920) that the retinal sensitivity curve of the human subject fits the theoretical curve of a bimolecular reaction and it seemed probable that the bleaching and regeneration of visual purple was due to a reversible bimolecular reaction. The work of Wald (1934) further suggested that vitamin A was one of the breakdown products of visual purple during bleaching and a visual purple—visual yellow—vitamin A cycle was postulated and formed a physiological background to clinical observations that subjective night blindness may be cured by vitamin A concentrates.

Recently, however, there have been critics of this hypothesis. Krause and Sidwell (1938) found no evidence of vitamin A, or substances of a carotenoid nature in the decomposition products of ox visual purple, and suggest that Wald's hypothesis was based on a non-specific colour reaction. Granit et al. (1939), in a series of well controlled experiments on frogs and cats, showed that retinal sensitivity, as measured by the electrical response, is not a simple function of visual purple regeneration, and that the progress of the latter does not fit Hecht's theoretical bimolecular curve. In the cat, the electrical response may be absent when as much as 40 per cent. of the maximum concentration of visual purple is present in the retina.

The Rôle of Substances Other than Vitamin A in Dark Adaptation.—Recently it has been claimed by Stewart (1939) that, whereas dark adaptation bore no relation to vitamin A intake, and administration of concentrates to "slow" subjects had no effect, the addition of large doses of ascorbic acid with the vitamin A caused an immediate response. Kimble and Gordon (1939) claim

that subjects who do not improve under intensive vitamin A administration respond to lactoflavin or to ascorbic acid.†

We find it difficult to support these results for the reason that in our survey reported above general dietary supplements were given, including vitamin C and lactoflavin (in natural food-stuffs). Furthermore, vitamin C saturation tests were made by Dr. J. Pemberton on 62 boys at the orphanage, on 50 of whom hemeralopia tests were also made. The saturation tests showed a complete cleavage between "fed" and "control" boys. Those in the "fed" group were "saturated" with vitamin C in the sense that a marked increase in urinary excretion followed administration of a test dose of ascorbic acid. The controls gave no response and a subgroup of them showed an average deficit of about 1 g. of ascorbic acid. There is no such division in the dark adaptation of the two groups of boys.

Hemeralopia in Pathological Conditions.—It has long been known that clinical night blindness may be associated with icteric conditions. This may be due to depletion of liver stores, or to solution of the visual purple in the presence of bile salts in the blood and its removal from the retina. Haig et al. (1938) report cure of hemeralopia in two of their cases of alcoholic cirrhosis by very high doses of vitamin A by mouth. Bushke (1937) obtained similar results.

Ezickson and Feldman (1937) describe severe hemeralopia in cases of urolithiasis which was not curable by vitamin A administration and postulate a failure of absorption or utilisation rather than a dietary deficiency.

Wohl and Feldman (1939) and Zaffke (1939) find hemeralopia to be associated with hyperthyroidism.

Certain other causes of hemeralopia are known. Thus Duke-Elder (1932) says that clinical night blindness may occur in the following conditions, in addition to vitamin A deficiency: diseases of the eye; congenital and hereditary conditions; pathological changes in the liver; and in association with neurasthenic and functional symptoms where pathological changes and nutritional disturbances are absent.

† Since this paper went to press we have received a paper by Pock-Steen (Geneesk. Tijdschr. Nederl.-Indië (1939), Vol. LXXIX, p. 1986) describing a condition in sprue patients characterised by "twilight blindness," dazzle in bright light, disturbances of accommodation and other abnormalities. There is no response in these cases to vitamin A, but treatment of the sprue by injection of lactoflavin cures all the ocular symptoms. To explain the results the theory is advanced that lactoflavin is the precursor of visual yellow; that visual yellow is the precursor of visual purple, and requires for conversion to visual purple an enzyme and an activator which is vitamin A. Hence, the author says, vitamin A deficiency slows the rate of dark adaptation but does not alter the threshold. Deficiency of lactoflavin (dietary or conditioned, as in sprue) means actual pigment deficiency and may therefore interfere with the extent of adaptation.

Among conditions causing hemeralopia not due to vitamin A deficiency retinitis pigmentosa has long been quoted. But recently some doubt has been cast on this view. Josephson and Freiburger (1937) and Tscherkes (1938) claim to have cured the hemeralopia of retinitis pigmentosa by injection of vitamin A.

There is also a possibility that severe deficiency in childhood may result in permanent hemeralopia. With reference to Hart and Guilbert's observations on domestic animals, Tansley (1939) says that "if the deficiency is allowed to become severe enough to affect the rod structure, the resultant night blindness is, in fact, incurable."

Clinical Night Blindness.—It has long been known that subjective night blindness may frequently be cured by liver or liver oils. More recent confirmation of this observation is given by Fisher (1938) and Vaillant and Gillis (1939).

It appears less certain that hemeralopia is an essential or early part of the vitamin A deficiency syndrome. Thus Ayuyao (1937) describing 393 cases of xerophthalmia in children says that only 44 were night blind, while Sweet and K'ang (1935) found only 50 cases of subjective night blindness in 203 cases of xerophthalmia in adults. Conversely, Aykroyd (1930) quotes Pillat's (1929) observation that of 90 Chinese soldiers complaining of night blindness only 49 showed eye lesions such as Bitot's spots, xerosis or keratomalacia. Aykroyd states that, in Labrador fishermen, night blindness occurs in the majority suddenly and in a severe form and in persons showing no other detectable signs of disease referable to vitamin A deficiency. It is cured, temporarily, within 24 hours, by a single dose of 1-2 oz. crude cod-liver oil. This contrasts oddly with the enormous doses and lengthy time required by Hecht and Mandelbaum (1939) in their four subjects on a diet of low vitamin A content, but it is not possible to draw any conclusions on the extent of cure in Aykroyd's cases except that subjective symptoms disappeared.

It is of interest to note that Aykroyd was unable to determine whether the night blind Labrador fisherman in the dark slowly adapts to the normal threshold. "In practice, a night blind individual does not linger in the dark. . . ." But that a significant degree of dark adaptation did occur is proved by the custom of bandaging one eye during the day so that it could be used at night.

The conclusions of Frazier and Li (1938) are of great interest as they appear to be the only workers who have measured hemeralopia (by the Birch-Hirschfeld method) on subjects who suffered from obvious clinical manifestations of vitamin A deficiency. They do not give full data, but some sentences may

be quoted from their discussion of the subject. "To assume, as others have done, that loss of dark adaptation is invariably present in states of vitamin A deficiency, and that it is a forerunner of other more severe manifestations of the disease is unwarranted. Clinical experience with well-differentiated cases does not support this view. Cases of vitamin A deficiency present themselves without ocular changes. . . . At present the sources of error attending the clinical application of photometry are so many that future developments in instruments and technique must be awaited before dependence can be placed on the data from this source."

Our own observations on subjectively night blind subjects are limited to two adults, but this does not exclude the possibility that there were others equally bad who were not conscious of the condition. Modern conditions of lighting make it difficult to discover hemeralopia. One of these adults remained night blind for months in spite of high doses of halibut liver oil, then suddenly became normal, but unfortunately under uncontrolled conditions which make it doubtful if the cause was vitamin A administration. He did not take any vitamin A concentrates for four months after the "cure" was discovered but did not change appreciably from his new level of dark adaptation.

The other subject, who complained of difficulty in seeing in the dark, and in driving a car at night, was having a good diet, and had been taking two capsules of halibut liver oil (17,000 I.U. vitamin A) daily for $1\frac{1}{2}$ years previously, except during the five weeks prior to her first test. At this time her rate of adaptation was so slow that the observations were not completed. After this test she took halibut liver oil again for seven weeks, which produced a significant improvement, but not a "dramatic" one. For the next week she took 100,000 I.U. of vitamin A daily (as "Vitamin A Oral"—Crookes), returning after that to halibut liver oil. The high dosage produced a marked improvement, but there was a slight relapse three days after returning to halibut liver oil. Finally 100,000 I.U. of vitamin A were injected intramuscularly, and a test was made 17 hours later. On this occasion her performance was completely normal.* The course of her power of dark adaptation is shown in Table V and in Graphs 6 and 7.

We do not propose to comment on these results, except to say that it seems that the hemeralopia in this subject was not due to any *dietary* deficiency of vitamin A. Nor was it due to any known disease or abnormality.

* Owing to the outbreak of war, observations were discontinued, but it is of interest that this subject reported that the "black-out" caused her no unusual inconvenience, and that she was able to go about at night without trouble.

TABLE V
(DATA FOR GRAPHS 6 AND 7)—EFFECT OF VITAMIN A ON A NIGHT BLIND SUBJECT
E. J. F., aged 28 years.

	9	8	7	6	5	4	3	2	
30/6/39	M. S. 2 35	M. S. 4 3	M. S. 4 43	M. S. 6 38	M. S. 11 25	M. S. 18 20	M. S. >60 0	M. S. >30 0	17,000 I.U. Vitamin A daily since previous test.
18/8/39	2 47	4 25	5 40	7 5	8 4	14 55	28 0	0	
22/8/39	1 48	3 0	4 23	5 24	7 52	14 40	19 26	31 25	100,000 "
26/8/39	1 50	3 25	4 0	4 44	6 30	9 22	14 24	17 20	100,000 "
26/8/39	1 10	1 31	3 50	5 10	8 17	13 30	16 32	26 10	17,000 "
30/8/39	1 20	2 5	3 15	4 42	5 55	8 7	10 32	11 45	100,000 " injected 17 hours before test.

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GRAPH 6.

E.J.F., aged 28.

GRAPH 7.

Conclusions

It would appear from our results that neither rate of dark adaptation nor light threshold of the fully dark adapted eye has necessarily a close correlation with intake of vitamin A *in the diet*. Considerable variation may occur in one individual and between individuals on the same diet.

Clinical observations and experiments in vitamin A deficiency have shown that vitamin A and dark adaptation are related. But it seems that in certain cases at any rate the speed and extent of cure of hemeralopia by vitamin A concentrates is subject to considerable variation.

The majority of workers believe that the study of dark adaptation can be used as a test for vitamin A deficiency, but until differences in technique and interpretation of results have been resolved, it is impossible to be certain how far their recorded observations represent physiological facts.

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