this part a quotation from the preface applies most directly. "A feature of the present volume on the physical and philosophical side is its consistent emphasis on the operational point of view and on the fundamental importance of Gibbsian assemblages of independent systems in the physical interpretation of the mathematical formalism." While the reviewer is in complete agreement with the second part of this statement, he does not agree so well with the first part. While it is valuable to know how far operational treatment is possible, one must start somewhere; and in many connections an alternative emphasis, stressing, with Norman Campbell, the theory-fact scheme of treatment of measurement, and allowing such ideas at least as probabilities of unmeasured positions in the theory, seems to be much more convenient, especially as, as Professor Kemble admits, in dealing with probability the operational theory presents difficulties, while an hypothesis-fact picture, such as that of Harold Jeffreys or such as the reviewer believes could be made with the aid of the "likelihoods" of R. A. Fisher, seems much simpler. But these are very much matters of opinion, and the difference may be mainly about words.

The next two chapters, ten and eleven, deal with matrix theory and perturbations not involving the time, including a discussion of the variational method. The following chapter is entitled "Quantum Statistical-Mechanics and the Einstein Transition Probabilities." The first part endeavors, in very small compass, to lay the foundations of statistical mechanics, using the methods of J. v. Neumann and directing the arguments towards a proof that, roughly speaking, as in classical mechanics, an assembly of molecules will tend to a state of statistical equilibrium—in classical mechanics such a proof makes use of the H-theorem or of continuity of path; so in quantum theory, a pure state of such an assembly will after some time be indistinguishable from a Gibbsian mixture. The reviewer finds this argument very difficult reading and has not satisfied himself that the steps all follow, though he feels sure that an argument can be carried through on these lines. He hopes that in some future edition this part of the book may be considerably expanded. He thinks that a discussion of the extension of Gibbs's own arguments, making use of maximum and minimum properties of canonical ensembles, to quantum theory, such as given by Delbrück and Molière, would find a place at this point; though perhaps that would be going further into statistical mechanics than the author intends. This statistical theory is then used to give a mathematically well-grounded first approximation treatment of absorption and stimulated emission of radiation.

The last two chapters contain discussions of electron spin and approximate relativistic theory and a rather detailed discussion of the problem of atomic structure, in which the assumptions and approximations made are carefully stated. The book concludes with appendices on particular mathematical points and name and subject indexes. It is well printed and this reviewer has discovered very few misprints. That, p. xviii, Condon and Shortley's "The Theory of Atomic Spectra" is attributed to "Oxford" instead of "Cambridge" may perhaps be noted.

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SPECIAL ARTICLES

ROD-CONE DARK ADAPTATION AND VITAMIN A

THE association of vitamin A with the visual cycle has by now been firmly established not only indirectly by the occurrence of nightblindness with vitamin A lack,[1] but by the direct chemical identification in the retina of vitamin A and the carotenoid retinene.[2] Because of the presence of nightblindness and of the relation of retinene to visual purple, this association has generally been attributed to the retinal rods, since they mediate vision at low illuminations and contain visual purple.

However, the behavior of the rods and cones is so alike in many visual functions[3] that the association of vitamin A with cone vision also seemed quite probable. This has now been demonstrated by Haig, Hecht and Patek's recent study[4] of the dark adaptation of persons with cirrhosis of the liver. Such individuals are less sensitive to light than normal people, and the loss of sensibility occurs both in cone vision and in rod vision. With substantial additions of vitamin A to the diet, the subjects improve in visual function and become normal. The essential point is that the two retinal systems behave in a parallel manner during the various stages of vitamin A therapy, indicating that vitamin A is just as essential for the restoration of cone visual function as for rod visual function.

In cirrhosis, the flow of vitamin A from food to eye is disturbed by the failure of liver function. One starts with an abnormal visual condition, and by the

[1] L. S. Fridericia and E. Holm, *Am. Jour. Physiol.*, 73: 63, 1925; K. Tansley, *Jour. Physiol.*, 71: 442, 1931.

[2] G. Wald, *Jour. Gen. Physiol.*, 18: 905, 1935, and 19: 351, 1935.

[3] S. Hecht, *Physiol. Rev.*, 17: 239, 1937; "La Base Chimique et Structurale de la Vision," Hermann and Co., Paris, 1938, 97 pp.

[4] C. Haig, S. Hecht and A. J. Patek, SCIENCE, 87: 534–536, 1938.

addition of vitamin A eventually reaches a normal state, which can be maintained only by large dietary supplements of vitamin.

Because of this pathological factor, it seemed desirable to test the conclusions of Haig, Hecht and Patek by a study of normal individuals. We therefore measured the dark adaptation of four normal young men, first on their regular and adequate diet, and then on a diet containing only about 150 units of vitamin A per day in order to see whether under these circumstances rod and cone behavior also run parallel courses. Jeghers[5] has already made measurements of dark adaptation on one person subjected to vitamin A deficient diet, but due to inadequate apparatus and procedure his data do not separate rod and cone adaptation and thus fail to answer the present question.

Our measurements were made under carefully specified conditions so as clearly to separate rod and cone adaptation. We used the new adaptometer described by Hecht and Shlaer[6] and adopted their standard procedure involving preadaptation to 1,500 millilamberts for 3 minutes, and measurements with extreme violet light of the adaptation of a retinal area 3° in diameter situated 7° nasally from the fovea.

The results show unequivocally that cone function is affected by vitamin A changes, just as rod function is affected by them. Fig. 1 gives five curves of dark

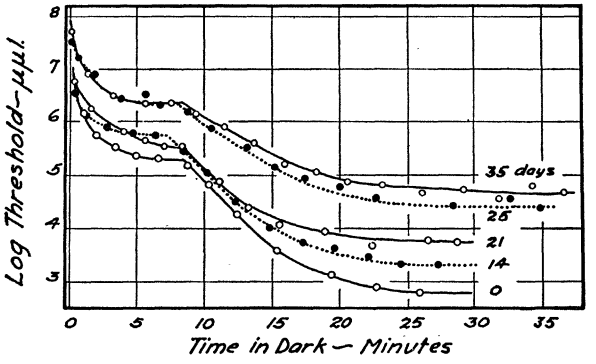

FIG. 1. Dark adaptation curves made at various times during a vitamin-A-free diet. Each point is a single observation.

adaptation made with one subject during different stages of the deficient diet. In all the curves, the first section, occurring fairly rapidly, represents cone adaptation; after this reaches a level in a few minutes, the second section representing rod adaptation begins fairly abruptly after about 7 minutes in the dark. This cone-rod transition point remains the same during all the vicissitudes of the diet, and this is true for all four subjects. Such was not the case with the cirrhosis subjects, who showed an initial displacement of the transition point to as long as 15 minutes and its gradual migration toward the normal time during the course of therapy.

Fig. 1 shows that as the stores of vitamin A in the body become exhausted, the general intensity level for both rods and cones rises. This is true not only for the final thresholds of cones and rods, but of the curves as a whole. The parallelism in behavior of the two functions is best shown in Fig. 2, where the data for

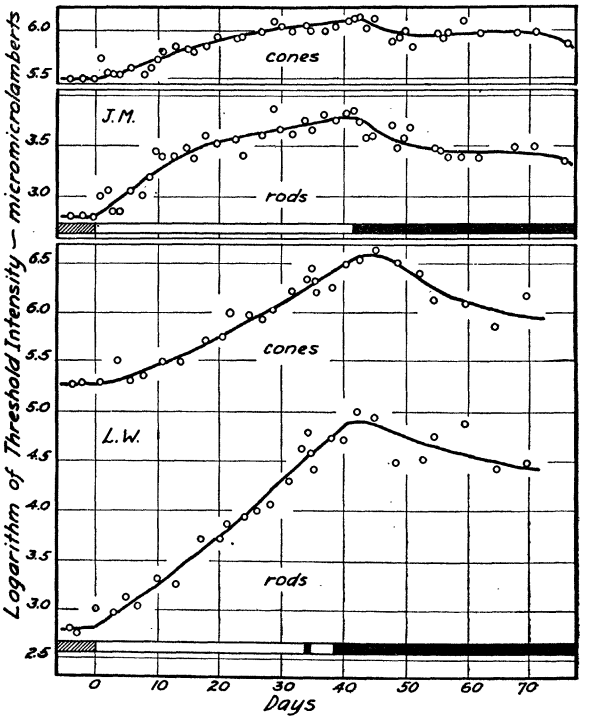

FIG. 2. The final rod and cone thresholds of two subjects on a vitamin A controlled diet. The diagonally shaded part represents a normal diet; the clear part is a practically vitamin-free diet; and the black part represents a normal diet plus 50,000 units of vitamin A daily. Note the points above the narrow black area for L. W. Both for rods and cones, this single administration of a large dose of vitamin A (100,000 units) seemed to cause a drop in threshold during the same day. In view of the prolonged time subsequently required for the threshold to come down to normal on a supplemented diet, we have not taken these points too seriously.

two subjects are drawn. Those for J. M. are about average, while L. W. represents the extreme effect of the four subjects. Each point is the final threshold secured either from the cone or the rod sections of such curves as in Fig. 1. All subjects had been studied for several weeks before beginning the diet, and the thresholds from the last two runs made on the normal diet are shown above the diagonally shaded area in Fig. 2. The clear area represents the duration of the deficient

[5] H. Jeghers, *Jour. Am. Med. Asn.*, 109: 756, 1938.
[6] S. Hecht and S. Shlaer, *Jour. Opt. Soc. Am.*, 28: 1938.

diet. The similarity in behavior of cones and rods in dark adaptation is obvious.

The black area means the return to a normal diet supplemented by 50,000 units of vitamin A per day. L. W. received 100,000 units in one day, but became ill for a few days following, during which he ate almost nothing and only resumed a supplemented normal diet later as indicated. The other two subjects merely returned to a normal diet without supplementary vitamin A. As Fig. 2 shows, there has been no spectacular return of visual function to normal on the resumption of regular and even excessive vitamin A consumption such as has been reported previously.[5, 7] There is a slightly rapid drop in threshold at first, but this gives way to a gradual decrease in threshold, and it may take longer to achieve complete recovery of function than it took to lose it.

For an understanding of the chemistry of vision, the significant thing is the almost parallel behavior of rod and cone thresholds during both the deficient and the recovery periods of the diet. This must mean that just as vitamin A enters into the chemical cycle of rod vision due to its association with visual purple, so it enters into the chemical cycle of cone vision, and that the cone sensitive substance[8]—iodopsin or visual violet—is very likely also a conjugated carotenoid protein like rhodopsin and porphyropsin.

This research was aided by a grant from the Rockefeller Foundation.

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NEW OBSERVATIONS ON THE VITAMIN K DEFICIENCY OF THE CHICK

IN view of the interest shown in vitamin K by biologists and clinicians, it is believed that recent observations made in this laboratory should become available to other investigators.

It was found that vitamin K will bring about a normal clotting time of the blood of the vitamin K-deficient chick within from 4 to 6 hours after oral administration by pipette and that the blood clotting time of the chick will become abnormally long again within a short time, depending upon the amount of vitamin K administered.

Chicks were reared on a vitamin K-low diet for 3 days, then on the vitamin K-deficient diet E of Almquist and Stokstad[1] for from 10 to 16 days. When the typical hemorrhagic diathesis had appeared, the chicks were fed 0.20 ml of cod liver oil containing 1 mg of vitamin K concentrate No. 13[2] prepared from alfalfa. At 2 hours' intervals after the administration of the concentrate, the blood-clotting time of the chicks was determined by the method of Almquist and Stokstad.[3]

The blood-clotting time was found to be more than 30 minutes after 2 hours; after 4 hours, the blood of about 50 per cent. of the chicks clotted within 10 minutes; and after 6 hours practically all the chicks were normal with respect to coagulation.[4]

The coagulation time of chicks which had received 1 mg of the vitamin K concentrate remained normal for more than 24 hours; at the end of the second day, the blood of about 50 per cent. of the chicks no longer clotted within 30 minutes; and at the end of the third day, all the chicks had an abnormally long coagulation time.

No change was observed in the blood-clotting time of chicks which had received 0.25 mg of vitamin K concentrate No. 13 dissolved in 0.20 ml of cod liver oil. Only a small percentage of the chicks responded to 0.5 mg. The effect of 2 mg, likewise administered in 0.20 ml of cod liver oil, was found to last for more than 48 hours; but at the end of the third day, all the chicks showed an abnormal clotting time. The administration of 3 mg of the concentrate in 0.20 ml of cod liver oil kept the coagulation power of the blood normal in about 50 per cent. of the chicks for 72 hours; it was found that 3.8 mg of the concentrate dissolved in 0.20 ml of cod liver oil was necessary to keep the blood-clotting time of all the chicks normal for 72 hours.

Obviously the above observations can be employed as the basis for a quantitative biological assay of vitamin K. Such a method has been used successfully with several hundred chicks and will be reported in full in the near future. This method would seem to fulfill the requirements of standardization studies for which there is an actual need, as pointed out recently in a paper by Smith *et al.*[5] on the effect of bile and vitamin K on bleeding tendency and prothrombin deficiency.

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JUNE 29, 1938
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[2] Unpublished data from this laboratory.

[3] H. J. Almquist and E. L. R. Stokstad, *Jour. Nutrition*, 14: 235, 1937.

[4] Since this paper was written, it was found that the clotting power of the blood of the vitamin K-deficient chick may become normal within 2½ hours after the feeding of a relatively high amount of the vitamin K concentrate.

[5] H. P. Smith, E. D. Warner, K. M. Brinkhous and W. H. Seegers, *Jour. Exp. Med.*, 67: 911, 1938.

[7] C. Edmund and S. Clemmesen, "On Deficiency of A Vitamin and Visual Dysaptation," Copenhagen, 1936, 92 pp.; C. Fridericksen and C. Edmund, *Am. Jour. Diseases of Children*, 53: 89, 1938.

[8] G. Wald, *Nature*, 140: 545, 1937; A. M. Chase, SCIENCE, 87: 238, 1938.

[1] H. J. Almquist and E. L. R. Stokstad, *Jour. Nutrition*, 12: 329, 1936.