SPECIAL ARTICLES

THE COMPARATIVE VALUE OF THE BLOOD PLASMA VITAMIN A CONCENTRATION AND THE DARK ADAPTATION AS A CRITERION OF VITAMIN A DEFICIENCY

RECENTLY several investigators have shown[1, 2, 3] that poor dark adaptation may occur before vitamin A deficiency becomes so extreme as to cause clinically manifest symptoms of this deficiency, such as night-blindness and xerophthalmia. In the present study, we have compared the results of dark adaptation tests with plasma vitamin A values in infants and children and have also investigated the relation between the plasma vitamin A concentration and the vitamin A intake in infants.

We have previously shown[4] that the concentration of vitamin A in the blood plasma reflects the level of vitamin A intake in the rat when this intake is less than 50 International units daily. Thus, at intakes of 0, 1, 2, 10 and 25 units daily for 6 weeks, the average plasma concentrations of vitamin A at the end of this time were, respectively, 0, 7, 14, 35 and 69 units per 100 cc. The plasma vitamin A concentration reached an optimal value (about 100 units per 100 cc) at an intake of 50 units daily, and remained at this optimal level for intakes up to 1,000 units of vitamin A daily. There was no storage in the liver, the chief reservoir of vitamin A in the body, at plasma vitamin A concentrations less than 35 units per 100 cc, slight storage at concentrations between 35 and 50 units per 100 cc, and increasingly larger storage at blood plasma concentrations above 50 units per 100 cc.

Forty-six infants, 3 weeks to 6 months of age, receiving 1,200 to 1,500 units of vitamin A daily in their diet showed a mean plasma vitamin A concentration of 74 units per 100 cc. This value differed significantly from the mean value, 93 units per 100 cc, in a group of 47 infants of the same age and on the same diet, but receiving a supplement of 17,000 units of vitamin A daily. Dark adaptation tests revealed no difference between the mean final rod threshold values of two groups such as described above; the technique for determining dark adaptation in infants was previously described.[5] In these 93 normal infants, we encountered no plasma vitamin A concentration below 45 International units per 100 cc; this value would therefore seem to be the lower limit of normal, on the basis of our analyses.

Six infants, 3 weeks to 2½ months of age, were placed for periods of from 2 to 4 months on a diet which contained about 335 units of vitamin A daily, or one fourth the vitamin A content of the average diet for this age. The average concentration of vitamin A in the plasma before the institution of this diet was 74 units per 100 cc; at the termination of this diet the average plasma vitamin A concentration had fallen to 61 units per 100 cc. There was a decrease in the plasma concentration of vitamin A in every case, ranging from 4 to 23 units. Yet, in no instance did the dark adaptation become abnormal.

A second group of 12 infants, 1½ to 4 months of age, was placed on a diet devoid of vitamin A for periods of from 2 weeks to 4½ months. During this time the infants appeared normal, gaining well and being no more susceptible to infections than those receiving large quantities of vitamin A. Of 4 infants who received the vitamin A-free diet for a period of 2 to 6 weeks, one showed a plasma vitamin A concentration of 37 units per 100 cc, well below the lower limit, 45 units per 100 cc, of the normal range in infants of this age. Of the 8 infants who were on the diet for 2 to 4½ months, 6 showed low values ranging from 11 to 44 units per 100 cc. The 2 infants whose plasma concentration of vitamin A did not fall below 45 units had received 17,000 units of vitamin A daily for one month prior to the beginning of the vitamin A-free diet and presumably had accumulated large stores.

All 7 infants who had low plasma vitamin A concentrations—that is, concentrations below 45 units per 100 cc, also had abnormal dark adaptation. Five of these infants were then given 150 units of vitamin A daily for one month. As shown in table 1, the dark adaptation became normal in every instance, although the plasma concentrations of vitamin A remained low. In other words, at this stage the plasma vitamin A level revealed clearly the known history of a greatly restricted vitamin A intake, whereas the dark adaptation tests gave no suggestion of it.

Nineteen normal children, 6 to 12 years of age, showed an average plasma vitamin A concentration of 117 units per 100 cc (range: 70 to 197 units). Dark adaptation tests revealed normal final rod thresholds in every one of these 19 children. In contrast, 118 children of the same age group who had been admitted to the hospital because of malnutrition, upper

[1] S. Hecht and J. Mandelbaum, *Jour. Am. Med. Assn.*, 112: 1910, 1939.
[2] J. M. Lewis and C. Haig, *Jour. Pediatrics*, 16: 285, 1940.
[3] P. C. Jeans, E. L. Blanchard and F. E. Satterthwaite, *Jour. Pediatrics*, 18: 170, 1941.
[4] J. M. Lewis, O. Bodansky, K. G. Falk and G. McGuire, *Proc. Soc. Exptl. Biol. Med.*, 46: 248, 1941.
[5] J. M. Lewis and C. Haig, *Jour. Pediatrics*, 15: 812 (1939).

TABLE I

THE EFFECT OF THE ADMINISTRATION OF 150 UNITS OF VITAMIN A DAILY FOR A PERIOD OF FOUR WEEKS ON THE PLASMA VITAMIN A CONCENTRATION AND ON DARK ADAPTATION IN INFANTS PREVIOUSLY FED A VITAMIN A-FREE DIET FOR TWO TO FOUR MONTHS

Name	Age	Plasma vitamin A concentration		Final rod threshold	
		Prior to administration	After administration	Prior to administration	After administration
	Months	Units per 100 cc		Log micromicro-lamberts	
J. K. ...	3½	13	16	4.4	3.3
A. I. ...	3½	44	48	4.4	3.0
N. R. ...	5½	11	16	5.0	3.0
J. R. ...	6	23	35	4.7	3.3
L. R. ...	3¾	30	26	3.8	3.0

respiratory infections, rheumatic fever, dysentery, etc., showed an average plasma vitamin A concentration of 89 units per 100 cc (range: 25 to 198 units). It should be emphasized that these children were tested when they were afebrile, as it has been shown[6] that the concentration of vitamin A in the plasma falls precipitously during fever and returns to normal rapidly after defervescence. Twenty-two or 19 per cent. of these 118 children had plasma vitamin A concentrations below 67 units per 100 cc, the value we designated as the lower limit of normal in this age group. Only one of these 118 children exhibited abnormal dark adaptation.

The above results demonstrate that the plasma vitamin A concentration is a considerably more sensitive indicator of vitamin A deficiency than is the dark adaptation. We have recently observed an instance of malnutrition in an adult which illustrates this point strikingly. A woman in the seventh month of pregnancy had subsisted for several weeks on a diet consisting chiefly of coffee. She had developed marked anemia and polyneuritis; the latter cleared up promptly following thiamin chloride therapy and was evidently due to vitamin B_1 deficiency. The dark adaptation test showed a normal final rod threshold. In sharp contrast, the plasma vitamin A concentration was 40 units per 100 cc, a value considerably less than the lowest value obtained by Kimble[7] in a series of 34 normal women, namely, 64 units per 100 cc.

OSCAR BODANSKY
J. M. LEWIS
CHARLES HAIG
THE PEDIATRICS SERVICE, BETH ISRAEL HOSPITAL, AND THE DEPARTMENT OF PEDIATRICS, NEW YORK UNIVERSITY COLLEGE OF MEDICINE, NEW YORK CITY

[6] S. W. Clausen and A. B. McCoord, *Jour. Pediatrics*, 13: 635, 1938.

[7] M. S. Kimble, *Jour. Lab. Clinical Med.*, 24: 1055 (1939).

PATHOGENESIS OF ERYTHROBLASTOSIS FETALIS: STATISTICAL EVIDENCE[1]

IT was recently suggested[2] that erythroblastosis fetalis, a familial hemolytic disease of the newborn, results from the passage of the mother's immune agglutinins through the placenta to act on the susceptible blood of the fetus. The evidence indicates that the mother is immunized by a particular blood factor, Rh, transmitted from the father to the fetus but lacking in the mother. This isoimmunization of the mother was proposed as the explanation of the cause of hemolytic transfusion accidents associated with pregnancy.[3,4,5]

The agglutinable substance involved is the Rh factor recently discovered by Landsteiner and Wiener with the aid of rabbit sera obtained by immunization with rhesus blood.[6] Such agglutinins were shown to give reactions which ran parallel to the atypical agglutinins in the mothers' sera, induced, presumably, by isoimmunization with fetal blood.

To obtain further data on the relationship of the Rh factor and anti-Rh agglutinin to this disease, a statistical study was undertaken which forms the basis of this paper. The isoimmunization theory requires that the mothers of infants with erythroblastosis fetalis be Rh negative, while the affected child and the father must be Rh positive. Consequently, a selected population of such mothers should show a higher incidence of Rh negative than the random population. Furthermore, the fathers and the affected children should invariably be Rh positive. The results in Table 1 which conform to the theoretical expecta-

TABLE I

	Rh positive	Rh negative
Random population		
Male 829	86.2 per cent.	13.8 per cent.
Female 206	88.4 " "	11.6 " "
111 mothers of infants with erythroblastosis fetalis ..	9.0 " "	91.0 " "
66 husbands of Rh-negative mothers	100.0 " "	
58 affected infants	100.0 " "	

[1] From the Division of Laboratories, Newark Beth Israel Hospital, Newark, N. J., and the Laboratories of Mt. Sinai Hospital, New York, and the Woman's Hospital, New York. Aided by a grant from the Blood Transfusion Betterment Association of New York City.

[2] P. Levine, E. M. Katzin and L. Burnham, *Jour. Am. Med. Asn.*, 116: 825, 1941.

[3] P. Levine and R. E. Stetson, *Jour. Am. Med. Assn.*, 113: 126, 1939.

[4] A. S. Wiener and H. R. Peters, *Annals Int. Med.*, 13: 2306, 1940.

[5] P. Levine and E. M. Katzin, *Proc. Soc. Exp. Biol. and Med.*, 45: 343, 1940.

[6] K. Landsteiner and A. S. Wiener, *Proc. Soc. Exp. Biol. and Med.*, 43: 223, 1940.