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.

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[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.

tion provide striking evidence to support the importance of the Rh factor in the etiology of erythroblastosis fetalis.

In a general way it may be assumed from these findings that isoimmunization of the Rh negative mother by the Rh factor of the fetus may explain the incidence of erythroblastosis fetalis in 91 per cent. of the families studied. That other blood factors are capable of inducing isoimmunization is shown in one of the 10 Rh positive mothers whose blood contained an atypical agglutinin of an entirely different specificity.[7] Still another blood factor identified by an agglutinin recently described by Levine and Polayes[8] is capable of inducing isoimmunization. This woman, who suffered a transfusion accident during her puerperium of her twelfth pergnancy, had 4 miscarriages but no infants with erythroblastosis fetalis.

The studies on the specificity of various anti-Rh sera produced by isoimmunization in these mothers showed that these sera differ somewhat in their specificity. While the great majority of bloods give identical reactions when tested with various anti-Rh sera, several bloods inactive with a particular serum were found to react with other sera. A similar finding was observed by Landsteiner and Wiener.[9]

Consequently, the bloods of the remaining 9 Rh positive mothers not containing atypical agglutinins will have to be retested with the new agglutinins as well as with a variety of anti-Rh sera.

The correlation of anti-Rh agglutinins and the postpartum interval when the first tests were done, is shown in Table 2.

TABLE II

Incidence of anti-Rh agglutinins in 101 Rh-negative mothers

Interval after last delivery of an affected infant	Agglutinins present	Agglutinins not found
2 months	24	23
2 months to 1 year	3	7
1 year or longer	2	36
No data	0	6
Total	29	72

Atypical agglutinins in the Rh negative mothers were found in 50 per cent. of the cases in tests made within the first two months after delivery of an infant with erythroblastosis fetalis. It may be assumed that the incidence of anti-Rh agglutinins will be higher if such mothers are tested at intervals in the course of subsequent pregnancies which may result in other affected infants.

[7] This case, a patient of Dr. C. Javert, will be published separately.

[8] P. Levine and S. H. Polayes, *Annals Int. Med.*, 14: 1903, 1941.

[9] K. Landsteiner and A. S. Wiener, personal communication.

It is of interest that in 2 cases atypical agglutinins could still be demonstrated 2 and 2½ years, respectively, after the last delivery of an infant with erythroblastosis fetalis.

According to the concept of isoimmunization, the mother's immune agglutinins pass through the placenta and exert lytic action on the susceptible fetal blood. However, this could not occur if the Rh factor had a wide distribution in tissue cells and body fluids, which would specifically bind the anti-Rh agglutinins. Tests made with numerous specimens of saliva and a small number of specimens of seminal fluid and sperm cells of Rh positive individuals indicated that the Rh factor was not present in this material. Thus there is justification, at least for the present, to assume that the Rh factor may be limited to red blood cells.[10] However, a comprehensive study of various organs and body fluids is desirable.

In a future publication evidence will be presented that the familial nature of erythroblastosis fetalis depends upon the heredity of the blood factors involved. The striking incidence in certain mothers and the sporadic occurrence in others depends upon the homozygosity or heterozygosity of the father's blood. That the Rh factor is inherited as a mendelian dominant property was recently demonstrated by Landsteiner and Wiener.[9]

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MOSAIC, CHLOROSIS AND NECROSIS IN VIRUS-INFECTED PERENNIAL PEPPER CAUSED DIRECTLY BY PRODUCTS OF A DERANGED METABOLISM[1]

IN *Capsicum frutescens* L., a tropical perennial pepper, the level of concentration for Nicotiana Virus 1 is relatively low under all conditions of growth studied. When the leaves are wiped with virus local necrotic lesions develop and the leaves abscise.[2] When the inoculated plants are cultured near 32° C. small quantities of virus pass from the inoculated leaf, and systemic infection occurs,[3] but does not when cultured near 23° C. At the high temperatures the branches, stems, taproots and roots become necrotic. These tissues develop a dark brown to black color and death results. Old woody plants are more resistant than young succulent plants.

[10] *Cf.* A. S. Wiener and S. Forer, *Proc. Soc. Exp. Biol. and Med.*, 47: 215, 1941.

[1] Studies conducted under Bankhead-Jones Project S.R.F. 2–17, U. S. Department of Agriculture, Bureaus of Plant Industry and Agricultural Chemistry and Engineering cooperating.

[2] F. O. Holmes, *Phytopathology*, 26: 896, 1936.

[3] H. H. McKinney, *Jour. of Heredity*, 28: 51, 1937.