Staff Meeting Bulletin Hospitals of the » » » University of Minnesota

Vitamin A in Pregnancy

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INDEX

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William A. O'Brien, M.D.

I.

UNIVERSITY OF MINNESOTA MEDICAL SCHOOL
CALENDAR OF EVENTS
April 16-21, 1945

No. 67

Monday, April 16

9:00 - 10:00 Roentgenology-Medicine Conference; L. G. Rigler; C. J. Watson and Staff; Todd Amphitheater, U. H.

9:00 - 11:00 Obstetrics and Gynecology Conference; J. L. McKelvey and Staff; Interns Quarters, U. H.

12:30 - 1:30 Pathology Seminar; Schistosomiasis Japonicum; Roberta G. Rice; 104 I.A.

8:00 - Dight Institute Lecture; Biological Aspects of Some of our Social Problems; Elmer Roberts, University of Illinois, Museum of Natural History Auditorium.

Tuesday, April 17

9:00 - 10:00 Roentgenology-Pediatrics Conference; L. G. Rigler, I. McQuarrie and Staff; Eustis Amphitheater, U. H.

11:00 - 12:00 Urology Conference; C. D. Creevy and Staff; Main 515 U. H.

12:30 - 1:30 Pathology Conference; Autopsies; Pathology Staff; 104 I. A.

12:30 - 1:30 Physiology-Pharmacology Seminar; The Study of Human Performance as a Whole by the Simultaneous Observation of Component Functions; Ancel Keys and Josef Brozek; 214 M. H.

4:00 - 5:00 Physiological Pathology of Surgical Diseases; Physiology and Surgery Staffs; Todd Amphitheater, U. H.

4:30 - 5:30 Obstetrics and Gynecology Conference; J. L. McKelvey and Staff; Station 54, U. H.

4:00 - 5:00 Pediatrics Grand Rounds; I. McQuarrie and Staff; W-205 U. H.

4:30 - 5:30 Ophthalmology Ward Rounds; Erling Hansen and Staff; E-534, U. H.

5:00 - 6:00 Roentgen Diagnosis Conference; H. O. Peterson, 515 U. H.

8:15 - Minnesota Pathological Society; Presidential Address; Wesley W. Spink, 15 M.S.

Wednesday, April 18

9:00 - 11:00 Neuropsychiatry Seminar; J. C. McKinley and Staff; Station 60; Lounge, U. H.

11:00 - 12:00 Pathology-Medicine-Surgery Conference; Tuberculous Pneumonia; E. T. Bell, C, J. Watson, O. H. Wangensteen and Staff; Todd Amphitheater, U. H.

12:30 - 1:30 Pediatrics Seminar; The Abuse of Too Much Rest in Heart Disease; Robert Gibbs, W-205 U. H.

12:30 - 1:30 Physiological Chemistry Literature Review; Staff; 116 M. H.

4:30 - 5:30 Neurophysiology Seminar; Pathology of Movements in Man on Basis of Action Potential Studies; James F. Boxma; 214 M. H.

Thursday, April 19

9:00 - 10:00 Medicine Case Presentation; C. J. Watson and Staff; Todd Amphitheater, U. H.

12:30 - 1:30 Physiological Chemistry; Intermediary Metabolism of Carbohydrates; M. F. Utter; 116 M. H.

4:00 - 5:00 Pediatric Journal Club; Review of Current Literature; Staff; W-205,U.H.

4:30 - 5:30 Ophthalmology Ward Rounds; Erling Hansen and Staff; E-534, U. H.

4:30 - 5:30 Roentgenology Seminar; The Effects of Radiation of the Ovaries on Carcinoma of the Breast--Review of Recent Literature, Margaret Tucker; M-515 U. H.

Friday, April 20

9:00 - 10:00 Medicine Grand Rounds; C. J. Watson and Staff; Todd Amphitheater, U.H.

10:00 - 12:00 Medicine Ward Rounds; C. J. Watson and Staff; E-214 U. H.

10:30 - 12:30 Otolaryngology Case Studies; L. R. Boies and Staff; Out-Patient Otolaryngology Department, U. H.

11:45 - 1:15 University of Minnesota Hospitals General Staff Meeting; Medical Social Service; Frances Money; Powell Hall, Recreation Room.

1:00 - 2:30 Dermatology and Syphilology; Presentation of Selected Cases of the Week; Henry E. Michelson and Staff; W-206 U. H.

1:30 - 3:00 Roentgenology-Neurosurgery Conference; H. O. Peterson, W. T. Peyton and Staff; Todd Amphitheater, U. H.

Saturday, April 21

8:00 - 9:00 Surgery Journal Club; O. H. Wangensteen and Staff; M-515 U. H.

9:00 - 10:00 Pediatrics Grand Rounds; I. McQuarrie and Staff; Eustis Amphitheater, U. H.

9:15 - 10:30 Surgery Roentgenology Conference; O. H. Wangensteen, L. G. Rigler and Staff; Todd Amphitheater, U. H.

9:00 - 10:00 Medicine Case Presentation; C. J. Watson and Staff; M-515 U. H.

10:00 - 12:00 Medicine Ward Rounds; C. J. Watson and Staff; E-221 U. H.

11:30 - 12:30 Anatomy Seminar; The Anatomies of Bichot; S. P. Miller, 226 I.A.

II. VITAMIN A IN PREGNANCY

Curtis J. Lund

Nearly all of the known nutritional functions of vitamin A can be summarized by saying that it is essential for the development and preservation of epithelial tissues. Certain aspects of these functions assume special significance in obstetrics where we are dealing not only with the mother's health but also the infant's. It has been clearly shown that vitamin A is indispensable for fetal development. For example, Warnaky[1] has been able to produce repeatedly a series of optic lesions in the guinea pig by withholding vitamin A from the maternal diet. These malformations consisted of congenital blindness, a fusion of cornea and eyelids, fibrosis of the vitreous, etc. All were prevented in control animals by maintenance of adequate vitamin A. Before these results are translated into terms of human nutrition and development it is well to remember that extreme degrees of deficiency were necessary for the production of these lesions. Actually the deficiency was so great that only a few of the animals were fertile and the reproductive rate was low. Such degrees of deficiency in the human are medical curiosities, at least in this country.

In addition to the normal nutritive functions of vitamin A certain pharmacodynamic actions have been suggested. Among these has been an ability to reduce blood pressure, however, present opinion doubts the therapeutic effect of vitamin A when administered to persons having normal nutrition.

Metabolism

Many factors are known to influence the availability and utilization of vitamin A and its provitamin, carotene.

The first and obvious modifying factor is the nutritional intake. Intake may be modified by many circumstances such as: (a) economic state--foods containing vitamin A are not the least expensive; (b) food habits--food fads, food allergies, etc.; and (c) food rationing, which at the present time provides temporary restrictions of foodstuffs rich in vitamin A.

Of greater importance, at least in this well-fed country, are disturbances of the normal physiologic processes concerned with absorption and metabolism of these substances. Disturbed absorption and utilization can occur from a multitude of causes such as: vomiting, diarrhea, diseases of the liver, faulty intake of dietary fat, excessive use of mineral oil and others. These individually or collectively may produce a deficiency of vitamin A even though an adequate amount is ingested. Popper[2] has recently reviewed this problem.

Increased need is another factor which is probably best exemplified by pregnancy. In spite of the fact that there is no completely satisfactory method for the accurate determination of human requirements in either the pregnant or nonpregnant individual, it is clear that the otherwise rather constant adult requirements are increased during gestation.

Finally, it is well to remember that carotene apparently is utilized only after it has been converted into vitamin A; yet individuals apparently vary in their ability to convert the provitamin into the vitamin. Thus a diet adequate in carotene does not necessarily insure adequacy for vitamin A.

Requirements

Probably no words in nutrition are more maligned than are requirements and deficiency. When these terms, so difficult of definition, are further narrowed by such modifying terms as borderline, minimal, maximum, optimal, etc., their meaning is even more obfuscated. If minimal requirement is defined as the least amount compatible with health, then what is health? When carried to further lengths the thing becomes fatuous as well as absurd.

The daily requirement of vitamin A during pregnancy is not known although estimates have been made from data obtained by dark adaptation tests and by

nutritional surveys. In 1935 the Technical Commission of the Health Committee of the League of Nations[3] suggested that the minimal daily requirement was 5,000 I.U. (International Units). This figure has been increased by the Food and Nutrition Board of the National Research Council[4] to 6,000 I.U. daily during the last half of pregnancy and 8,000 I.U. daily during lactation. Other investigators have arrived at somewhat similar conclusions; however, it is safe to say that none represents more than a general estimate of the exact requirements.

Many attempts have been made to determine the frequency and severity of vitamin A deficiencies in pregnancy. The results of such studies depend to a great extent upon the methods employed and the criteria used in interpretation. Williams and Fralin[5] found that 96.5 per cent of a selected group of pregnant women failed to obtain 6,000 I.U. of vitamin A daily. The British survey by the Peoples League for Health[6] indicated that rather more than half of all mothers were taking less vitamin A than they required. Thus on a basis of dietary history the incidence of deficient nutrition seems high.

The use of clinical signs and symptoms as a guide to human requirements is quite unreliable, except of course in advanced stages of deficiency. The skeptic who insists that gross visible changes are necessary for diagnosis would, if consistent, not admit the presence of acidosis unless the subject considered was semi-comatose and had acetone upon the breath. Clinical manifestations of vitamin A deficiency are rarely seen in pregnancy. One explanation offeres is that conception is unlikely when severe degrees of deficiency exist, at least such appears to be true in animals[1].

Laboratory investigations have not always confirmed the findings of dietary surveys. For example, Williams et al[7] found that only 37.5 per cent of the "deficient" mothers had poor dark adaptation. In a large continental charity hospital[8] fully half of the pregnant women had poor dark adaptation while another study in this country produced only 0.62 per cent of poor visual adaptation in a group of 380 pregnant women.

More recent estimates of vitamin A requirements have been made by studies of blood plasma. These photocolorimetric methods have been widely used for the study of nonpregnant individuals[2] but have not been applied to pregnancy except in isolated instances.

From a survey of the literature we can say definitely that pregnancy increases the need for vitamin A. On the other hand there has been no complete agreement about the magnitude of the need, the manner in which it should be met nor the consequences of failure to meet it. It is the purpose of this paper to determine the normal variations of maternal plasma vitamin A through pregnancy, delivery and the puerperium; to determine the influence of diet and of vitamin supplements; to determine the relationship of certain complications of obstetrics; and finally to determine the maternal-fetal relationship of vitamin A and carotene and its significance in the placental transmission of these substances.

Methods of Study

Certain peculiarities of metabolism make the study of vitamin A difficult. It is fat soluble and readily stored. Methods commonly used, such as urinalysis or fecal analysis, are either unreliable or inapplicable. It is not the purpose of this paper to compare critically the various methods for measuring vitamin A in the human. Nevertheless, a brief consideration of the available methods, of their reliability and of their significance seems to be indicated.

Clinical manifestations of vitamin A deficiency, as we have said, are rare in this country. Attempts to produce a deficiency syndrome have met with little success as Brenner[9] has recently shown. Her human subjects, although maintained for months on a diet free from vitamin A, revealed no significant changes of epithelium tissues. On the other hand Hsu[10] found the distinct characteristic clinical changes of the eyes and the skin in a group of deficient Chinese. The inferences which may be drawn are not en-

tirely clear but they support the notion that clinical manifestations are not an early sign of deficiency and that extreme deficiencies are uncommon.

The newer literature concerning the merits of the dark adaptation test and the photocolorimetric determination of plasma vitamin A has been reviewed by Haig and Patek[11]. These investigators could not correlate the two tests within groups of similar patients but both methods reflected the general trend of vitamin A values. Youmans et al[12] in a series of articles concluded that the test of dark adaptation as a measure of vitamin A can be criticized on the basis of accuracy as well as specificity. Only half of their subjects with impaired adaptation had vitamin A deficiency. Apparently both methods record quantitative variations in two related but not necessarily identical aspects of vitamin A metabolism.

We believe that far more reliance can be placed in the photocolorimetric determination of plasma vitamin A although reservations must be used in the interpretation of results in terms of clinical significance.

In this study vitamin A and total carotene were determined from the blood plasma under fasting conditions according to the technic described by Kimble[13]. Briefly, the method involves extraction of the plasma carotinoids with ethyl alcohol and petroleum ether, determination of the carotene from the amount of yellow color imparted to the ethereal extract, removal of this solvent so that the remaining material can be dissolved in chloroform, and the development of the standard Carr-Price reaction by the addition of antimony trichloride in chloroform. This chemical procedure has become so well standardized that colorimetric readings yielded by a given vitamin-containing preparation can readily be duplicated from one laboratory to another and under physiologic conditions the vitamin A level is constant for a given individual throughout the day and on consecutive days. Then why are so many conflicting results scattered throughout the literature?

Interpretation of the chemical findings in terms of units or weights of the vitamin represented still varies grossly in different hands. These uncertainties involve the correction for color formed by carotene, and the interchange of chemical or "blue" units with actual weights of the vitamin. At the present time it must be emphasized that in any work concerning vitamin A, both the technic of assay and the method of calculation of results must be uniform before comparisons among different sets of data can be attempted.

(Within the past fortnight news of a dual form of vitamin A has appeared. In addition to the crystalline form an oily substance has been isolated in the pure state. If such is the case then more accurate standardization will be possible and will naturally be followed by more uniform data from different laboratories.)

The values for vitamin A in the plasma of 50 healthy nonpregnant women were found to lie, for the most part, between 75 and 120 I.U. per cent. These nonpregnant controls represented essentially the same sort of population as the mothers in the present study. The average value for plasma vitamin A was 96 I.U. per cent. Three other laboratories using the same technic and calculations obtained average normal values of 95, 87, and 87 I.U. per cent. For carotene we obtained an average value of 203 gamma per cent (micrograms per 100 ml.) while others recorded figures of 197 and 227 for similar groups of women. What then, are the interpretations of these determinations?

At the present time we believe that high blood levels (90 I.U. per cent or greater) indicate an adequate intake and, as a rule, adequate storage of vitamin A in normally healthy individuals. Patients with renal disease occasionally exhibit high plasma values even when stores of the vitamin are low[2]. Low plasma values are indicative of depleted stores in normal individuals, (below 60 I.U. per cent in our study) or they may indicate severe infectious diseases or hepatic damage. The significance of intermediate plasma values is not clear; although they indicate a diminished

amount of vitamin A in the circulation they probably do not always reflect the condition of the stores.

Plan of Study

Repeated observations of a single individual are usually more illuminating that separate observations of several individuals. This is especially true in a study of this sort where variations within a group are apt to be greater than the variation within an individual. Therefore, our plan was to observe a small number of women several times during the course of pregnancy. The total group included 215 pregnant women who represented various social and economic classes. No attempt was made to obtain random sampling; on the contrary, we included deliberately, a large number of patients representative of each class. For convenience the study was arbitrarily divided according to the trimesters of pregnancy. Thirty two patients were observed during the first trimester, 65 during the second, 75 during the third, and 143 at the time of delivery. Approximately 75 per cent of the patients who began the study, regardless of the duration of pregnancy at the initial visit, were observed throughout the remainder of pregnancy and delivery[14].

Each patient had an estimate of vitamin A intake based on careful questioning and from this history she was placed into one of four classes: (1) adequate diet, which supplied in excess of 6,000 I.U. of vitamin A daily; (2) fair diet, which supplied between 3,000 and 6,000 I.U. daily; (3) poor diet, all other substandard diets; (4) optimal diet, which included a fair or adequate diet plus 10,000 I.U. or more of vitamin A daily in the form of fish liver oil.

Results

No attempt was made to determine an average plasma vitamin A value for pregnant women. Such a figure would be artificial and meaningless. The significance of this statement will become apparent as results are described.

Diet--There was distinct correlation between intake of the vitamin and plasma levels when comparisons were limited to a definite time during pregnancy. Only 5 per cent of patients using substandard diets had individual plasma levels above 90 I.U. per cent at the time of delivery and over half had values below 60 I.U. per cent. On the other hand less than 15 per cent of those with completely adequate diets had values below 60 I.U. per cent while the majority had values above 90 I.U. per cent. These differences are statistically significant and indicate a positive correlation between the intake of vitamin A and its concentration in the plasma.

Plasma carotene levels varied directly as the intake of carotene. It was noteworthy that the plasma value in pregnant women with an adequate diet average approximately 20 per cent higher than the control values obtained from healthy nonpregnant women. We were unable to show relationship between the provitamin, carotene, and vitamin A in the blood. Any plasma carotene value, however high or low, might be paired with any vitamin A value.

Season--Seasonal variations in plasma vitamin A could not be demonstrated. On the other hand, the carotene level of the plasma, which in contrast to vitamin A does not vary with the duration of pregnancy and is known to reflect short-time changes in intake, showed a distinct and significant seasonal variation. During the summer half of the year the values were 22 per cent higher than the winter half of the year. In this latitude the high plasma levels corresponded roughly with the season in which vegetables are abundant.

Pregnancy, Labor and Puerperium--The change in plasma vitamin A during the course of pregnancy, labor and the puerperium is strikingly significant. In spite of reasonably constant intake the plasma values decreased during the course of pregnancy. While it is true that individual findings deviated occasionally, nevertheless, the trend of the group was uniform. On the other hand, this decrease did not always appear at the same time; instead the time of appearance de-

pended, at least in part, on the intake of vitamin A. In other words, diminished values usually appeared early in pregnancy when the diet was poor and later when the diet was good. For example, during the first trimester all patient had plasma values above 90 I.U. per cent except a small group whose dietary intake had been reduced, primarily because of nausea and/or vomiting of pregnancy. During the second trimester only those patients who had received an "adequate" or an "optimal" diet were able to maintain a mean plasma level above the level of 90 I.U. per cent; while those with "fair" diets had an average plasma value slightly but significantly below the optimum. Plasma values of women with "poor" diets remained very low. Three months later, during the third trimester, women with "poor" diets had plasma values within the deficiency range; i.e., below 60 I.U. per cent. A decline was also observed in those who received "fair" or "adequate" diets and neither had maintained optimal levels. Only the group who received an "optimal" diet remained above 90 I.U. per cent. By the time of delivery the plasma values of these had declined also: although it did not fall significantly below the level of 90 I.U. per cent. The averages of blood values within the other dietary groups remained essentially unchanged from the levels of the third trimester. Carotene values, in contrast, showed no tendency to decline during pregnancy as long as dietary intake did not change.

If plasma vitamin A values for the end of pregnancy, which are based on determinations made at the time of delivery, are valid, it is necessary to eliminate labor as a cause of a sudden, temporary change. Twenty-one women were examined just before or at the onset of labor and again at the time of delivery. Their plasma levels averaged 79 and 72 I.U. per cent respectively: although there was a slight decline in average values, a comparison of these means showed no difference statistically.

Most striking changes of plasma vitamin A took place immediately after delivery. In 39 of the patients observed at delivery, the plasma vitamin A determination was repeated within 48 hours. Usually the test was repeated about 24 hours after delivery. The shortest period was 6 hours and the longest was 48 hours. Little or no vitamin A was ingested during this interval; supplements were withheld, and all patients had fasted for at least 14 hours before the second sample was withdrawn. Yet in every instance the vitamin had increased during this short interval. Individual increases ranged from 5 to 66 I.U. per cent while the average for the group was 31.6 I.U. per cent, an increase of roughly one third the normal value.

Of particular interest was the group whose vitamin A fell during pregnancy from fully normal to the borderline group, i.e., 60-90 I.U. per cent. With a single exception every patient of this category had an immediate puerperal elevation to 90 I.U. or above.

The values for plasma carotene served as a control, during the same interval they showed a slight but statistically insignificant decrease of 20 gamma per cent.

To rule out the factor of labor as a cause of the early puerperal rise in plasma vitamin A, we observed five women who were never in labor but were delivered by elective cesarean section. Within 24 hours all five had the characteristic puerperal increase.

It is a well known fact that ingestion of alcohol will cause a mobilization of vitamin A in the blood stream[15]. In order to eliminate inhalation analgesia and anesthesia as agents producing a similar effect, three patients were delivered without the use of analgesia or anesthesia. All three exhibited the characteristic reaction; the amount of increase was 31, 41, and 53 I.U. per cent respectively.

Supplements--To test the effect of supplements of vitamin A on the plasma values, a group of patients were given standardized amounts of halibut liver oil throughout pregnancy in addition to their usual diet. Ingestion of 5,000 I.U. daily kept the blood level adequately high during the first and second

trimesters but it fell rather sharply afterwards. The use of 10,000 I.U. daily maintained optimal levels well into the third trimester and there was only an insignificant drop by the time of delivery. Twenty thousand I.U. daily produced a similar result. When the dose was increased to 60,000 I.U. daily the blood level rose and was maintained above 110 I.U. per cent during the entire time of administration. Finally, two patients received 330,000 I.U. daily for 6 and 18 days and their plasma values were 151 and 145 I.U. per cent respectively.

The later puerperium is not characterized by notable changes in vitamin A levels. Five women were observed through the sixth week post partum. All lactated and all had plasma levels in the optimum range and maintained these levels without difficulty and without the use of supplements. This is of some clinical importance as it differs from the generally accepted idea that lactation produces a severe strain and increases the requirements for vitamin A.

A number of statistical correlations were made by comparing the plasma vitamin A with complications of pregnancy and labor, puerperal morbidity, length of labor, administration of prenatal care, etc. The results, though interesting, probably do not warrant more than brief mention. Certainly any conclusions must be drawn with reservations.

A group of 33 women observed for the first time at delivery, having had no prenatal care had an average plasma vitamin A of 56 I.U. per cent. A comparable group who received prenatal care but no supplements of vitamin A had a plasma level of 71 I.U. per cent. Finally, 48 women received prenatal care and supplements of vitamin A and their average value was 87 I.U. per cent.

Twenty eight patients had some type of complication of pregnancy of labor. Such a grouping is obviously open to criticism but the wide variety of complications in so few patients made this necessary. Every patient in this group had a plasma vitamin A value of less than 90 I.U. per cent.

The duration of labor was in no way associated with the plasma vitamin A values.

Fetal-Maternal Relationships

Several rather conflicting reports have appeared during the past 10 years concerning the amount of vitamin A and carotene present in the blood and tissues of the newborn infant. It is well to remember that earlier workers were handicapped by the intricacies and inaccuracies of a poorly understood procedure. Therefore many of their detailed findings must be accepted with reservations[16]. The data obtained from these several sources showed few points of complete agreement. All agreed that the infant is relatively low in vitamin A and carotene. Many thought that the infant always had lower levels than the mother. Some believed the placenta impervious to carotene and others believed it impervious to vitamin A. If a single generalization is permissible from these varied observations and opinions, it would be that values of vitamin A and carotene in the newborn infant are low compared to those of the mother, and this difference suggests some impedence of the placenta.

A series of 143 determinations of vitamin A and of carotene were made on the plasma of apparently normal infants delivered at term and 5 additional determinations were made from premature infants. The blood was collected from the cut end of the umbilical cord immediately after delivery and the tests made according to methods outlined earlier in this paper.

Results

Values in the Newborn--The plasma vitamin A values of the newborn were lower generally than those considered normal for an adult. From the 143 determinations mentioned the lowest recorded value was 24 I.U. per cent and the highest 79. The mean plasma vitamin A for all the infants was 49 I.U. per cent with a standard deviation of 12.2 and a coefficient of variability of 25 per cent. Fifty five of 143 were within the range

of 40 to 50 I.U. per cent and the remainder were not far from the mode.

Relationship of Fetus to Mother.--Next we attempted to see if there was a direct relationship between the maternal and fetal values even though the latter were usually the lower. A simple correlation coefficient of 0.22 was obtained which might be significant for a series of 143 observations. Further examination and subdivision of the data suggested a spurious correlation from some extraneous cause. This was substantiated by a scattergraph and by inspection of a graph pairing maternal and fetal values. Some of the highest fetal values were found paired with the lowest maternal values and, conversely, some low fetal values accompanied the highest maternal ones.

At first we believed, as had other investigators, that maternal values always exceeded those of the fetus. Later we found this to be true only as long as the mother's value was fully normal (above 90 I.U. per cent). When maternal values dropped below 80 I.U. the fetal values were sometimes essentially equal to the mothers' and sometimes greater. This upset we have called inversion. There were 91 mothers with vitamin A values below 80 I.U. per cent, and 19 of these (21 per cent) exhibited inversion. Inversion increased as the maternal values decreased and it was present in nearly half of those mothers whose vitamin A level was below 50 I.U. per cent.

When it became evident that the fetal plasma vitamin A might be independent of the mother's, whether she was normal or not, we undertook to elevate the maternal values by feeding large amounts of the vitamin. If fetal blood levels were directly related to the concentrations in the maternal blood stream then such an experiment should show it. As was mentioned earlier 60,000 and 333,000 units of vitamin A daily would raise the mother's blood level to a high point but in no instance was there any visible effect on fetal values. For example, one mother received two million units of vitamin A and her plasma level rose to 151 at the time of delivery yet the fetus had a value of 32, one of the lowest recorded.

Vernix caseosa.--Straumfjord[17] suggested that the formation of vernix caseosa might be a manifestation of vitamin A deficiency. By prolonged administration of large doses of the vitamin to mothers he was able to reduce the frequent appearance of vernix caseosa in newborn infants. The amount of vernix caseosa was compared with the plasma levels of vitamin A. Suitable records of 65 infants permitted classification according to the amount of vernix caseosa present. It is very difficult to measure the amount of this substance accurately but experience quickly enabled us to classify the babies into three general groups: scanty, average, and excessive. The average plasma vitamin A values of each group was, for practical purposes identical--48, 49, and 49 I.U. per cent respectively.

Prematurity.--Five premature infants were studied and although the data from so few infants were of little statistical value it was interesting to note that all of them fell below the general average and three were very low. This suggested the possibility of some relationship between weight and plasma vitamin A. The results obtained by plotting infants' weight against plasma vitamin A indicates that infants with a low birth weight tend to have low plasma vitamin A while the heavier babies have an equal distribution of plasma values. Thus it would seem that low vitamin A values are related to a low birth weight or possibly to some element associated with low birth weights.

Fetal carotene.--The plasma carotene of cord blood is very low. The mean value for 149 normal infants was 23 gamma per cent (micrograms per 100 ml.), the lowest value was 9 and the highest was 75. In general, fetal values were about one-tenth those of the mother. Correlation is obvious by inspection of a scattergraph plotting maternal against fetal values. The multiple correlation coefficient of the entire series was 0.71, which appears to be highly significant. By statistical criteria, a somewhat curvilinear regression was found to describe the series slightly better than a straight line, and the following formula

was derived: $IC = 4.06 + 0.063\ MC + 0.0001\ MC^2$. When the values for maternal carotene, MC, are known, corresponding values for the infant, IC, can be estimated by the above formula. As a convenient rule of thumb the fetal values may be estimated as one-tenth the maternal value if the mother is within the middle range. If maternal values are low the fetus has approximately one-eighth as much and when maternal values are high the fetus has about one-twelfth as much.

In spite of the fact that this direct linear relationship existed between maternal and fetal carotene there was neither correlation between fetal carotene and vitamin A nor between maternal carotene and fetal vitamin A.

Discussion

The preceding results have given evidence of the value of plasma vitamin A determinations as an aid to the clinical study of vitamin A nutrition during pregnancy. In the hands of a competent chemist, the photocolorimetric method of determining the blood values is simple and accurate. It is true that storage and the efficiency with which the vitamin is used cannot necessarily be estimated by this method; neither can any other single criterion decide these complex problems.

Although we did not attempt to determine the frequency of vitamin A deficiency during pregnancy, we were impressed with the infrequency of such states among our patients. In fact, the study was prolonged because of our desire to include a representative number of patients with a poor intake of vitamin A. Several factors may have been responsible for the generally good intake of vitamin A. The first of these, adequate finances, permitted most of the women to purchase the proper foodstuffs and vitamin supplements if necessary. Few of the patients were destitute. Education to understand the importance of prenatal care was another factor. If the patient reported regularly for prenatal care she was usually able to understand the importance of diet and was willing to obtain the proper foods. Finally all of these patients were living in an area of the nation abundantly rich in milk and dairy products which are known to be a most desirable source of vitamin A.

Throughout the study we were able to establish a satisfactory correlation between the intake of vitamin A and the plasma values. This was always true for groups of patients and usually for individuals. Occasionally unexpected and unexplained results were obtained. For example, 5 of 56 patients with an optimal intake of vitamin A had plasma values below 60 I.U. per cent. It is incredible that a vitamin A deficiency could exist when the daily intake of that substance was at least 12,000 to 15,000 I.U.

The need for vitamin A apparently increased as pregnancy progressed. During the first trimester, a diet which was adequate for nonpregnant women was also adequate for the pregnant women. Only the best diet met the needs of the second trimester and during the third trimester satisfactory plasma levels could not be maintained without the addition of supplements. However, 10,000 I.U. of vitamin A were ample and no benefit could be seen following the use of larger amounts. Several explanations for this progressively increasing demand are apparent. The simplest one would be the normal physiological hydremia which accompanies pregnancy. Yet two facts speak against this idea. In the first place there was no decline in carotene values of the same patients during the same period of time. Secondly the greatest drop in plasma vitamin A came late in the third trimester--the time that the hydremia begins to diminish.

Another explanation might be the increasing demands of the growing fetus which reaches a maximum just before delivery. This may well be the case but another mechanism is apparently active also. The puerperal mobilization of vitamin A in the blood stream brought most of the borderline values up to fully optimal levels. To meet this requirement there must be storage of vitamin A

in the tissues during pregnancy, probably at a rate greater than normal. This storage, perhaps acting in combination with increased fetal demands, tends to reduce plasma levels during pregnancy. At the time of delivery some mechanism, as yet unknown, but associated with the removal of the uterine contents, releases the vitamin from the stores and mobilizes it into the blood stream. On the basis of determinations post partum the average for the group studied was 93.3 I.U. per cent, a completely normal figure. Only those mothers with values below 60 I.U. per cent at the time of delivery failed to have values above 90 I.U. per cent in the post partum period. This suggests that values from 60 to 90 I.U. per cent, which are considered as borderline for the nonpregnant individual, may be normal values for term pregnancy.

The normal infant at birth has less vitamin A circulating in the blood than does its normal mother. This relationship extends to the tissues as well, for the fetal liver contains less vitamin A than the maternal liver. Nevertheless, these low concentrations of vitamin A do not necessarily signify deficiency; rather they should be considered as physiologic for the newborn infant.

There was no correlation between the values of maternal and fetal plasma vitamin A. This lack of correlation suggests that the amount of vitamin A in the fetal circulation is independent of the amount in the maternal circulation. Other observations which support this thesis were inversion and the failure of fetal response to excessive maternal intake of vitamin A. Obviously, inversion could not occur until the maternal values dropped below the highest fetal values. It increased in frequency as maternal values declined but we found no point at which all fetal values were higher than all maternal ones. Theoretically this could happen only when the maternal vitamin A drops below 24 I.U. per cent which is the lowest fetal value recorded by us. Maternal deficiencies of this order must be exceedingly rare. Thus it appears that the infant in utero acts more or less as a parasite and obtains whatever vitamin A it needs regardless of the mother.

Just how this vitamin A is obtained is not clear. If the vitamin is transmitted directly through the placenta it is not by a simple filtration process related to the concentration in maternal blood. If the fetus does not receive vitamin A from the mother there is but one other logical source: synthesis from carotene. The blood carotene concentrations of the newborn infants are very low, much lower than the mothers', yet in spite of this disparity, there is a definite relationship between the two throughout the entire range of values. This suggests a small but regular transfer of carotene from mother to fetus which may be the source of fetal vitamin A. The relationship can be traced no farther as there is no apparent correlation between the levels of carotene, either fetal or maternal, and fetal plasma vitamin A.

Summary

Maternal plasma vitamin A values during pregnancy reflected, in general, the dietary intake of the vitamin. However, the blood levels tended to decrease as pregnancy progressed and reached a low point at about the time of labor. Storage of the vitamin plus increased demands of pregnancy probably accounted for this decline. At the time of delivery the infant's vitamin A was always lower than its mother's as long as she maintained normal values, but it was entirely unrelated to maternal values. When maternal values were low inversion could occur. This was characterized by fetal values which were higher than maternal ones. Neither maternal deficiency nor abundance affected fetal plasma values. Fetal plasma carotene varied regularly with maternal carotene and could be estimated with considerable accuracy from maternal values. This suggested the possibility that vitamin A was synthesized from carotene by the fetus.

If optimal plasma values were to be maintained during pregnancy it was necessary that the woman take a diet supplying about 6000 I.U. during the first trimester. During the second and third trimesters daily supplements of 5,000 and

10,000 I.U. of vitamin A respectively were necessary for the maintenance of optimal levels in the plasma.

Immediately after delivery there was a mobilization of vitamin A into the blood stream which produced a rapid rise of plasma values. The increase was so great that maternal values which were borderline at the time of delivery became fully normal within 24 hours. These levels were usually well maintained during the remainder of the puerperium.

Complications of pregnancy and labor, and puerperal morbidity were less frequent when the plasma levels were fully normal; however, it is hazardous to attribute the responsibility of cause to a vitamin A deficiency when so many other factors were also involved.

We believe that these data accurately record the behavior of plasma vitamin A and carotene in normal pregnancy. On the other hand interpretation of the data, or any other similar data, in terms of deficiency or requirements must be made with caution.

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III. GOSSIP

From the mailbag! --

"As I listened to your talk last Saturday as I usually do and really, to be eridict, I don't think you give us much help, as mostly you plug for the Doctors by saying be sure to see your Doctor in time. That is just why I feel like writing you this note. When I heard you say that on your cancer talk last Saturday which you have done before, how many people when they feel good, go to their doctors only to be taken too much for granted, that nothing serious is the matter with them, and so they go on till its too late. Many of us have a friend who looked in perfect health but she was doctering for the last 2 years by her own doctor and this one and that one, all thinking it was her age at 48 years, till 2 months ago she went to a specialist and he told her husband she was already too far gone with cancer so there was nothing to do for her to help her any. Now Dr. O'Brien, I think it would be a good suggestion to see to it that all Doctors look for cancer from the very first symptoms of feeling ill. When people come to them first you could lessen the deaths from cancer, but most doctors get serious first when people are dying. We see that in too many cases. Tell people to live on a well balanced diet and free their mind of worry and I think you'll give them the right help.

A Listener to your talks."

..."I saw in the papers lately that Minnesota has so many feeble minded children (or people) that there is no place or room for them anywheres. A good many of this unfortunates can easily be restored to normal health by putting their feet on a warm iron two or three times a day until well again. The reason of this is the skin, the pores are too large, too much air is drawn into the body. This makes the muscles too strong, so that the head has no chance. I hope and pray that you are able to help them."

Former Minneapolis Nurse
is Promoted in Italy -

At a General Hospital of the AAF Service Command in Italy--Promotion to a first lieutenancy was recently awarded to Nurse Dorothy B. Truax, daughter of Mr. S. M. Truax of 5703 Grand Ave., West Duluth, Minnesota. Graduating from Denfield High School in Duluth, Miss Truax enrolled in the Northwestern Hospital School of Nursing in Minneapolis and upon finishing her training she became a technician in the Cancer Institute at the University of Minnesota.

1st Lt. Truax entered the Service in March 1942 at Ft. Snelling, Minnesota, and was sent to Ft. Sill, Oklahoma where she was assigned to a general hospital, with which unit, somewhere in Italy, she is now caring for patients from the famous 15th Air Force. Shipped overseas nearly 29 months ago, her tour of duty has taken her to England, North Africa, and Italy and entitles her to wear the European-African-Middle East campaign ribbon with three battle stars...

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Gilbert J. Thomas, M.D., F.A.C.S.
and
Frederick C.Schlumberger,M.D., F.A.C.S.

formerly with Moore-White Clinic of Los Angeles, announce the opening of their offices at 9622 Brighton Way, Beverly Hills, California.

Practice limited to Urology Diagnosis, Surgery and Consultations.

Dr. Frederick C. Schlumberger on active duty in United States Navy.

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One hundred physicians attended the course in Surgery at the Center this week. Allen O. Whipple, guest surgeon for the week, was an excellent teacher. In his quiet, unassuming way, he effectively presented his concepts of surgical problems in the upper abdomen. For some time, we have noted that the men we invite here from the East have certain features in common. Dr. Whipple is no exception to the rule for he, too, spent part of his life in the Midwest (in Duluth)...Postwar opportunities for physicians to come back for courses will be greatly hampered unless a large meeting place is provided at the hospitals. All the students and staff should attend as many of these sessions as possible, but crowding is so bad now that it is difficult to see and hear. We had to reject nearly 100 registrations of physicians who wanted to come to the surgery course, because of amphitheater lack...