XIX. VITAMIN A AND CAROTENE

XIV. THE VITAMIN A RESERVES OF THE HUMAN INFANT AND CHILD IN HEALTH AND DISEASE

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A preceding paper by one of us [Moore, 1937] deals with the vitamin A reserves of the human adult in health and disease. In attacking the same problem in regard to the infant and child it is necessary to face the complication that the reserves at birth are usually of a very low order. Not only, therefore, will the typical reserve in health increase with age, but it will be impossible, until we have knowledge of the rate of increase of the reserve, to decide whether low reserves are to be correlated with disease or merely with early age. Moreover, even when infancy is passed, and the reserves have reached a more or less static level, the requirements of the child for purposes of growth may well cause a relatively greater rate of expenditure than in the adult. The metabolic rate is also much greater than in later life. Data obtained on adults and children may not therefore be strictly comparable.

For these reasons it was thought undesirable to include results on infants and children in the preceding communication. A considerable bulk of such data was, however, collected in the course of this work, while in addition joint experiments were undertaken by both of us upon children dying from various infectious diseases (mostly measles) at the Grove Fever Hospital. The present paper has been based on the combined data so obtained.

Experimental

The experimental technique and method of calculation of results were exactly as described in the previous paper.

Increase of the vitamin A reserve with age. In an ideally planned experiment the increase of the vitamin A reserve with age would obviously be studied in cases of accidental death. Cases of accidental death in infants are, however, rather infrequent, and the accumulation of the necessary data would require either a very long time for collection or the collaboration of a very large number of hospitals. In the present work the data collected on accident cases alone were quite inadequate for this purpose. For reasons of expediency rather than perfection, therefore, the increase with age has been studied in cases dying from all causes. It is to be expected that the rate of increase should be reliably established in this way, although the values obtained at various ages might be expected to fall below the health level.

The results obtained on 106 cases under 3 years of age are shown in Table I. It will be seen that the vitamin A reserves were low during the first 3 months of life. In the 4–8 months' group there was a marked increase. The reserves from 9 months to 3 years were of the same order.

Table I

Age group	No. of cases	Vitamin A reserve I.U. per g. L.	M.	H.	Mean
0–4 weeks	11	1	17	67	**27**
5 weeks–3 months	21	4	14	93	**37**
4–8 months	18	54	100	230	**130**
9–18 months	37	24	73	210	**100**
19 months–3 years	19	45	99	312	**150**

The vitamin A reserve in health. Acting on the basis of the above information it was decided to omit all cases under 4 months of age from calculations of reserves in health or disease, and to combine all cases between 4 months and 14 years in single groups. Table II gives the results obtained for 12 cases of accidental injury resulting in death within 7 days. In view of the small number of cases available, calculations are also shown when six additional cases not strictly satisfying these conditions are introduced. The additional cases included one case of death 14 days after burns, one case dying 17 days after scalding, two cases of poisoning and two of sudden death in otherwise healthy boys from haemorrhage resulting from arterial abnormalities. The introduction of the additional data does not affect the median value (130 I.U. per g.).

Table II. *Accidental death*

No. cases	Details	Age group	Mean age	Vitamin A reserve I.U. per g. L.	M.	H.	Mean
12	Death within 7 days of accident	4 months–14 years	$5\frac{7}{12}$	31	**130**	230	130
18	Above with 6 additional cases (see text)	4 months–14 years	$5\frac{8}{12}$	46	**130**	240	140

The vitamin A reserve in disease. The results obtained in those diseases for which sufficient cases were available to form groups are given in Table III. In Table IV individual values are given for cases dying from more or less rare diseases. The data in this table are admittedly of little significance without support, but are placed on record in the hope that they may prove of some value to other workers in the field.

Table III. *Diseases*

	No. of cases	Mean age	Vitamin A reserve I.U. per g. L.	M.	H.	Mean
Other infections	18	$7\frac{7}{12}$	11	**47**	160	71
Head infections	33	$4\frac{10}{12}$	24	**68**	250	110
T.B.	25	$4\frac{4}{12}$	32	**140**	400	200
Measles *et sequelae**	16	$1\frac{8}{12}$	28	**110**	360	160
Respiratory diseases	18 (pneumonia)	$4\frac{9}{12}$	23	**78**	305	140
	30† (with bronchitis and empyema)	$4\frac{9}{12}$	20	**76**	280	120
Heart disease	9	$9\frac{8}{12}$	2	**15**	67	28

* Not including the treated cases given in Table V.
† Including the 18 cases of pneumonia.

Table IV

Disease	Sex	Age	Vitamin A reserve I.U. per g.
Exophthalmic goitre	♀	3	300
Congenital syphilis	♂	$1\frac{2}{12}$	5
Diabetes	♂	$\frac{10}{12}$	380
Renal rickets	♀	14	0
Infantile hemiplegia	♀	$\frac{8}{12}$	150
Acute poliomyelitis	♂	2	380
Acute leucaemia	♂	10	180
Myelogenous leucaemia	♂	14	180
Acute lymphatic leucaemia	♂	12	15
Lymphoid hyperplasia	♀	2	75
Erythema multiform	♂	$1\frac{6}{12}$	180
Purpura	♂	12	30
Pink disease	♀	$1\frac{4}{12}$	75
"	♂	$\frac{4}{12}$	380
Pyelitis (uric acid infarcts)	♀	$\frac{6}{12}$	50
Acute cystitis	♀	$5\frac{1}{12}$	150

Notes on Table IV. The high values found in cases of exophthalmic goitre and diabetes are in agreement with results for adults. The value in the case of acute cystitis is much above the adult median for urinary infections.

The efficiency of absorption of therapeutic doses of vitamin A concentrate by fever patients. Table V gives the reserves found at autopsy in the livers of infants suffering from measles or pertussis, who had been unsuccessfully treated by

Table V. *Storage of vitamin A administered in treatment of infants suffering from acute infectious diseases*

Case	Sex	Age	Disease	Duration of vitamin A therapy days	Total amount of vitamin given I.U.	Vitamin A reserve per g. liver	Total reserve	Maximum storage %
E. W.		$1\frac{5}{12}$	Measles. Bronchopneumonia. Acute laryngitis	10	140,000	30	9,000	6
D. L.	♂	$1\frac{1}{12}$	Measles. Bronchopneumonia. Otitis media	6	84,000	60	16,000	19
G. M.	♂	$1\frac{4}{12}$	Pertussis. Bronchopneumonia. Convulsions	16	230,000	60	17,000	8
R. W.	♀	$\frac{9}{12}$	Measles. Bronchopneumonia. Marasmus	4	29,000	75	19,000	65
J. M.	♀	$\frac{11}{12}$	Measles. Bronchopneumonia	10	140,000	90	23,000	16
M. F.	♂	$1\frac{6}{12}$	Measles. Bronchopneumonia	9	130,000	150	45,000	34
G. R.	♀	$1\frac{7}{12}$	Pertussis. Measles. Bronchopneumonia	9	130,000	300	93,000	100
J. C.	♀	$1\frac{10}{12}$	Measles. Bronchopneumonia	4	58,000	380	124,000	100
D. A.	♀	2	Measles. Scarlet fever. Mastoiditis. Bronchopneumonia	21	150,000	380	130,000	85

vitamin A therapy. The vitamin A was given in the form of the concentrate "adexolin", and was kindly provided by Messrs Joseph Nathan and Co. Ltd. In calculating the total reserve of the liver the weight of this organ has been estimated from a curve based on representative weights at different ages.

Discussion

The vitamin A reserves of the new-born infant. The work of Wolff [1932] and of Toverud & Ender [1935], who used the colorimetric method of assay, and of Debré & Busson [1933, 1] using the biological method, makes it clear that in the human being just as in all lower animals so far investigated, the vitamin A reserve at birth is usually much lower than in the adult. As in the adult considerable individual variation is found, but results obtained in different laboratories on groups of cases appear to be in close agreement[1] (Table VI). Since the number of specimens from new-born infants examined in the present work was insufficient for forming a separate group, data on infants dying within a few weeks after birth have been given for purposes of comparison.

Table VI. *Vitamin A reserves of new-born infants*

	No. of cases	Mean vitamin A reserve (I.U. per g.)
Wolff [1932] (Amsterdam)	24 (full term)	44
	18 (premature)	41
Toverud & Ender [1935] (Oslo)	50 (full term)	39
	47 (premature)	65
Ellison & Moore (1937)	11 (0–4 weeks)	27
	21 (5–12 weeks)	37
Moore [1937]	40 (adults, 15–59 years)	290

The increase of the vitamin A reserve with age. Our finding of a sharp rise between the 5 weeks–3 months group (median 14) and the 4–8 months group (median 100) is of interest in suggesting that the reserve reaches a more or less static level during what would be, under normal circumstances, the later stages of lactation. Since the nutritional history of individual cases was seldom available we cannot exclude the possibility that in some cases the increase in reserves may have been partly due to the use of cod liver oil, or other rich sources of the vitamin. It seems reasonable to assume, however, that in most cases the diet was human milk, cow's milk or proprietary foods not exceeding cow's milk in their vitamin A content. Assuming a diet of whole cow's milk, we may draw up the following rough comparison. (The vitamin A content of butter fat is taken at 30 I.U. per g., a value intermediate between the summer and winter levels.)

Vitamin A ingested	Vitamin A stored
Mean consumption = 30 oz. of cow's milk per day = 34 g. of butter fat per day = 1020 I.U. per day of vitamin A	Weight of liver at 200 days = 220 g. Median reserve = 100 I.U. per g.
Total vitamin ingested in 200 days = 204,000 I.U.	Total reserve = 22,000 I.U.

If we take the vitamin A expenditure in the infant as similar to that in the rat, weight for weight, we may very roughly estimate that the daily requirement of a baby of 11 lb. is 500 I.U. per day. For 200 days therefore the requirement should be 100,000 I.U. It is clear, therefore, that the difference between the amount of vitamin ingested (200,000 I.U.) and the amount required (100,000 I.U.) may be sufficient to account for the accumulation of reserves of the magnitude actually observed. This point is of interest because milk cannot be regarded as a rich source of vitamin A. In the infant, however, it is the principal, and often the sole, component of the diet, and the dilution of the vitamin may be compensated by the large amounts ingested.

The drain of lactation on the maternal reserve. Debré & Busson [1933, 2], using a biological method of assay, found human milk to be slightly inferior to cow's milk in vitamin A content. Eekelen & Haas [1934], using colorimetric methods,

[1] The results of Toverud & Ender have been adjusted to make allowance for their use of a blue unit of different magnitude from that of the other workers.

found the vitamin A and carotene contents of milk from both sources to be very similar. Assuming the correctness of the latter finding, and making no allowance for the increased vitamin A content of the colostrum, we may calculate the total vitamin secreted during 9 months of lactation as 300,000 I.U. If the mother were placed on a diet deficient in vitamin A, and the liver reserve were used for purposes of lactation, the total excretion would represent about 200 I.U. per g. of liver, an amount approximating closely the whole typical reserve. The importance of an adequate supply of vitamin to the mother is obvious, and appears quite as essential as the additional supply of vitamin to the child at weaning advocated by Dann [1932].

The vitamin A reserves in health (Table II). The median reserve (130 I.U. per g.) found for cases of accidental death in children between the ages of 4 months and 14 years was lower than the value for adults (220). In view of the small number of child cases available, complete confidence cannot be placed in the general applicability of this result. A lower reserve in childhood might possibly result from a greater expenditure of the vitamin for purposes of growth. It must not be forgotten however that in the child the liver represents a greater fraction of the total body weight than in the adult. The reserves in the child per kg. of body weight must therefore be relatively greater than the values expressed in units per g. of liver would indicate.

The vitamin A reserves in disease (Table III). In those diseases where groups of cases were collected the median reserves per g. were generally no lower than for adults. Since, as stated above, the median value in health was lower than in adults the disparity between the values in health and disease in children was correspondingly less pronounced, although still considerable. Otherwise there was good general agreement between the results for adults and children. Of the diseases for which data were available for both adults and children tuberculosis in each case showed the highest vitamin A reserve, although in children the median (140) was much higher than in adults (96). This finding may possibly be ascribed to a greater use of cod liver oil therapy in children. Pneumonia gave medians of the same order in both age groups (children 78, adults 63). The two septic disease groups, head infections (children 68, adults 73) and septic diseases (children 47, adults 51) gave virtually identical values. In valvular diseases of the heart low reserves were observed in both age groups, but the median in children (15) was much lower than in adults (60). This result is of interest in view of the suggestion [Rinehart & Mettier, 1933; 1934; Rinehart, 1935; Stimson *et al.* 1934] that rheumatic disease in children may be related to vitamin C deficiency.[1] As pointed out in the preceding paper [Moore, 1937] a diet low in vitamin A would probably be deficient in other factors, including vitamin C.

The substantial agreement between the results obtained in adults and children must increase confidence in the conclusion that the median values obtained, although admittedly at the mercy of chance "runs" of low or high values, are in practice of genuine significance.

The vitamin A reserves in measles. The median reserve in measles (110) was only slightly below the health level. Similar results were observed in the few cases of pertussis examined (individual values 60, 90, 140). These results are in contrast with those observed in head infections and septic diseases. Judging from these results it appears that low vitamin A reserves are frequent in "septic" diseases but not in "acute infectious diseases". The observation of comparatively

[1] Abbasy *et al.* [1936] have recently shown that low vitamin C reserves, as measured by urinary excretion, are found in children suffering, or convalescent from, rheumatic disease.

high reserves in measles is difficult to reconcile with the finding of one of us [Ellison, 1932] that vitamin A therapy had a favourable influence on the survival rate. A solution of the problem may well be deferred until more is known of the beneficial effects, if any, of the possession of a vitamin A reserve greater than the bare minimum supposed to be necessary to satisfy immediate requirements.

Efficiency of absorption of vitamin A. The results shown in Table V indicate that the efficiency of storage of vitamin A concentrate may be very low. Even if we assume that the liver reserves at the commencement of dosing were entirely negative, and that the reserves observed at autopsy were accumulated exclusively during dosing, the maximum possible storage so calculated was in some cases very low (6 %). A better assessment of the probable amount of vitamin actually stored by the whole group may be based on a calculation of the difference between the mean observed in the treated group (170) and the mean observed in a similar group of 17 non-treated cases (140). On this basis we find that a total administration of 1,100,000 units of vitamin A caused a mean increase of 30 units per g. in 2600 g. of liver (78,000 units in all), giving a percentage storage of 7. The smallness of the difference in the mean values, and the small number of cases available make the reliability of this calculation very questionable, but at any rate it is clear that the percentage storage is low. This result is in agreement with the observations of Green [1932] on cases of puerperal septicaemia. That the percentage of storage may be low even in health may be inferred from the results of animal experiments. Thus Davies & Moore [1934] found that when young rats were given large doses of vitamin A the proportion stored was generally only about 15 %.

SUMMARY

1. Vitamin A was estimated in livers of about 200 children under 15 years of age dying by accident or from disease.

2. The variation of the vitamin A reserves with age was studied by combining cases dying from all causes. In confirmation of previous workers the vitamin A reserves were found to be very low in young infants (0–4 weeks, median 17 I.U. per g.; 5 weeks–3 months, median 14). After the first 4 months the reserves rose to a much higher level (4–8 months, median 100; 9–18 months, median 73; 19 months–3 years, median 99). Calculations show that a diet of cows' milk, and probably also human milk, should contain sufficient amounts of vitamin to permit the accumulation of reserves of the order of magnitude observed.

If a mother having a vitamin A reserve equal to the typical value found in health were restricted during lactation to a diet deficient in vitamin A the total secretion, if maintained at the normal rate, would represent almost the whole liver reserve.

3. The median value for a group of 12 healthy children dying by accident between the ages of 4 months and 14 years was 130 I.U. per g. of wet liver. This value is lower than in the healthy adult. The relatively greater size of the child's liver must however be taken into account in comparing total reserves.

4. The vitamin A reserves in disease were as follows. *High reserves*: tuberculosis (median 140). *Moderate reserves*: measles *et sequelae* (110). *Low reserves*: pneumonia (78), head infections (68), septic diseases (47), heart diseases (15). In those diseases for which data on adults are also available the general agreement with the above results is good, and particularly so in the septic diseases. Low reserves were not found in acute infectious diseases.

5. A comparison of the reserves found at autopsy in 9 cases of measles treated with vitamin A concentrate with those found in a group of similar untreated cases indicates that the percentage of the vitamin ingested which is stored in the liver may sometimes be very low.

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