VITAMIN A DEFICIENCY IN CHILDREN

Part II.—Vitamin A requirements of babies: Skin lesions and vitamin A deficiency

BY

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Do bottle-fed babies require more vitamin A than they are likely to get if no special precautions are taken to provide an extra source of this vitamin? We know that in Great Britain, in the absence of special precautions, vitamin D deficiency is widespread among babies in winter, and vitamin C deficiency may occur on various types of artificial feeding. Of the extent of other vitamin deficiencies in this country, if they exist, we have scarcely any knowledge. At the present time potent vitamin D preparations, prepared by irradiation of ergosterol and devoid of vitamin A, are widely displacing cod-liver oil (which contains both D and A) for the prophylaxis of rickets. Are we thereby running the risk of widespread, if slight, vitamin A deficiency? And what are the signs of slight A deficiency in babies? If either of the names 'growth promoting' or 'anti-infective' vitamin, which have gained wide acceptance, are justified in any special sense, presumably defective growth and lowered resistance to infection would be early symptoms of vitamin A deficiency. The investigation described in this paper was undertaken in the hope of obtaining an answer to some of these problems.

Nature of present investigation.

This investigation, begun in January, 1931, lasted for nearly two years, and was concerned with artificially-fed babies and young children up to 2 years of age living in their own homes. The work was prophylactic. The babies were divided into two groups and conditions for the two groups were kept as similar as possible except in the matter of vitamin A intake. The controls received only what vitamin A or carotene was normally present in the dried milk or 'table food' (i.e. mixed diet) they received. The group with which they were compared received additional vitamin A, both incorporated in their milk and also as an emulsion. The author⁸ in her work on infantile anaemia has shown that the influence of iron deficiency in lowering resistance to infection and retarding growth can be clearly

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demonstrated by an investigation carried out on similar lines to the present one: hence if these babies suffered from vitamin A deficiency the effects should be apparent. Except in this one point of vitamin A intake the two groups of babies were fairly matched and similarly treated and should provide a definite answer to some of the problems put forward.

Clinical material.

The babies attended the out-patient department of the Queen's Hospital for Children, which is in a poor district in the East End of London. Babies of the poorest social class, children whose fathers were out of work, were intentionally included among the numbers, as it was presumed that any vitamin A reserves obtained by the foetus from the mother would be lowest among such infants.

Number of babies.—The babies numbered in all 171, but of these only 118 were included in the final comparison: 58 of these served as controls, and the remaining 60 were given extra vitamin A, and will henceforth, for the sake of brevity, be called the 'A group.' The 53 children finally rejected from the comparison were excluded for the most part on account of insufficient attendance or insufficient treatment. No child was included who did not attend, and, if in the A group, receive extra vitamin A for at least four weeks. A few have been omitted for other causes; such, for example, as habit vomiting (2 cases), evidence of mental deficiency (2 cases), symptoms of thyroid insufficiency (1 case), or the administration of cod-liver oil by the mother to a control.

Age of infants.—On coming under observation the age distribution of the 118 children was as follows: 65 infants (55 per cent.) were under 3 months old; 45 (38 per cent.) were between 3 and 5 months old; and the remaining 8 (7 per cent.) were between 5 and 7 months old. Thus 93 per cent. of the babies were under 5 months old when first included in the series, the youngest being 29 days. The oldest child at the end of the observation was 25 months old.

Period of attendance.—The period of attendance varied from 4 weeks to $20\frac{3}{4}$ months, and averaged about 8 months (table 2).

Clinical condition of infants.—The majority of the babies were brought to the hospital for underfeeding, or other feeding difficulties, with or without some minor infection such as bronchitis or thrush. Of the rest, a few were patients discharged from the wards after an acute illness, e.g. pneumonia or enteritis, and others attended for such conditions as bronchitis (10 cases), otorrhoea (2 cases), enteritis (2 cases), prematurity or low birth weight (6 cases, 2 with rickets), etc. Nearly all were under normal weight when first seen, and many were in poor general condition, but no baby on first inclusion was seriously ill with any infection. The great majority made good general progress as can be seen in table 2 where it is shown that in the winter of 1930-31 and the summer of 1931 (when the babies were for the

most part young) the weekly gain averaged approximately $5\frac{3}{4}$ to $6\frac{1}{2}$ oz. (163 to 184 gm.) and in the two following seasons (when most of the babies were older, a number being in the second year of life), the weekly gain averaged $3\frac{1}{2}$ to 4 oz. (99 to 113 gm.)

Economic status of families.—The fathers were mostly manual workers. A number were out of work and in receipt of either unemployment allowance or public (municipal) assistance. Out of the 118 families, 26 received a milk grant from the borough, i.e., were in receipt of an income held by the community to be insufficient to maintain health. A further 10 were granted extra nourishment from charitable sources after investigation of the circumstances by the hospital almoner. Thus approximately 30 per cent. were at some time in receipt of additional food from charitable or municipal sources. It is fairly certain that in the face of privation the baby of the family will be the last to go short of any food which the mother realises he requires, and even in the poorest families the child's feeding usually appeared to be in the main according to instructions. On the other hand, as already indicated, there seems a likelihood that the baby may be born with small vitamin A reserves, as the brunt of a poor diet will probably fall on the mother of the family². It should be noted, however, that the parents were not all poverty stricken and included small shop keepers and others in more comfortable circumstances and in regular work.

Attendance of infants.—During the first few weeks of attendance mothers were asked to bring their babies to hospital weekly or even oftener, but once a child was established on its diet, a fortnightly attendance was asked for. Many attended with great regularity. A child who for any reason, other than an infectious fever, was not seen at the clinic for six weeks (even though taking the food prescribed), was counted as having ceased to attend. At each attendance the child was weighed and was examined naked by the author, a detailed record being kept of its clinical condition.

The diet given.

All the babies until such time as they were put on a mixed diet, were given dried milk with added sugar, together with supplements of iron to prevent anaemia, irradiated ergosterol to provide vitamin D and to prevent rickets, and orange juice to provide vitamin C and prevent scurvy. All the A group received additional vitamin A. After the child was 7 to $7\frac{1}{2}$ months old the mother was asked gradually to reduce the dried milk to 1 lb. weekly and concurrently to introduce other food into the child's diet. When the child was 8 to $8\frac{1}{2}$ months old the diet advised was medicated dried milk, 1 lb. packet weekly, fish on two to three days weekly, eggs, 3 or more in the week, and fruit daily, besides milk puddings, bread and other cereal food, vegetables, gravy, broth, etc. The mother was advised to start the child on meat at about 11 to 12 months of age.

Dried milk.—The milk supplied was a roller-process dried milk made by Messrs. Cow & Gate. One advantage of using dried milk and not fluid dairy milk in such work was that by incorporating extra vitamin in the milk and keeping a register of milk packets sold it was possible to know whether or not babies were receiving the vitamin ordered. The milk was that of Devon cows from a Dorset farm. Since these cows supply a milk of high fat content, it was skimmed at the factory and the fat standardised at 3.48 per cent. before drying. To all the milk before drying was added iron and ammonium citrate ($31\frac{1}{2}$ grains to each pound of the dried milk), and also irradiated ergosterol to increase its vitamin D value. In addition to the iron and irradiated ergosterol, vitamin A was also incorporated in the milk given to the A group. (For the vitamin values of these additions, see discussion at the end of this section.)

Messrs. Cow & Gate prepared the milk at intervals of approximately 2 to 3 weeks or occasionally 4 weeks, and nearly all the milk was consumed well under 6 weeks from the date of preparation. The two dried milks will in future be referred to as Hemolac + D and Hemolac + D + A respectively.

The dried milk was sold to the mothers at the hospital at cost price. In the case of necessitous families receiving a free milk grant from the borough, it was arranged that the mother should either get milk free through the hospital (the cost being defrayed by the borough), or should get plain dried milk from her borough and exchange it weekly at the hospital for the medicated milk. A record was kept of each packet of medicated milk supplied to a mother, and the quantity used was checked by the feeds ordered for the baby and the packets sold. Up till the age of 7 to $7\frac{1}{2}$ months practically all the calorie needs of the babies were supplied in dried milk and sugar, say 90 to 135 calories daily in sugar and the rest in milk, with the small supplements mentioned. Thus a baby of 9 to 10 lb. body weight probably consumed the contents of a 1 lb. packet of dried milk weekly (equivalent to a little under 1 pint, or about half a litre of fluid milk daily), increasing steadily to about two 1 lb. packets weekly (say $1\frac{1}{2}$ pints, or about 1 litre, of fluid milk daily) by 7 months old. At this age mixed food was started, and the dried milk proportionately reduced, until a child of 8 to 9 months and upwards would be getting about 1 lb. of the dried milk weekly.

Sugar.—The mother was advised to add either 1 drachm (about 4 gm.) or usually $1\frac{1}{2}$ drachms of castor sugar to each bottle feed, i.e., about 90 to 135 calories daily were given in added sugar. Younger babies received a higher percentage of sugar in the milk than older babies, since increases in food were made in milk with no corresponding increase in sugar.

Iron.—A baby getting 1 lb. of dried milk weekly received incorporated in it $31\frac{1}{2}$ grains (about 2 gm.) of iron and ammonium citrate, equivalent to a daily allowance of about $4\frac{1}{2}$ grains of iron and ammonium citrate. Babies on larger milk allowances received proportionately more. When mixed food was given the natural iron in the diet was, of course, much increased.

Vitamin C.—Every mother was advised to give her baby a minimum of one teaspoonful of orange juice daily. Many babies, especially if constipated, were given much larger amounts. From the age of 7 to 8 months other fruit was given.

Vitamin D.—Besides the natural vitamin D of dried milk or 'table food,' each baby received irradiated ergosterol both incorporated in the dried milk and also as an emulsion administered by the mother. This added irradiated ergosterol emulsion, however, was not given during the early weeks of 1931 to the first 17 babies included in the investigation, but was subsequently ordered for all the babies so as to provide an additional source of vitamin D should the mother, by any chance, temporarily run out of the medicated dried milk.

All the vitamin additions were prepared, standardized and emulsified with Irish moss (carrageen) and acacia by The British Drug Houses Ltd., and were supplied in the form of an emulsion both to Messrs. Cow & Gate Ltd., for incorporation in the milk, and to the hospital for dispensing.

The quantities of vitamin D provided were as follows:—

To each pound of dried milk was added before drying 9,800 international units of vitamin D in the form of irradiated ergosterol emulsion, the potency of which had been determined by the line test on rats. Thus if the mother omitted to give any of the extra emulsion a baby of 10 lb. weight would still receive, say, 1,400 international units daily incorporated in his dried milk. In addition to the vitamin D in the milk, babies were ordered 1,050 units of D daily in the form of a separate emulsion (1 drachm—about 4 c.c.—twice daily). If, on first inclusion in the investigation there were any delay in changing the baby from his previous feed on to the medicated milk, the amount of emulsion ordered was increased to 1 drachm three times daily, or 1,575 units per day. Thus, if no vitamin D was destroyed in the process of drying the milk, the total vitamin D supplement would have amounted to, say, 2,450 international units per day for a baby of 10 lb. body weight. This is nominally the equivalent in vitamin D of say 24 c.c., or a little under 1 oz., of a good cod-liver oil daily. In cod-liver oil this is an enormous dose, but some vitamin D may have been destroyed during the drying of the milk, and moreover it seems probable that rat units do not satisfactorily indicate the relative dosage of different substances required for the prevention or treatment of rickets in children^{1, 3}, nor, for that matter, in other young animals¹⁴. The amount of vitamin D given prevented the development of rickets in all the children included in the series. That a vitamin D supplement is required by artificially-fed babies in winter is already definitely established, and was, as it happens, also demonstrated by a baby in the series who had been given by the mother only a small and uncertain amount of the medicated milk (with unmedicated dried milk in the intervals) and no extra emulsion, and who consequently developed rickets in April, 1931. He was one of those rejected from the investigation on account of insufficient treatment. No ill effects were observed in any children from the dosage of irradiated ergosterol employed.

Vitamin A in the diet.—The controls received the natural vitamin A contained in the dried milk or 'table food' (i.e., the mixed diet described) only. The A group received in addition vitamin A incorporated in the dried milk and also in the form of a separate emulsion. Thus the control group were given Hemolac+D and an emulsion of vitamin D, and the A group Hemolac+D+A and an emulsion of vitamin D+A. As noted under the heading 'Vitamin D,' the emulsions administered by the mother were not in use during the first weeks of the observation.

The vitamin A concentrate, prepared from mammalian livers, was dissolved in arachis oil, and was standardized and emulsified by The British Drug Houses. There is no doubt that the A group received far more vitamin A than the controls, but to state positively how much more is not possible.

a. **VITAMIN A IN THE DIET OF CONTROLS.**—To begin with let us consider the natural vitamin A content of the milk given to the controls. (Table 1.) Comparatively little information appears to exist concerning the effect on the vitamin A of milk of drying by the roller process on a commercial scale.

TABLE 1.—VITAMIN A VALUES OF THE DRIED MILKS USED IN TERMS OF STANDARD COD-LIVER OILS.

Approximate date estimated.	Cod-Liver Oil Equivalents.		Cod-Liver Oil Standard employed.	Approximate date of drying.	Estimated by.	Method of Estimation.
	Hemolac + D	Hemolac + D + A				
Nov.-Dec., 1930	per lb. 15.3 gm. (A)	per lb. —	12.0 blue value	Nov. 17th, 1930	K. Coward	Biological
Jan.-Feb., 1931	8.7 gm. (A)	29.7 gm. (a)				
14th April, 1931	11.5 c.c. (B)	100 c.c. (b)	7.5 blue value	April, 1931	F. H. Carr	Colorimetric
3rd June, 1931	12.0 c.c. (B)	98.5 c.c. (b)				
26th Sept., 1931	2.09 c.c. (C)	67 c.c. (c)	7.5 blue value	Sept. 10th, 1931	F. H. Carr	Colorimetric
Oct.-Nov., 1931	13.0 gm. (c)	45.4 gm. (c)	12.0 blue value	„	K. Coward	Biological

The letter following the cod-liver oil equivalent of Hemolac + D and Hemolac + D + A indicates the batch of milk; two figures followed by the same letter represent two different estimations of the A value of one batch of dried milk.

Sherman and Smith¹³ give the average vitamin A content of fluid milk as about 2 units per gramme, and of dried whole milk as 16 units per gramme. If these estimations were carried out on milk from the same source before and after drying, they would imply no destruction.

Two sets of figures on the vitamin A content of Hemolac + D are available:—

1. Dr. Katharine Coward generously undertook for the author in the laboratories of the Pharmaceutical Society of Great Britain a biological comparison of the vitamin A content of Hemolac + D and Hemolac + D + A respectively. No simultaneous test on a cod-liver oil was made, but it is possible to give the approximate A value in terms of a standard cod-liver oil by comparing the dose of Hemolac + D which brought about the increase in weight of the rats in this test with the dose of cod-liver oil which brought about the same increase in weight when the curve of response to doses of vitamin A (which is used in the Pharmaceutical Society's Laboratories) was made. Two tests on this sample of Hemolac + D were carried out. The values found by the two tests were:—

(See 'A' in table 1.) Vitamin A value per lb. equivalent to 15.3 gm. cod-liver oil of 12.0 blue value.

(See 'A' in table 1.) Vitamin A value per lb. equivalent to 8.7 gm. of the same cod-liver oil.

This might appear to indicate a loss of vitamin A potency during the six weeks interval between the two tests, but Dr. Coward has shown, by a series of tests of the same sample of cod-liver oil carried out in successive months, that its apparent vitamin A value may show a two-fold variation from month to month. Without simultaneous tests on a standard, she is of opinion that it is impossible to regard the above figures as evidence of deterioration of the Hemolac + D.

About a year later Dr. Coward estimated the value of another sample of Hemolac + D again, for comparison with a sample of Hemolac + D + A. By

comparison with a simultaneous test made on the sample of cod-liver oil mentioned above, the following result was obtained:—

(See 'C' in table 1.) Vitamin A value per lb. equivalent to 13.0 gm. of the same cod-liver oil.

2. Dr. F. H. Carr, of The British Drug Houses Ltd., very kindly undertook a comparison by the colorimetric method. To carry out this test the dried milk was extracted with chloroform, filtered, the chloroform distilled in vacuo and the residue dissolved in chloroform and tested with the antimony trichloride reagent by the method of Carr and Price. Dr. Carr's figures for the vitamin A content of Hemolac + D in terms of a cod-liver oil of 7.5 blue units value were as follows for two estimations carried out on one sample:—

(See 'B' in table 1.) Vitamin A value per lb. equivalent to 11.5 c.c. of cod-liver oil; and

(See 'B' in table 1.) Vitamin A value per lb. equivalent to 12.0 c.c. of cod-liver oil.

The second estimation was made two months after the first. These figures suggest that the A value is well maintained during two months' storage.

Messrs. Cow & Gate kindly allow the author to state that estimations on their full-cream dried milk carried out by Prof. H. Steudel, of Berlin University, support this conclusion. He showed that its vitamin A content was almost unchanged after nine months' storage in closed tins.

Dr. Carr also carried out an estimation on the same sample of Hemolac + D as was last examined by Dr. Coward, and whereas her biological estimation indicated an A content equivalent to 13.0 gm. of cod-liver oil per lb., his colorimetric estimation gave a value equivalent to 2.09 c.c. of cod-liver oil of a much lower blue value. Dr. Carr considers that his figures may be too low as some vitamin A may be destroyed in the process of extraction for the colour test.

It is obvious that there are discrepancies in these findings, but as far as the author is able to ascertain the majority give for reconstituted dried milk vitamin A values of a similar order to those obtained for fresh cow's milk.

The natural vitamin A and carotene obtained by the babies from the 'mixed feeding' given after 7 months of age was fairly liberal. The eggs, fish, dripping, green vegetables, fruit, and, later, meat fat, would all supply vitamin A.

b. VITAMIN A IN THE DIET OF 'A CASES.'—So far we have considered the quantity of vitamin A in the diet of controls. If we consider the vitamin A intake of the 'A group,' we can safely assume that it was at the very least a number of times as great as that of the control group, for they received vitamin A from the same natural sources as the controls, and were given in addition extra vitamin A both incorporated in their milk (Hemolac + D + A) and in the form of an emulsion (Emulsion D + A).

With regard to the milk, Dr. Coward finds by biological tests that Hemolac + D + A contained 3 or 4 times as much A as Hemolac + D when batches of milk prepared on the same date are simultaneously estimated. Dr. Carr finds by the colour test that it contains 8 to 30 times as much when batches of milk prepared on the same date are compared (table 1).

The usual dose of vitamin A emulsion given to the A cases in addition was 2 drachms daily, estimated by Dr. Carr to be equivalent in vitamin A value to 3 drachms ($10\frac{1}{2}$ c.c.) of cod-liver oil of 7.5 blue units value. If we accept Dr. Carr's average vitamin A value for the Hemolac + D, we find that the daily dose of 2 drachms of emulsion contained as much vitamin A as about $1\frac{1}{4}$ lb. of the milk given to the controls, i.e., that in one day in the emulsion alone the 'A group' received as much vitamin A as did many controls in a week's supply of milk.

Hence, although it is impossible to make any definite statement in figures as to the relative vitamin A intake of the controls and the A cases, we can safely assume that at the lowest estimate the A intake of the A group was many times greater than that of the controls.

Results.

As will be seen from table 2, the children of the two groups were fairly evenly matched as regards age, sex and weight at the outset of the investigation. The average duration of attendance differed by only a few days, and consequently the average age of the children in the two groups throughout the investigation was similar.

TABLE 2.—THE AGES AND WEIGHTS OF THE VITAMIN A CASES AND CONTROLS COMPARED.

WHOLE PERIOD.	No. of Cases	Sex. M. F.		Average Age.				Average Weight.				Average total gain		Average weekly gain		
				First		Last		Average		First					Last	
				Attendance	Attendance	Attendance	Attendance	Attendance	Attendance	Attendance	Attendance					
				mths.	days	mths.	days	mths.	days	lb.	oz.	lb.	oz.	lb.	oz.	oz.
A cases	...	60	40 20	2	24.5	10	28.5	8	4.0	9	2.9	18	12.6	9	9.7	4.41
Controls	...	58	39 19	2	28.9	11	6.4	8	7.5	9	10.4	19	7.2	9	12.8	4.43
SUB-DIVIDED BY SEASON																
Winter 1930-31																
A cases	...	20	13 7	2	28.3	4	18.7	1	20.4	9	9.4	12	4.5	2	11.1	5.99
Controls	...	19	11 8	3	6.9	5	4.4	1	27.5	9	7.1	12	12.2	3	5.1	6.46
Summer 1931																
A cases	...	38	24 14	3	24.3	7	4.1	3	9.8	10	12.9	15	13.2	5	0.3	5.63
Controls	...	36	23 13	3	28.4	7	3.8	3	5.4	11	4.1	16	1.2	4	13.1	5.66
Winter 1931-32																
A cases	...	45	31 14	5	25.2	10	25.6	5	0.4	13	9.9	18	9.3	4	15.4	3.70
Controls	...	42	29 13	5	15.8	10	8.4	4	22.6	13	15.4	19	1.0	5	1.6	4.01
Summer 1932																
A cases	...	31	22 9	9	10.5	12	17.3	3	6.8	16	6.0	19	11.9	3	5.9	3.90
Controls	...	33	24 9	8	20.8	12	15.1	3	24.3	17	5.9	20	13.5	3	7.6	3.41

Weight.—The control group averaged 4 days older and $7\frac{1}{2}$ oz. heavier at the outset. If we assume that the normal rate of growth in the third month of life is 6 oz. (170 gm.) weekly, this would imply that age for age the controls averaged $3\frac{1}{2}$ oz. (about 99 gm.) heavier than the A cases at the outset. This slight superiority in weight was maintained, so that the average weekly gain of the two groups was almost identical, namely, 4.43 oz. and 4.41 oz. respectively, a difference of only $\frac{1}{10}$ th of an ounce in favour of the control group (table 2).

If the groups are subdivided by season it will be seen that the seasonal distribution is fair, and that in the smaller subdivisions sometimes one group, sometimes the other shows a slight superiority in rate of gain. Hence we may say that added vitamin A did not increase the rate of growth.

Morbidity rates.—a. **GENERAL.** Morbidity rates were ascertained and compared in the manner already described in the author's work on nutritional anaemia in infancy⁸. The illnesses were counted from the babies' weight charts. Any infection accompanied by a retardation of gain in weight or an actual loss in weight was counted as an illness. Specific fevers (whether or not the baby's weight was available) and attacks of otorrhoea were also counted as illnesses. On the other hand a loss in weight attributed to under-feeding was disregarded. In spite of the subjective nature of such illness counts the author believes that carried out with care they afford fair comparisons.

Reckoned in this way the A group and controls showed morbidity rates which were closely similar as will be seen from table 3. This holds good not only for all illnesses, but also for diseases of the respiratory tract, diseases of the digestive tract and specific fevers when estimated separately. Again if the cases are subdivided by season, a superiority of a small A group in one season is counterbalanced by the superiority of a similar control group in another. (Table 4.) Hence added vitamin A did not reduce the general morbidity rate.

b. **LESIONS AFFECTING SKIN, MOUTH AND EYES.** Lastly, the incidence of lesions of the skin, mouth and eyes was compared in the two groups (table 5). The incidence of eye infections is similar in the two groups. The controls show a slight superiority over the whole period, but this is not constant in the seasonal subdivisions (table 6), and the numbers are small.

Again in lesions of the mouth, the incidence is higher in the A group, but the difference is not uniform over the seasons. In the first two seasonal subdivisions the controls are superior, in the second two seasonal subdivisions the incidence is similar (table 6) and the difference is probably a matter of chance. The actual difference was that in a period of nearly two years 12 more attacks of thrush occurred in the A group than in the controls; there were 19 attacks in the A group and 7 among the controls.

As regards skin lesions an interesting fact is revealed. The incidence of 'infective' lesions of the skin was in the A group approximately half what it was in the control group. The lesions included as 'infective' may for the most part be regarded as due to some form of local irritation with an infection (by local organisms of low virulence) taking temporary root as a result, e.g., sore buttocks, sore scrotal skin or foreskin, intertrigo, dribbling eruptions, etc. Tables 5 and 6 show that each type of infection of the skin included is more common in the controls than in the A group, and that this is so in each of the four seasons under consideration, facts which lend strong support to the view that the difference is significant and not the result of chance. This difference in the incidence of infective skin lesions is the only difference between the two groups which is uniform over the seasons.

If, on the other hand, we examine lesions of the skin with no evidence of microbial infection (urticaria, rough face and sweat rash or erythema), the incidence in the two groups is closely similar all the way through.

TABLE 3.—GENERAL MORBIDITY RATES. VITAMIN A CASES AND CONTROLS COMPARED.

	Vitamin A Cases.			Controls.	
No. of infants	60	...	...	58	
Average attendance ...	8.1 months	...	...	8.2 months	
No. of child-months ...	485.6	...	...	476.1	
Disease.	No. of attacks.	No. per 100 child-months.		No. of attacks.	No. per 100 child-months.
Respiratory tract.					
Cold in head and sore throat	44	9.1	18.5	43	9.0
Bronchitis	35	7.2		47	9.9
Pneumonia	0	—		1	0.2
Otorrhoea	11	2.3		3	0.6
Digestive tract.					
Stomatitis	5	1.0	7.8	2	0.4
Diarrhoea & vomiting or either.	33	6.8		34	7.1
Specific fevers.					
Scarlet fever	0	—	3.3	2	0.4
Measles	12	2.5		9	1.9
German measles	1	0.2		1	0.2
Whooping cough ...	2	0.4		5	1.1
Chicken pox	1	0.2		0	—
Meningococcal meningitis	0	—		1	0.2
Other diseases	4	0.8		4	0.8
TOTAL	149	30.8		152	31.9
Deaths	1	0.2		2	0.4

In order further to test this difference in skin infections between the two groups, the number of babies with infective skin lesions was examined, and in table 7 the number of babies affected is shown, whereas in the previous tables 5 and 6, the number of attacks of infection were counted, and one baby might have had several attacks. When the number of babies was

counted it was found that in the control group of 58 there were 30 children (52 per cent.) who had suffered from one or more infective skin lesions, whereas in the vitamin A group of 60 children the number was only 16 (27 per cent.), i.e., roughly half the number affected in the control group. Dr. A. Bradford Hill, of the Statistical Department of the Medical Research Council, has very kindly examined these figures and concludes that this difference (25 per cent. $\pm$ 8.98) is unlikely to have arisen merely by chance since not only is it two and three-quarter times its standard error, but is to be observed in each season.

TABLE 4. GENERAL MORBIDITY RATES. VITAMIN A CASES AND CONTROLS COMPARED: SUBDIVIDED BY SEASON.

	Winter 1930-31.		Summer 1931.		Winter 1931-32.		Summer 1932.	
	A cases	Controls	A cases	Controls	A cases	Controls	A cases	Controls
No. of child-months	33.6	36.4	126.4	114.4	225.6	199.5	100.0	125.7
	No. Per 100 of child attacks mths.	No. Per 100 of child attacks mths.	No. Per 100 of child attacks mths.	No. Per 100 of child attacks mths.	No. Per 100 of child attacks mths.	No. Per 100 of child attacks mths.	No. Per 100 of child attacks mths.	No. Per 100 of child attacks mths.
Diseases of respiratory tract	5 14.9	7 19.2	14 11.1	17 14.9	47 20.8	49 24.6	24 24.0	21 16.7
Diseases of digestive tract	1 3.0	1 2.7	10 7.9	10 8.7	14 6.2	13 6.5	13 13.0	12 9.5
Specific fevers ...	0 —	0 —	1 0.8	2 1.7	13 5.8	10 5.0	2 2.0	6 4.8
Other diseases ...	0 —	0 —	0 —	1 0.9	3 1.3	1 0.5	2 2.0	2 1.6
Total ...	6 17.9	8 22.0	25 19.8	30 26.2	77 34.1	73 36.6	41 41.0	41 32.6

If we compare the total number of lesions of the epithelial structures less the 'infective' skin lesions (table 5), we find in the A group an incidence of 16.1 and in the controls of 14.1 per 100 child months, or, as shown in table 7, 63 per cent. of the children in the A group and 57 per cent. of the children in the control group suffered from one or other of these lesions of epithelial tissue. Hence, exclusive of the 'infective' skin lesions, the difference between the two groups of babies is slight.

The findings, therefore, certainly suggest that added vitamin A diminished the susceptibility to infections of the skin, for the difference (1) is statistically significant between the total groups; (2) shows itself both in the total number of 'attacks' and in the number of children affected, so that it is not only a question of some few children having repeated attacks; (3) is apparent in each seasonal subdivision of the total groups; and (4) is

TABLE, 5—LESIONS OF SKIN, MOUTH AND EYE. VITAMIN A CASES AND CONTROLS COMPARED.

	Vitamin A Cases.			Controls.	
No. of infants	60	...	...	58	
Average attendance ...	8.1 months	...	...	8.2 months	
No. of child-months ...	485.6	...	...	476.1	
Lesion.	No. of attacks.	No. per 100 child-months.	No. of attacks.	No. per 100 child-months.	
Skin.					
'Infective'—Napkin rashes, intertrigo, external otitis, septic spots etc.	21	4.3	34	7.1	9.7
Dribbling rash	1	0.2	4	0.8	
Boils or whitlow... ..	1	0.2	3	0.6	
Eczema... ..	1	0.2	4	0.8	
Ringworm	0	—	1	0.2	
'Non-infective'—Sweat rash or erythema	4	0.8	9	1.9	8.6
Rough face	8	1.6	5	1.1	
Urticaria	25	5.1	27	5.7	
Anus and urethral orifice.					
Anal fissure or sore at urethral orifice ...	4	0.8	3	0.6	
Mouth.					
Ulcer of palate	1	0.2	3	0.6	2.7
Thrush or other stomatitis	19	3.9	7	1.5	
Cracked lip	2	0.4	3	0.6	
Eyes.					
Conjunctivitis	12	2.5	8	1.7	2.1
Stye	3	0.6	0	—	
Blepharitis	0	—	2	0.4	

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TABLE 6. LESIONS OF SKIN, MOUTH AND EYE. VITAMIN A CASES AND CONTROLS COMPARED: SUBDIVIDED BY SEASON.

No. of child- months	Winter 1930-31.				Summer 1931.				Winter 1931-32.				Summer 1932.			
	A cases		Controls		A cases		Controls		A cases		Controls		A cases		Controls	
	No. of attacks	Per 100 child mths.	No. of attacks	Per 100 child mths.	No. of attacks	Per 100 child mths.	No. of attacks	Per 100 child mths.	No. of attacks	Per 100 child mths.	No. of attacks	Per 100 child mths.	No. of attacks	Per 100 child mths.	No. of attacks	Per 100 child mths.
33-6	36-4	126-4	114-4	225-6	199-5	100-0	125-7									
Lesion.																
Skin.																
'Infective'																
Napkin rashes, intertrigo, etc.	2	6-0	4	11-0	7	5-5	10	8-7	8	3-5	11	5-5	4	4-0	9	7-2
Dribbling rash	0	—	1	2-7	0	—	1	0-9	0	—	1	0-5	1	1-0	1	0-8
Boils or whitlow	0	—	0	—	0	—	0	—	0	—	1	0-5	1	1-0	2	1-6
Eczema ...	0	—	0	—	1	0-8	3	2-6	0	—	1	0-5	0	—	0	—
Ringworm ...	0	—	0	—	0	—	0	—	0	—	1	0-5	0	—	0	—
'Non-infective'																
Sweat rash or erythema	0	—	0	—	0	—	6	5-2	1	0-4	0	—	3	3-0	3	2-4
Rough face ...	0	3-0	0	2-7	1	0-8	0	—	4	1-8	4	10-5	3	3-0	1	0-8
Urticaria ...	1	3-0	1	2-7	8	6-3	6	5-2	2	0-9	2	1-0	14	14-0	18	14-3
Anus and urethral orifice.																
Anal fissure or sore at urethral orifice ...	0	—	0	—	1	0-8	3	2-6	3	1-3	0	—	0	—	0	—
Mouth.																
Ulcer of palate	0	—	0	—	0	—	0	—	0	—	2	1-0	1	1-0	1	0-8
Thrush or other stomatitis ...	4	11-9	1	2-7	8	6-3	2	1-7	4	1-8	2	1-0	3	3-0	2	1-6
Cracked lip ...	0	—	0	—	1	0-8	1	0-9	1	0-4	1	0-5	0	—	1	0-8
Eyes.																
Conjunctivitis	3	8-9	0	—	0	—	1	0-9	6	2-7	5	2-5	3	3-0	2	1-6
Stye ...	0	—	0	—	0	—	0	—	1	0-4	0	—	2	2-0	0	—
Blepharitis ...	0	—	0	—	0	—	2	1-7	0	—	0	—	0	—	0	—

TABLE 7. LESIONS OF SKIN, MOUTH AND EYE. NUMBER OF BABIES AFFECTED IN VITAMIN A GROUP AND IN CONTROLS COMPARED.

	Vitamin A cases.		Controls.	
No. of infants.	60		58	
Lesion.	No. of infants affected.		No. of infants affected.	
Skin.				
‘Infective.’ Napkin rash, intertrigo, external otitis, septic spots, etc.	15	} 16 = 27 per cent.	24	} 30 = 52 per cent.
Dribbling rash	1		4	
Boils or whitlow	1		3	
Eczema	1		2	
Ringworm	0		1	
‘Non-infective.’ Sweat rash or erythema	4	} 22 = 39 per cent.	7	} 24 = 41 per cent.
Rough face	8		5	
Urticaria	18		19	
Anus and urethral orifice.				
Anal fissure or sore at urethral orifice	4	= 7 per cent.	3	= 5 per cent.
Mouth.				
Ulcer of palate	1	} 19 = 32 per cent.	3	} 12 = 20 per cent.
Thrush or other stomatitis	17		8	
Cracked lip	2		2	
Eyes.				
Conjunctivitis	11	} 12 = 20 per cent.	8	} 8 = 14 per cent.
Stye	3		0	
Blepharitis	0		1	

Since one infant might suffer from more than one lesion (e.g., a napkin rash and a dribbling rash) the figures following the bracket is usually less than the sum of the bracketed figures.

apparent in each subdivision for the different types of lesions, though figures are admittedly small in these subdivisions.

TEXTURE AND MOISTURE OF SKIN AND MUCOUS MEMBRANES. No difference was noted in the texture of the skin or in the degree of moisture of skin or mucous membranes in the two groups. The 'rough face' recorded appeared usually to be an effect of weather or of the soap used. Thus susceptibility to skin infections preceded any obvious clinical changes in the skin, such as have been frequently reported as present before the appearance of xerophthalmia. Nor was any dryness or desquamation discovered in other epithelial structures. At the end of the period of observation the quantity of epithelial cells in the urine of a group of controls and a group of A cases was roughly compared. The number of cells showed very wide variations from individual to individual in both groups, but the average for controls was actually slightly higher than that for A cases.

Discussion of results.

Xerophthalmia and keratomalacia are rare diseases in this country. Yet if it be granted that the evidence here provided proves that the control infants (or a proportion of them), chosen at random from hospital out-patients, and fed in accordance with the author's ordinary hospital teaching (except for the omission of a cod-liver oil supplement) suffered from a slight deficiency of vitamin A, resulting in diminished resistance to infective skin lesions, this slight deficiency must be far from rare among babies not given cod-liver oil, or some other vitamin A supplement. Until working out the data the writer did not realize that the two groups under consideration showed this difference in susceptibility to skin infections. Yet a study of the published clinical accounts of xerophthalmia from this angle brings out forcibly the fact that references to skin changes and infections are very common in any general account of the disease where the attention is not focussed almost exclusively on the eye changes. In rat's eyes slight infection, as evidenced by puffiness of the lids and slight discharge, is apparently usually the first eye change noted¹³. Obvious xerosis appears later, though presumably it is the microscopic epithelial change which has allowed the infection to supervene. It would, therefore, appear that the control children suffered from a degree of vitamin A deficiency which so affected the microscopic structure of their skin as to render it more susceptible to infection, although changes in the skin texture were not apparent on clinical examination. If these babies suffered from vitamin A deficiency, then in view of the apparent rarity in this country at the present time of xerophthalmia in children, one must conclude that xerophthalmia indicates a fairly gross deficiency of vitamin A. Clinical accounts of the disease show that dryness of the skin often precedes dryness of the conjunctiva (Mori¹⁰, Kirkpatrick⁵, Pillat¹¹, Frazier and Hu⁴), so that our cases presumably suffered an even slighter degree of deficiency than would cause obvious dryness of the skin. If the grade of vitamin A deficiency among the controls was so very slight, then the A cases must

have received a large excess of vitamin A. This large excess did not increase the general resistance to catarrhal or other infections.

The question will naturally be asked: Are the babies under consideration representative, or were they receiving less vitamin A than is usual in this country? The babies came from a poor working class district and it is very probable that they were born with smaller vitamin A reserves than babies of parents in good social circumstances. As compared with babies given cod-liver oil, and hence a liberal supplement of vitamin A, our controls were getting much less vitamin A. But there is a tendency nowadays to replace cod-liver oil by other anti-rachitic agents containing no vitamin A, and babies given these are likely to be almost entirely dependent on milk for their vitamin A until they start solid food.

The babies under observation were fed on milk dried by the roller process, and it is the writer's impression that in London more infants are given roller-process dried milk than any other form of artificial food, though, of course, this does not apply to the whole of England, nor to Scotland. The milk used was mostly prepared at intervals of 2 to 3 weeks and was nearly always well under 6 weeks old when consumed, so that if keeping causes slow deterioration of the vitamin A value it compared very favourably with dried milk bought in the open market, which may be months old.

If we consider other forms of milk used in infant feeding we must bear in mind two points: (1) the vitamin A value of the milk itself, and (2) the proportion of the total energy needs supplied in milk and in vitamin A-free carbohydrates respectively. It appears that spray-process dried milk is likely to suffer a greater destruction of vitamin A than roller-process milk, and presumably condensed milk still more so. Some of the infants with xerophthalmia whose histories are recorded in the literature are said to have been fed on condensed milk, though the quantity is not stated (Thalberg¹⁵, Wilson and Dubois¹⁶, Ross¹²). If so-called 'humanized' dried milks, sweetened condensed milks or proprietary foods with dried milk as a basis are employed, the vitamin A content of the diet is likely to be considerably lower than that of our control babies, because a considerable proportion of the total calorie needs of the infants would be supplied in carbohydrate.

It is known that the natural vitamin A content of milk, both of human milk⁹ and of cow's milk⁷ shows wide individual variations, depending largely on the diet. Macy and Outhouse found that the vitamin A content of the pooled milk of 12 wet nurses with healthy babies, and that of the pooled milk of a herd of Holstein cows was about the same. But if the mother's diet is sufficiently deficient in vitamin A, even a breast-fed baby may develop xerophthalmia (Thalberg¹⁵, Mori¹⁰) so the possibility of minor grades of vitamin A deficiency occurring in breast-fed infants of impoverished mothers in this country cannot be excluded, though there is no evidence to prove that it occurs. Possibly an investigation of skin infections in breast-fed babies in a poor district might provide evidence on this point.

What of babies fed on fluid cow's milk? As already stated, the figures of Sherman and Smith would suggest no great destruction of vitamin A in

the process of drying, but further information on this point seems to be needed. If we suppose that some of the vitamin A is destroyed by drying, it does not follow that the baby given fluid milk will get more vitamin A in his feeds, for since fresh cow's milk is less easily tolerated than dried milk, the tendency when giving fluid milk is to supply a larger proportion of the calorie requirements of the babies in vitamin A-free carbohydrate and a smaller proportion in milk.

If we consider the diet after 7 to 8 months old, there is no doubt that the controls received a more liberal amount of vitamin A than do great numbers of our child population. The milk allowance was fairly liberal and the diet was mixed, instead of being heavily overloaded with carbohydrate as happens so often, especially among the poor.

If confirmation of the results recorded in this paper is forthcoming, it would seem reasonable to conclude that slight vitamin A deficiency is widespread, and that a greater deficiency than that shown by the control series in this observation is probably not uncommon.*

With the recognition of the need of systematic anti-rachitic prophylaxis, cod-liver oil has been used on a vast scale in many different countries during the last 12 to 13 years with the excellent result that rickets is becoming a comparatively uncommon disease in many areas. During the last few years with the introduction of irradiated ergosterol, highly potent preparations of vitamin D are tending to displace cod-liver oil, which supplies both D and A, and in this there seems a possible danger unless other means are taken to supply extra vitamin A.

Extra vitamin A can be supplied incorporated in dried milk, as was done in this investigation, and this has the advantage of promoting more regular administration in the case of the less careful mothers. At the present time this would be a somewhat expensive procedure, because the original cost of the vitamin A extract is comparatively high, and because of the amount destroyed in drying the milk. Dr. F. H. Carr estimated that the emulsion of vitamin A derived from mammalian liver added to each pound of dried milk was equivalent to 196 c.c. of cod-liver oil of 7.5 blue value, whereas the quantity present after drying was, by his estimate, equivalent to 67-100 c.c., and by Dr. Coward's estimate equivalent to approximately 30 gm. of cod-liver oil of 12.0 blue value. It has been suggested that the natural vitamin A of the milk is in some way better protected and will withstand procedures which cause a large amount of destruction in added vitamin A.

There is considerable uncertainty as to what is an adequate dose of vitamin D, in the form of irradiated ergosterol, for use in the prophylaxis

* In August, 1933, shortly after these papers had been submitted to the Medical Research Council, Hess, Lewis, and Barenberg, published in the United States the result of a somewhat similar investigation carried out in a home for babies. They concluded there was no evidence of vitamin A deficiency in their control group of infants who received the usual diet of the institution with no supplement of cod-liver oil or vitamin A concentrate, nor did they find any evidence of increased susceptibility to infections of the skin. (*J. Am. Med. Ass.*, 1933, CI, 657.)

of rickets in children, because it appears that there are unexplained discrepancies between the vitamin D value, as calculated from rat experiments, and the requirements of different species of animals. Hence for large scale routine use as a prophylactic for rickets a standardized cod-liver oil appears preferable to irradiated ergosterol in the present state of knowledge. When to this we add the fact that cod-liver oil also provides vitamin A and apparently provides it more cheaply than any of the potent preparations now on the market, it seems that for routine clinical use the profession would do well to stick to cod-liver oil or other standardized fish oils, until such time as a cheaper and better substitute is readily available. A good standardized cod-liver oil can be bought by a hospital at 135 shillings for 25 gallons. Thus 7 pence is the wholesale price of sufficient cod-liver oil to supply a baby with $\frac{3}{4}$ drachm daily for six months, a quantity sufficient to protect him from rickets and, presumably, to provide him also with an adequate supplement of vitamin A.

Summary.

Nature of investigation.—Evidence was sought concerning the existence of a possible vitamin A deficiency in the diet of London babies getting a liberal allowance of milk, and later ‘table food’ in addition, and on the effect on the health of babies should such a deficiency exist. Between January, 1931, and October, 1932, a period of 22 months, two groups of artificially-fed babies were kept under observation in the out-patient department of the Queen’s Hospital for Children. The average period of attendance was approximately 8 months. All were fed on a roller-process dried milk containing iron and ammonium citrate (Hemolac) to which were added vitamin D, orange juice and sugar. From the age of 7 or 8 months, solid food (including eggs, fish, vegetables and meat) replaced part of the milk ration. Approximately half the children (60) received in addition extra vitamin A; the other half (58 children), serving as controls, were dependent for vitamin A on that naturally present in their dried milk or ‘table food.’ The vitamin A intake of the A cases (though difficult to compute quantitatively, even for the babies entirely bottle-fed, on account of the variations in the estimated vitamin A values of the milk), was, even at the lowest estimate, a number of times as great as that of the controls.

Results.—The addition of vitamin A had no influence on the general health; rate of gain in weight, or on the general resistance to infection, whether to infections of the respiratory or digestive tract or to specific fevers. On the other hand, the incidence of minor ‘infective’ skin lesions (sore buttocks, intertrigo, etc.), was approximately double in the control group what it was in the A group, and this difference was found to be statistically significant. No difference in the degree of moisture of the skin or in its texture was noted in the two groups. The incidence of urticaria and other non-bacterial skin lesions was approximately the same in the two groups.

The evidence obtained, therefore, strongly suggests that;—

1. Slight vitamin A deficiency existed in our control group, and hence is probably of common occurrence in artificially-fed babies in this country, unless this vitamin is specifically added to their diet by the administration of cod-liver oil or some other potent source of vitamin A.

2. The effect of this slight vitamin A deficiency on the health of infants is to diminish their resistance to infections of the skin such as occur with sore buttocks, intertrigo and dribbling rashes, this susceptibility preceding the obvious clinical changes in the skin texture which have been noted by many observers.

3. Diminished resistance to general infections is not among the first effects of slight vitamin A deficiency in infants, and a large excess of vitamin A does not raise the general resistance.

4. Diminished growth is not among the first effects of vitamin A deficiency in infants.

Further work is desirable to confirm point (2), namely, diminished resistance to skin infections, on which the other conclusions depend, but in view of the uniformity of the results obtained in each season and for each type of skin lesion, it seems most improbable that the difference between the two groups in incidence of infective skin lesions is a matter of chance. No other difference between the two groups was found to be uniform over the seasons. This view is further supported by the high incidence of skin infections and the changes in the skin frequently reported in clinical accounts of xerophthalmia and keratomalacia. These results, if they are confirmed by further work, which the author is undertaking, indicate that artificially-fed babies fed on dried milk, and probably also on fresh dairy milk, require as a routine a vitamin A supplement to their bottle feeds. It is possible that many breast-fed babies of impoverished mothers also require this. It can be supplied, like vitamin D, incorporated in dried milk, but, in the present state of our knowledge, cod- or other fish-liver oil, known to be potent in both vitamins, is probably the most economical supplement for providing the fat-soluble vitamins, and should be used as a routine.

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REFERENCES.

1. Barnes, J., Brady, M. J., & James, E. M., *Am. J. Dis. Child.*, Chicago, 1930, XXXIX, 45.
2. Cathcart, E. P., Murray, A. M. T., & Shanks, M., *Med. Res. Council, Spec. Rep. Series*, No. 151, London, 1931.
3. De Sanctis, A. G., & Craig, J. D., *J. Am. Med. Ass.*, Chicago, 1930, XCIV, 1284.
4. Frazier, C. N., & Hu, C. K., *Arch. Int. Med.*, Chicago, 1931, XLVIII, 507.
5. Kirkpatrick, quoted by Wright, R. E., *Brit. J. Ophth.*, London, 1922, VI, 164.
6. Lossouarn, E., *Presse med.*, Paris, 1932, XL., 745.
7. Luce, E. M., *Biochem. J.*, Camb., 1924, XVIII, 716, 1279.
8. Mackay, H. M. M., & Goodfellow, L., *Med. Res. Council, Spec. Rep. Series*, No. 157, London, 1931.
9. Macy, I. G., & Outhouse, J., *Am. J. Dis. Child.*, Chicago, 1929, XXXVII, 379.
10. Mori, M., *Jahrb. f. Kinderh.*, Berlin, 1904, LIX, 175.
11. Pillat, A., *China M. J.*, Shanghai, 1929, XLIII, 907.
12. Ross, S. G., *Am. J. Dis. Child.*, Chicago, 1921, XXII, 232.
13. Sherman, H. C., & Smith, S. L., *The Vitamins*, second edit., New York, 1931, 272, 274.
14. Steenbock, H., & Kletzien, S. W. F., *J. Biol. Chem.*, Baltimore, 1932, XCVII, 249.
15. Thalberg, J., *Arch. f. Augenh.*, Munich, 1883, XII, 315.
16. Wilson, J. R., & Du Bois, R. O., *Am. J. Dis. Child.*, Chicago, 1923, XXVI, 431.