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THE RELATION OF VITAMIN A TO GROWTH, REPRODUCTION AND LONGEVITY

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It is of more than historical interest that the existence of a fat-soluble vitamin (now called vitamin A) was discovered through experiments made simultaneously by McCollum and Davis[1] and by Osborne and Mendel[2] in which it was found that young animals on food mixtures alike in all other respects would continue to grow and thrive or would soon stop growing and shortly thereafter die, according as the fat in these food mixtures was butter-fat or lard, that is, the fat of milk or of the adipose tissue. In the same papers, it was shown that egg-yolk fat resembles milk fat in containing notable amounts of vitamin A. The relatively high concentration of this vitamin in milk and eggs suggests its importance in reproduction and in the development of the young. Its relation to growth has been much more extensively studied than its relation to reproduction or to longevity.

Both the adequate characterization of the vitamin and the correct appraisal of its true significance as a factor in food values depend upon full and accurate knowledge of the relation of quantitative differences in the vitamin-A value of the food to growth, reproduction and longevity, and to the health and vigor of the individual throughout the entire life cycle.

No complete review of work in this field can be attempted here; but mention must be made of the studies of Steenbock and his associates[3] showing increased susceptibility to lung disease among animals on diet lacking or poor in vitamin A, and that of Evans and Bishop,[4] who found that diets containing enough vitamin A for growth and protection from eye disease may still require enrichment with this vitamin in order to meet the added demands of reproduction.

Experimental Part

In the present investigation, parallel groups of experimental animals (rats) were fed upon two diets, one of which was rather low and the other fairly high in vitamin A. The latter consisted of two-thirds wheat and one-third whole milk powder or an equivalent mixture of skimmed milk powder and butter fat; the former (diet low in vitamin A) consisted of two-thirds wheat and one-third skimmed milk powder or a mixture of

[1] McCollum and Davis, *J. Biol. Chem.*, **15**, 167 (1913).

[2] Osborne and Mendel, *ibid.*, **15**, 311 (1913); **16**, 423 (1913).

[3] Steenbock, Sell and Buell, *ibid.*, **47**, 89 (1921); **56**, 327 (1923).

[4] Evans and Bishop, *Anat. Record*, Jan., **1922**.

skimmed milk powder with lard or coconut oil in place of the whole milk powder of the other diet. Sodium chloride was added to each diet in the proportion of 2% of the weight of the wheat. Several previous investigators have reported that lard and coconut oil are either free from vitamin A or contain only negligible amounts of it. Experiments in this Laboratory have indicated that wheat contains about 2% as much vitamin A, and skimmed milk powder probably about 10% as much of this vitamin, as does whole milk powder. Therefore, the relative amounts or concentrations of vitamin A in the diets here compared were approximately as seven to one.

In our first test, the experimental group placed on each of the two diets consisted of two females and one male, all transferred from our Diet B to these experimental diets at the age of four weeks and continued on these diets as long as they lived. Here as in all other tests of the series described in this paper, the parallel lots of animals on the two diets had exactly the same inheritance and previous dietary history, each male or female placed on one diet being paralleled by a twin brother or sister placed at the same time upon the other diet. The sexes were allowed to grow up together in parallel breeding lots and no restrictions were placed upon their opportunities for reproduction. In this first comparison, the two diets used differed only in that one (Diet 13) contained one-third whole milk powder and the other (Diet 41) contained skimmed milk powder in equal proportion. The animals on the skimmed milk diet grew at a normal rate to nearly average adult size but never reached as high a maximum weight as did the parallel animals on the whole milk diet. Neither of the females on the skimmed milk diet (low in vitamin A) produced any young; whereas the two females on the whole milk diet (fairly high in vitamin A) produced a total of 110 young of which 63 were raised (a normal percentage for the rigorous experimental conditions here employed). The animals receiving the diet richer in vitamin A also lived longer than their twin brothers and sisters whose diet was poorer in this factor.

Using the same diets, similar comparisons were made with four other pairs of females and the result of the comparison of the two diets was the same in that the animals on the diet richer in vitamin A showed better results in size, breeding and longevity than their twins on the diet poorer in vitamin A, even though the latter were able to make normal growth to nearly average adult size.

In order to determine definitely that the differences found were due to the differing vitamin-A contents of the diets and not to the fact that they differed in fat content, new experiments were made upon diets containing exactly the same amounts of wheat, skimmed milk and fat; but differing in the fat used, the use of butter fat giving a diet (Diet 90) presumably about seven times richer in vitamin A than when lard or coconut fat was

used instead (Diets 91 and 191, respectively). The results paralleled those of the previous comparisons so closely as to show conclusively that the differences found are attributable strictly to the differences in vitamin A contents of the diets compared.

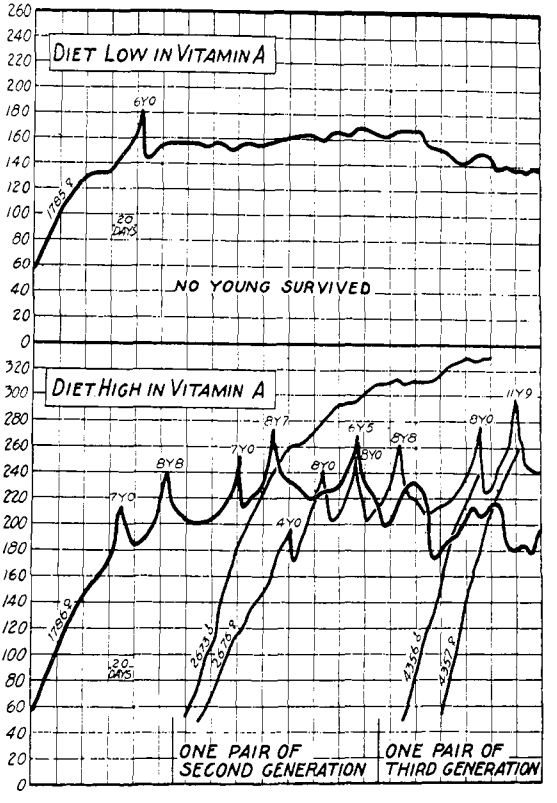

Fig. 1.—Illustrating the importance of quantitative differences in the vitamin-A content of the food. Rats 1785 and 1786 were twin sisters and were mated with twin brothers. The higher proportion of vitamin *A* in the food proved essential to successful reproduction and rearing of young. In most cases the difference in reproduction was even more marked than here shown, for the majority of the females on diet low in vitamin A gave birth to no young whatever.

That the diets containing the higher proportion of vitamin A were fully adequate, and that the experimental animals were capable of fully normal growth and reproduction, is illustrated by the typical case shown in Fig. 1, and demonstrated beyond possibility of doubt by the combined results of the experiments as a whole, which may be summarized as follows.

A total of 17 females and 5 males were continued until natural death on each of the two types of diets. Each animal on the diet high in vitamin A was matched against an animal of the same sex and litter on the diet low in vitamin A, the parallel groups having exactly the same inheritance and previous nutritional history, and being kept under conditions alike in all respects except that one received a diet richer in vitamin A than the other, either because of the use of whole milk versus skimmed milk powder or of butter fat versus lard or coconut fat. Growth in both series was good for some time, although the animals on the diet with the smaller amount of vitamin A did not reach as high maximum weights as those with the larger amount of the vitamin. The average maximum weight of the 17 females on the high-vitamin diets was 259 g. and for the 5 males, 352 g., while for the females on the low vitamin diets the average maximum weight was 181 g. and for the males, 244 g.

The average length of life for the 17 females and the 5 males on the diets low in vitamin A was 369 days, while the animals on the diets high in vitamin A lived an average of 746 days or slightly over twice as long.

The most pronounced effect of the difference in intake of vitamin A appeared in the breeding records. The 17 females on the diets higher in vitamin A had a total of 477 young, of which 264 were successfully suckled and weaned at a fully average size and vigor. Of the total of 31 young born to the 17 females on the diets low in vitamin A, none survived more than two days after birth.

In every one of the five pairs of lots into which the animals were grouped in the carrying out of the experiments, the same striking contrast appears between the diets higher and lower in vitamin A as regards their ability to support successful reproduction.

Of the females receiving the larger amount of vitamin A, all of the 17 individuals bore young; 15 of the 17 reared young, and young were successfully reared in all five of the experimental groups. In contrast with this, of the five groups receiving the smaller amount of vitamin A none reared any young, and of these 17 females only six bore any young and all of these six were individuals which had some advantage in previous nutritional history. Three had come from families on diets richer in vitamin A than our usual laboratory diets; two from usual diets had been allowed to remain upon these diets somewhat beyond the usual age of four weeks before transferring to the experimental diets here described; and one, transferred from Diet B when four weeks old as usual, was unusually well-developed for that age. Hence it would appear that only those individuals which for one reason or another had unusually good bodily stores of vitamin A when transferred to the diet low in this vitamin, were able to produce young on this diet, and even they were not able to rear any of their young. That the diet thus signally failing to support reproduction was

adequate in all respects other than fat-soluble vitamin is shown by the excellent results obtained from rats of the same family history fed on diets differing only in that they contained butter-fat instead of lard or coconut fat. That the fat-soluble factor concerned is vitamin A and not the substance X recently discovered by Evans and Bishop is assured by the fact that all of our experimental diets furnished this latter factor in liberal amounts, since all contained the same high proportion of ground whole wheat which supplies it in abundance.

Summary and Conclusions

Experiments are described in which parallel groups of rats of identical previous history were fed upon two types of diet, one rather low and the other fairly high in vitamin A, from soon after weaning-time until natural death.

The smaller amount of vitamin A proved sufficient for normal growth up to nearly average adult size, but not for successful reproduction, and rarely did it support satisfactory longevity. The parallel animals receiving the more liberal allowance of vitamin A grew to fully average adult size, were successful in reproduction and the rearing of young and lived on the average a little over twice as long as those on the diet equally good in all other respects but lower in vitamin A.

These experiments show strikingly that a proportion of vitamin A in the food sufficient to support normal growth and maintain every appearance of good health, for a long time at least, may still be insufficient to meet the added nutritive demands of successful reproduction and lactation.

Along with the failure to reproduce successfully there usually also appeared in early adult life an increased susceptibility to infection and particularly a tendency to break down with lung disease at an age corresponding to that at which pulmonary tuberculosis so often develops in young men and women. The bacillus involved is different; but the close parallelism of increased susceptibility of the lung to infection at this stage of the life history appears very significant, especially in view of the fact recorded in one of our previous papers that the vitamin-A content of lung tissue varies with that of the food.

Thus it is clearly shown that vitamin A is an even more important factor in the chemistry of food and nutrition than has previously been appreciated, for it must be supplied in liberal proportion not only during growth but in the food of the adult as well, if a good condition of nutrition and a high degree of health and vigor are to be maintained.

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