

rabbits which react poorly or not at all to the intradermal injection of histamine.

Whether this high amount of histamine in the skin of very young rabbits bears some relationship to the physiology of the skin is an open question.

11759

Influence of Nutritional Intake Upon Concentration of Vitamin A in Body Tissues.

HSUEH-CHUNG KAO AND H. C. SHERMAN.

From the Department of Chemistry, Columbia University, New York City.

Batchelder's finding¹ that systematically increased intakes of vitamin A resulted in progressively more vigorous offspring even beyond the level at which the parents had reached the plateau of outwardly apparent wellbeing, suggests that liberality of intake of vitamin A may be a significantly influential factor in the body's internal environment, and adds importance to the question how generally the concentration levels in the body are influenced by the level of intake.

That the vitamin A content of the liver varies widely with the level of intake has been universally recognized since the quantitative work of Baumann, Riising, and Steenbock.² More recently Steininger, Roberts, and Brenner³ have investigated the fluctuations of the vitamin A concentration in the blood. Are there corresponding fluctuations in the muscles? Conclusive experimental demonstration is difficult because the concentration of vitamin A in the muscles is so low. Boynton's bioassays⁴ indicated that muscle contained only 0.25% to 0.5% of the concentration of vitamin A found in the livers of the same animals. Baumann, Riising, and Steenbock² reported "negative results" from their tests for vitamin A in the blood and muscles of normally nourished rats, but also spoke of their findings as in harmony with those of Boynton.

¹ Batchelder, E. L., *Am. J. Physiol.*, 1934, **109**, 430.

² Baumann, C. A., Riising, B. M., and Steenbock, H., *J. Biol. Chem.*, 1934, **107**, 705.

³ Steininger, G., Roberts, L. J., and Brenner, S., *J. Am. Med. Assn.*, 1939, **113**, 2381.

⁴ Sherman, H. C., and Boynton, L. C., *J. Am. Chem. Soc.*, 1925, **47**, 1646.

The present paper reports the results of a reinvestigation of the vitamin A contents of the livers and muscles of rats receiving diets of different vitamin A values. These rat tissues were assayed by the single-feeding method first worked out by Todhunter,⁵ and now further developed to include the use of side-by-side controls receiving systematically graded amounts of the official U.S.P. reference cod liver oil, and the statement of the data in terms of International Units. The positive control animals, to the numbers of 17, 19, 29, and 22, respectively, were fed 7.5, 15, 30, and 45 International Units each in a single dose. The corresponding measured areas representing the gains in body weight and length of life over the negative control animals were 138, 254, 368, and 567, respectively. By the use of these quantitative data, the results of feeding the parallel test animals with weighed amounts of the tissues under investigation become quantitative measures of the vitamin A concentration in terms of International Units per gram. We have further verified the findings by making use both of simple direct interpolation and of the "curve of response".

Like Steenbock and coworkers,² we find that a predominant proportion of any *surplus* intake is stored in the liver, so that an increment of intake may result in a greater than arithmetically proportionate increase in the concentration of vitamin A in the liver. Thus in typical experiments, they found that doubling the intake increased the concentration in the liver about five-fold (from 23 to 105 "Blue units"); and we find that raising the level of intake about four-fold results in a ten-fold increase of concentration in the liver, *viz.*, from 9 I.U. to 96 I.U. per gram, and in some of our experiments a still more marked increase. Further details of our data on liver may be omitted to economize space, inasmuch as our findings are here so largely confirmatory of the Wisconsin work.

In the case of muscle, while the low concentration makes quantitative measurement and interpretation of vitamin A values quite difficult, the discrepancy, between the "negative" findings at Wisconsin and the measurements previously made by Boynton, calls for fuller consideration of our present data. In 4 series of experiments comparing the tissues of animals reared on each of 2 adequate diets containing 4 to 5 I.U. of vitamin A per gram of dry food and on the same diets enriched to a value of 16 to 20 I.U. per gram by the addition of cod liver oil, and making such comparisons on both 30-day-old and 60-day-old rats, the average measurements summarized in Table I were obtained. As all these figures are near the limit of accuracy attainable in any individual measurement, there

⁵ Sherman, H. C., and Todhunter, E. N., *J. Nutrition*, 1934, **8**, 347.

TABLE I.
Concentrations of Vitamin A Found Per Gram of Muscle.

Description	From rats which had received:			
	Basal diet		Enriched diet	
	(No. of cases)	Mean value I.U.	(No. of cases)	Mean value I.U.
"Diet 13" rats at 30 days	(6)	0.0	(6)	0.4
" 132 " " 30 "	(6)	0.3	(7)	0.4
" 13 " " 60 "	(6)	0.3	(6)	0.4
" 132 " " 60 "	(7)	0.2	(6)	0.4
Average of the 4 series	(25)	0.2	(25)	0.4

may be room for difference of scientific opinion in their interpretation. In our opinion, the strongest probability is that the very low concentration of vitamin A in muscle is influenced by the nutritional intake. Any one of the 4 comparisons (Table I) standing alone might well be regarded as inconclusive; but in view of the fact that there is a difference in each of the 4 series and always in the same direction, and the further fact that in the average of the 4 series comprehending 25 individuals each on basal *versus* enriched diet there appears to be twice as much in the muscles of the animals which had received the higher intake, it seems to us distinctly more probable that this difference is significant than that it is merely accidental.

It is consistent with previous knowledge of the distribution of vitamin A in the body that the responses of blood-concentration to intake should influence the muscle-concentration in the same direction, even though in lesser degree. It is also consistent that a four-fold increase of intake should cause a more than four-fold increase of concentration in the liver and a less than four-fold concentration in the muscles.

Thus there is a consistent trend of evidence of different kinds bringing cumulative support to the view that healthy muscle contains a small amount of vitamin A as a normal constituent and that the concentration of vitamin A in the muscle is in some measure influenced by the level of nutritional intake.

Other researches in this laboratory seek to extend this field of investigation by experiments from different dietary starting points and by the development of improved methods of measuring the concentration of vitamin A in the tissues.

The assistance of grants from the Rockefeller Foundation and from the Carnegie Corporation of New York through the Carnegie Institution of Washington is gratefully acknowledged.