

from diets containing certain amino acids in quantities which are out of proportion to that found in most natural proteins.

Summary. The addition of 1% *dl*-phenylalanine and 1% *l*(-)-tyrosine to a purified diet containing 10% casein produced growth retardation and external lesions. Phenyl-

alanine is converted to tyrosine in the animal and so may add to the effect of the tyrosine. The addition of relatively large amounts of nicotinic acid or *l*(-)-tryptophane will appreciably alleviate the deleterious effects of these amino acids.

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Utilization of Intramuscularly Injected Carotene.

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Carotene administered parenterally has been shown to be poorly utilized.^{1,2} Subcutaneous injection of carotene in oil solution¹ or intravenous, intraperitoneal or intrasplenic injections² of aqueous colloidal suspensions of carotene have failed to increase stores of vitamin A in the liver of rats. Deficiency symptoms and death have occurred while considerable amounts of the injected carotene were still present in the body.^{1,2} Studies in this laboratory of intramuscularly-injected carotene in oil solution have yielded similar results. Carotene in sesame oil, with and without added tocopherols, when injected intramuscularly, has been found to restore growth to depleted rats for a short time only. Upon ensuing death, a considerable fraction of the carotene was found at the site of injection. After being solubilized in water by means of a suitable agent, intramuscularly-injected carotene was as efficiently utilized as carotene administered orally.

Experimental Methods and Results. When carotene is dissolved in Tween 80, (polyoxyalkylene derivative of sorbitan monoleate[†])

the solution may be diluted indefinitely with water without precipitation of the carotene. A comparative study of the absorption of carotene in Tween 80 solution and in sesame oil solution was made. 0.5 mg of carotene and 0.2 mg of α -tocopherol in 0.1 cc of solvent was injected into the thigh muscles of normal adult rats and the rate at which the carotene passed from the muscle determined. The data are presented in Table I.

The curative effect of intramuscularly-injected carotene as compared with that administered orally was measured by a study of the growth and duration of cure of vitamin A-depleted rats. Seventy male weanling rats were fed the U.S.P. XII vitamin A free diet. After 6 weeks on this diet, when cessation of growth and the appearance of ocular symptoms had marked the depletion of body stores of vitamin A, 40 of the most typically deficient rats were divided by weight into groups. Rats dying within 3 days after receiving the supplement were not included in the data. From a comparison of the growth curves and the data on duration of cure (Fig. 1) it may be seen that an intramuscular injection of carotene in sesame oil (Group 3) is poorly utilized as compared with the utilization of the same supplement given orally (Group 4). When the carotene was injected in Tween 80 (Group 1) the curative effect was as good as, if not better than, that obtained in the groups receiving carotene orally either in Tween 80 or oil (Groups 2 and 4).

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¹ Lease, V. G., Lease, E. J., Steenbock, H., and Baumann, C. A., *J. Lab. and Clin. Med.*, 1942, **27**, 502.

² Sexton, E. L., Mehl, J. W., and Deuel, H. J., *J. Nutrition*, 1946, **31**, 299.

[†] Atlas Powder Co.

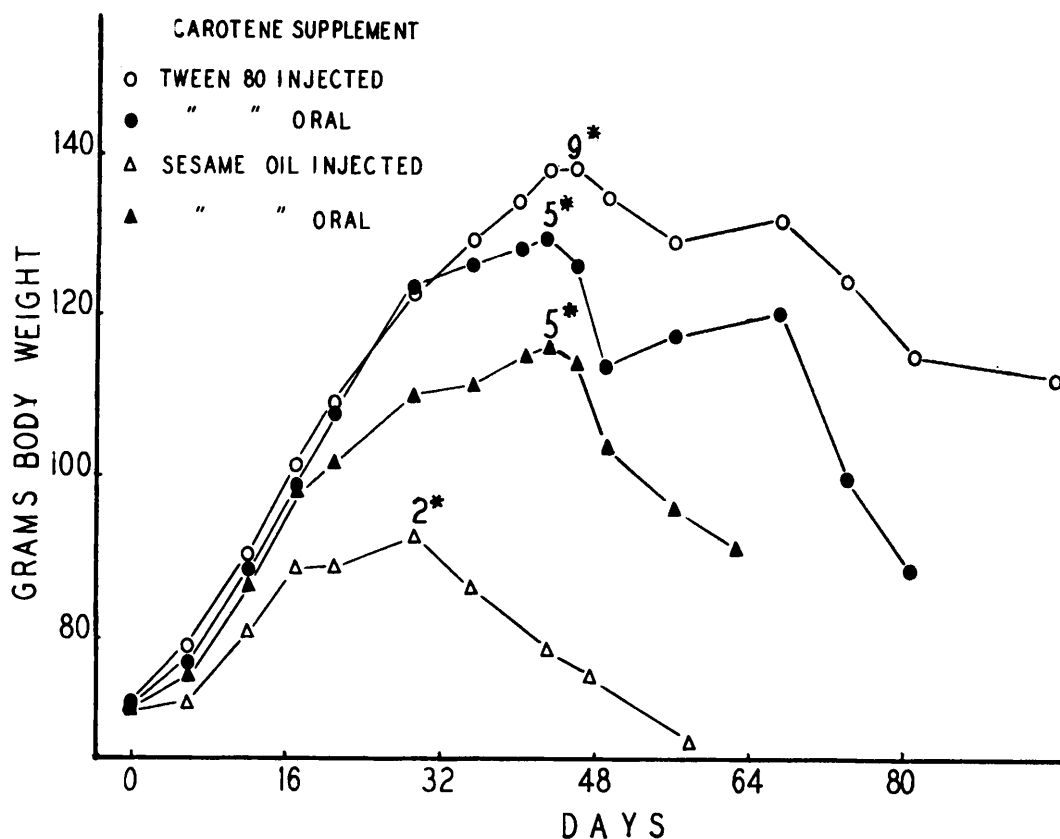


FIG. 1.

Growth of vitamin A depleted rats receiving single doses of carotene in sesame oil and in Tween 80, orally and intramuscularly.

- (1) —○— 0.44 mg of carotene + 0.2 mg alpha-tocopherol in 0.1 ml Tween 80 intramuscularly. (9 rats; average survival time—71 days.)
 (2) —●— Same as (1) but orally. (8 rats; average survival time—40 days.)
 (3) —△— 0.44 mg of carotene + 0.2 mg alpha-tocopherol in 0.1 ml of Sesame oil intramuscularly. (8 rats; average survival time—20 days.)
 (4) —▲— Same as (3) but orally. (9 rats; average survival time—40 days.)

* Number of rats alive at point of maximal growth.

The average survival time of the Tween-injected group exceeded that of either of the 2 orally supplemented groups; the time at which maximum growth was attained was about equal for the 3 groups. In Group 3, the carotene injected in oil was the most poorly utilized as judged by all criteria. After the death of each of the rats receiving an intramuscular injection, the thigh muscles were dissected and residual carotene was extracted and determined. The amount of carotene found remaining in the muscle tissue of the oil-injected rats varied from 27 to 76%, while only trace amounts were found in any of the Tween-injected rats.

TABLE I.
Recovery of 0.5 mg of Carotene in 0.1 ml of Tween 80 or Sesame Oil After a Single Injection into the Thigh Muscle of Rats.

Days after injection	% carotene* recovered from muscle	
	Tween 80	Sesame oil
2	7 (43)	98
7	trace (14)	63
15	none (20)	48
29	" (1)	33
37	"	18
65	"	21

* The number in the parentheses indicates the per cent of carotene recovered from subcutaneous tissue near the site of the injection. Only trace amounts were ever found in the subcutaneous tissue in the case of oil injections. Carotene was determined³ with the Beckman Spectrophotometer.

Discussion and Summary. These experiments show definitely that carotene administered parenterally may be effectively utilized provided the carotene has been water-solubilized by solution in Tween 80. In such a solution not only is there a much more rapid transport of carotene from the site of an intramuscular injection, but there also occurs an

effective conversion to vitamin A as demonstrated by the resumption of growth in vitamin A-depleted rats. These findings offer further support to the accumulating evidence^{2,4} that the state of dispersion of the carotene is of importance for participation in the physiological processes of absorption, transport and enzymatic conversion to vitamin A.

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⁴ Greaves, J. D., and Schmidt, C. L. A., *Am. J. Physiol.*, 1935, **111**, 492.

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Alterations in Body Fluids During Acute Infectious Hepatitis.

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It has long been known that convalescence in acute liver disease may be initiated by a diuresis. Jones and Eaton¹ in noting this phenomenon in an unselected group of patients with acute and subacute liver disease suggested that it may have a favorable prognostic significance. To imply that recovery from liver disease is associated with the production of a large volume of urine, suggests that during the acute phase of the infection there may be profound disturbances in water metabolism involving increased water storage and possibly alterations in the transport and excretion mechanisms. Recognition of the intimate relationship existing between hepatic and renal physiology has impelled clinicians to speak of the ill-defined and little understood "hepato-renal syndrome." The suppression of urine volume in "catarrhal jaundice" and acute yellow atrophy are old observations,² as is the oliguria accompanying cirrhosis of the liver, especially when associated with ascites.³ It is conceivable, therefore, that the latter may in part represent a more serious extension of the same mechanism

to an advanced period in the development of chronic liver disease. Indeed, recent evidence suggests that the movement of body fluids during liver disease may be under endocrine control.⁴ No available data exist that reveal the precise alterations of the fluid compartments of the body during the course of acute liver disease. Jones and Eaton¹ suggested that the observed diuresis of convalescence was a consequence of improved hepatic efficiency, resulting in a "shift of fluid from the tissues or serous cavities to the blood stream with the ultimate establishment of diuresis." Since adequate methods now exist for the simultaneous determination of approximate interstitial fluid (thiocyanate space), plasma volume and total blood volume, it was believed that a study of the distribution of body fluids during the course of acute infectious hepatitis would be of profit. In this disease one may work in a rapidly shifting metabolic scene.

Materials and Methods. Fourteen patients were studied as part of a group of acute infectious hepatitis cases observed in the Rockefeller Hospital.⁵ All were young, adult males

* Dr. Hoagland died Aug. 2, 1946.

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⁴ Ralli, E. P., Robson, J. S., Clarke, D., and Hoagland, C. L., *J. Clin. Invest.*, 1945, **24**, 316.

⁵ Hoagland, C. L., and Shank, R. E., *J. A. M. A.*, 1946, **130**, 615.