After the oral ingestion of "physiologic" (i.e., 1–2 μg) doses of radioactive vitamin B_{12}, there is a delay of three to four hours before radioactivity appears in the plasma, and the maximum is reached at about eight to twelve hours. If a much larger oral dose of vitamin B_{12} is given, radioactivity will appear in the plasma much sooner. This second mechanism for absorbing at higher oral doses appears to be intact in patients with pernicious anemia.

Sorbitol (D-sorbose) has been shown to enhance plasma vitamin B_{12} levels in normal subjects given oral doses of the vitamin. It is possible that this action is due to a stimulation of gastric secretion of intrinsic factor. Data showing the effects of D-sorbose on vitamin B_{12} absorption in patients unable to produce intrinsic factor will be helpful in understanding the mechanism of action of this compound in normals.

The above comments demonstrate a well-known truism in biology: the answers to yesterday's questions provide the framework for today's problems.[6]

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Letter to the Editor

ON ENHANCEMENT OF VITAMIN B_{12} ABSORPTION

Dear Sir:

The demonstration by Chow, Meier, and Free[1] of facilitation of enteral vitamin B_{12} absorption by admixture with D-sorbitol is of extreme interest, but this may not have been "the first substance other than intrinsic factor" shown to effect such absorption. Some time previously I reported in another connection[2] that on administration by mouth of crude, streptomyces-derived vitamin B_{12} concentrates emulsified in vegetable oil with sorbitan monooleate polyoxyethylene derivative (Tween 80) there appeared to be marked vitamin B_{12} assimilation as evidenced by the same pinkish "skin-flush" and copious diuresis which had been noticed in an occasional patient receiving large parenteral doses of cobalamine. Since the patients in the particular series reported were not those with Addisonian anemia (and therefore may have had absorption conditioned by intrinsic factor) another study was conducted with three patients with relapsant pernicious anemia.

It had been determined previously that hydroxycobalamine, cyanocobalamine, nitrocobalamine, and carbimidocobalamine were all soluble in oleic acid-glycerol trioleate mixtures and that such solutions immediately dispersed to less than 0.5 micron droplet size in aqueous menstruums when 2 to 20 per cent of Tween 80 was incorporated. A single, one ml dose of such Tween-oil-oleic acid solutions containing 500 μg of hydroxycobalamine was given orally to each of three patients with pernicious anemia in relapse.

However, because high oral dosing with ordinary vitamin B_{12} preparations was already known to be followed by remission of classic pernicious anemia, this eventuation in all three patients was not used as a criterion for absorption. Instead, total 24-hour urine outputs, both immediately before and after the test dosings were given to Dr. Roger Kersey of Chas. Pfizer and Company for vitamin B_{12} assay. These assays on the post-dosing specimens were rendered difficult because of unanticipated *high* vitamin B_{12} content which necessitated repeated dilutions to get within the range of the assay procedure.

It was finally determined that each patient excreted from 50 to 150 μg of vitamin B_{12} (activity) during the 24 hours following the 500 μg dose, an order of magnitude, which while not approaching that which would have followed

the parenteral administration of 500 μg of vitamin B_{12}, was certainly much greater than could be accounted for on the basis of intrinsic factor carriage.

I had speculated (in the publication cited above) that the enteral absorption of vitamin B_{12} in Tween-oil solution might be conditioned by those same factors which operated in facilitation by Tween of enteral absorption of any "fat-soluble" vitamin, which vitamin B_{12} becomes in this instance. Such facilitation is usually explained by circumvention of the portal circulation through the regular "fat-droplet" route into the lacteal villi and thence to the thoracic duct. There is as yet no good reason for abandoning this explanation although the thesis posed by Chow, Meier, and Free may offer an alternative one for the effects I observed. D-sorbitol is a constituent of the polysorbate macromolecule. Perhaps even as such it could effect transintestinal vitamin B_{12} transport. Polysorbate is hydrolyzed to some extent by pancreatic lipase;[3] one of its products could be D-sorbitol.

Lipases, like all other enzymes, have synthetic as well as degradative actions and it occurred to Gordon that intestinal synthesis of "tweens" might take place if suitable hexitols were fed. It was known that a crude, dried streptomycin beer, naturally rich in D-mannitol was effective when given orally in megaloblastic anemia.[4] He and his co-workers reported similar effectiveness of a vitamin B_{12} sweetened with D-mannitol[5] at about the same time as D-mannitol was found by Greenberg's group to have the same qualitative efficacy in facilitating vitamin B_{12} absorption by the intestinal tract of the rat, as does D-sorbitol.

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REFERENCES

1. CHOW, B. F., MEIER, P., and FREE, S. M : Absorption of vitamin B_{12} enhanced by D-sorbitol AM. J. CLIN. NUTRITION 6:30, 1958.
2. BARNARD, R. D.: The effect of streptomyces fermentation residue on "hemolytic" anemia with notes on some similarities of the effects of intestinal flora reversion and those of adrenocorticotherapy. *Int. Rec. Med.* 164:117, 1951.
3. CULVER, P. J., WILCOX, C. S., JONES, C. M., and ROSE, R. S., JR.: Intermediary metabolism of certain polyoxyethylene derivatives in man: recovery of polyoxyethylene moiety from urine and feces following ingestion of (20) sorbitan monooleate and (40) monostearate. *J. Pharmacol. & Exper. Therap.* 103:377, 1951.
4. BARNARD, R. D., CARACAPPA, J. M., SCHWARTZ, M., GORDON, G. B., and MOLDOVER, A.: Further observations on the response of erythroblastic, megaloblastic and radiation anemias to streptomyces-derived "animal protein factor" and antibiotics, *New York J. Med.* 51:1739, 1951.
5. GORDON, G. B., RUBIN, H., STEIN, S., and KESSLER, L. N.: The effect of D-mannitol incorporation on vitamin B_{12} dosage forms. Oncology Research Conference, Jewish Chronic Diseases Hospital, Brooklyn, January, 1958.
6. GREENBERG, S. M., HERNDON, J. F., RICE, E. G., PARMELEE, E. T., GULESICH, J. J., and VAN LOON, E. J.: Enhancement of vitamin B_{12} absorption by substances other than intrinsic factor. *Nature* 180:1401, 1957.