Proc. Nat. Acad. Sci. USA
Vol. 71, No. 10, pp. 4164–4168, October 1974

The Nutritional Teamwork Approach: Prevention and Regression of Cataracts in Rats

(galactose-induced cataracts/toxicity resistance/suboptimal nutrition/nutrient testing)

JAMES D. HEFFLEY AND ROGER J. WILLIAMS

Department of Chemistry, Clayton Foundation Biochemical Institute, The University of Texas, Austin, Texas 78712

Contributed by Roger J. Williams, May 10, 1974

ABSTRACT **We have taken advantage of a newly assimilated principle in nutrition: no nutrient by itself should be expected to prevent or cure any disease; nutrients as such always work cooperatively in metabolism as a team.**

By feeding galactose-containing diets to young rats, cataracts are regularly produced. When, however, we furnished galactose-fed animals with what may be considered a well balanced, full team of nutrients, cataract prevention was accomplished. On four galactose-containing diets supplied with a full team of nutrients, not a single cataract developed in 24 rats (48 eyes). On four diets using the same dietary galactose challenge, accompanied with inadequate nutritional teams, 47 out of 48 eyes developed cataracts. Diets of intermediate quality induced the development of intermediate numbers of cataracts. Cataracts once formed were regressed slowly and incompletely by shifting the animals to a diet similar to that which had previously been found to protect against cataract formation.

The significance of these findings for nutritional research and for attacks on the problems of human cataracts and other ailments is discussed.

The nutritional teamwork approach to the prevention or treatment of a diseased condition has been at least partially justified in earlier writings (1, 2). Many nutritional investigations of past decades support the teamwork concept, notably the very early finding that the deficiency of one amino acid (tryptophan) alone will cause cessation of growth in young animals, and the clear-cut early demonstration that calcium, phosphate, and vitamin D are implicated together in the etiology of rickets. Despite many supporting evidences, however, the teamwork idea has not, until very recently, been clearly expressed and what is far more important, it has not been accepted and applied as a working principle. Instead, there is the widely accepted idea, certainly not openly endorsed by more sophisticated investigators, that single nutrients, expecially vitamins, act like drugs or medicines, and their effectiveness, if any, resides in their ability to prevent or cure some specific diseased condition.

While this criterion of effectiveness is satisfied in some cases, e.g., thiamin-beriberi, niacinamide-pellagra, ascorbic acid-scurvy, it is fundamentally an erroneous criterion because it overlooks a basic universal fact, namely, that unlike drugs, single nutrients always act constructively like parts of a complicated machine, and are effective as nutrients *only when they participate as members of a team.* This does not prevent nutrients from having drug-like actions when used in amounts higher than the physiological levels.

When particular vitamins appear to cure specific diseases, it is because they round out the *team,* transforming a limping incomplete team into one that is complete enough to function with some degree of physiological adequacy. In order to bring a victim of beriberi, pellagra or scurvy back to health, it is required that the victim receive continually *every one* of the essential nutrients. While in one sense such nutrients as thiamin, pantothenic acid, manganese, zinc, or threonine have nothing to do with rickets, a victim of rickets must have all these nutrients (and others), in addition to proper amounts of calcium, phosphate, and vitamin D, in order to be brought back to health.

Testing nutrients for their effectiveness is thus entirely different from testing drugs. Unless a nutrient is tested under conditions which allow it to participate in teamwork, the results are likely to be seriously misleading.

Galactose-induced cataracts in rats

Mitchell and Dodge (3) showed in 1935 that rats, receiving a very high level of lactose in the diet, developed cataracts in their eyes with considerable regularity. Subsequent experience has demonstrated that galactose is a crucial agent involved in cataract formation in rats. A considerable literature related to this phenomenon has accumulated, as evidenced by two reviews (4, 5). In the latest review, van Heyningen concludes her discussion with the statement, "Although it is comparatively easy to find methods of *causing* cataracts in animals, prevention and cure of cataracts is a long term aim... I can think of no systemic treatment that has been proved to alter the course of cataract formation without also altering the level of blood galactose."

With this information as a background, we confirmed in preliminary experiments that galactose-induced cataracts are easy to produce, and then set out to study their nutritional control. We accepted as a working premise that no single nutrient would be able, by itself, to prevent cataracts, but that a complete team of nutrients might be effective. Since high levels of galactose are metabolically toxic to the lenses of the eyes of rats, we sought to find out: Can high quality nutritional teamwork successfully counteract such a metabolic poison?

EXPERIMENTAL

Eighteen different diets were fed *ad libitum* respectively to 18 groups of rats; each group consisted of six matched male weanlings. The diets, except the control diet, all contained

TABLE 1. *Number of cataracts produced in groups of six Holtzman rats on different galactose-containing diets*

Diets (numbers are % of total calories)	Number of cataracts				Weight (g)
	3 Weeks	5 Weeks	7 Weeks	9 Weeks	9 Weeks
1. 20 Gal, 80 L.C. + V.M.	0	0	0	2	372
2. 20 Gal, 80 L.C.	0	0	0	1	379
3. 20 Gal, 40 L.C., 40 Glc	0	0	2	2	323
4. 20 Gal, 20 L.C., 60 Glc	0	6	10	11	193
5. 20 Gal, 10 L.C., 70 Glc	5	12	12	12	108
6. 20 Gal, 80 Egg + V.M.	0	0	0	0	353
7. 20 Gal, 80 Egg	0	0	0	0	356
8. 20 Gal, 40 Egg, 40 Glc	0	2	6	6	240
9. 20 Gal, 20 Egg, 60 Glc	0	10	11	12	193
10. 20 Gal, 10 Egg, 70 Glc	0	5	10	12	122
11. 20 Gal, Syn. I(+)	0	0	0	0	294
12. 20 Gal, Syn. I	0	0	0	0	296
13. 20 Gal, 80 M. Milk + V.M.	0	0	1	1	332
14. 20 Gal, 80 M. Milk	0	1	6	8	330
15. 20 Gal, 40 M. Milk, 40 Glc	0	8	12	12	286
16. 40 Gal, Syn. II(+)	0	0	5	7	281
17. 40 Gal, Syn. II	0	11	11	12	229
18. 0 Gal, 100 L.C. (Control)	0	0	0	0	379

Abbreviations: Gal = galactose; L.C. = Purine Laboratory Chow; V.M. = vitamin mixture (see Table 3); Glc = glucose; Syn. I & Syn. II = semi-synthetic diets; Syn. I(+) & Syn. II(+) = supplemented semi-synthetic diets; (see Table 2); M. Milk = mineralized milk (dry whole milk + 0.014% $FeCl_3 \cdot 3H_2O$ + 0.1% $MnCl_2 \cdot 4H_2O$ + 0.006% $Cu(C_2H_3O_2)_2 \cdot H_2O$).

high levels of galactose which in most cases comprised 20% of the calories in the diet. The diets, as summarized in Table 1, were compounded so that some would furnish a relatively adequate team of nutrients; others, for comparison, often furnished the same nutrients but at inadequate levels. All rats were examined daily for cataracts during the 9 weeks of the test.

Of the 18 diets, nos. 1, 2, 6, 7, 11, and 12 were judged in advance to contain relatively well proportioned amounts of all the essential nutrients needed by rats—a complete nutritional team. In addition, there were two other diets, nos. 13 and 14, which also contained a good assortment of team members, but were not comparable to the other relatively good diets because these diets contained a high proportion of mineralized milk, an additional source of metabolic galactose. Diets nos. 1 and 2 contained 80% of a commercial "lab chow" and were judged to be reasonably adequate. Diets nos. 6 and 7 were regarded as probably adequate because they contained 80% whole egg which we have found by itself to be an unusually complete diet for rats (6). The basic semi-synthetic diets (nos. 12 and 17) were formulated variously to be relatively complete, but were further supplemented (diets nos. 11 and 16) with the vitamin mixture to see if they could be improved. Detailed information regarding the composition of diets nos. 11, 12, 16, and 17 and the vitamin mixture is presented in Tables 2 and 3.

Diets nos. 3, 4, 5, 8, 9, 10, and 15 were qualitatively similar to more complete diets, but were quantitatively deficient in varying degrees, because the relatively complete food was diluted in each case with various amounts of glucose which furnishes only energy.

A second experiment involved feeding 13 male weanling rats a deficient cataract-producing diet (diets no. 4, Table 1) until at least one eye of each rat exhibited a cataract. The second day after the initial appearance of a cararact, each rat was shifted to an excellent diet for 9 weeks to see if there would be regression of the cataracts. The diet used was the same as no. 6, Table 1, except that the galactose was absent. In every animal, a second cataract developed within a week even though the diet had been changed, so that a total of 26 cataracts were under observation.

RESULTS

The results of the preventative experiment are summarized in Table 1. They are clear-cut and require little explanation. Although the dietary galactose challenge was the same in diets nos. 1 through 12 (20% of the total calories), no cataracts

TABLE 2. *Composition of semi-synthetic diets (g/kg)*

	Casein	Galactose	Glucose	Triolein	Salt mix*	Vitamin mix†
Diet 11 Syn. I(+)	200	234	496	50	50	60
Diet 12 Syn. I	130	197	561	50	50	12
Diet 13 Syn. II(+)	200	437	227	50	50	60
Diet 14 Syn. II	130	427	302	50	50	12

* Salt mix: Briggs-Fox (11) + 0.01% $CoCl_2 \cdot 6H_2O$ + 0.05% NaF + 0.005% $NaMoO_4 \cdot 2H_2O$ + 0.002% $NaSeO_3 \cdot 3H_2O$.
† Vitamin mix: see Table 3.

TABLE 3. *Nutrient amounts (per 100 calories) furnished by vitamin mixture in diets nos. 1, 6, 11, 13, and 16*
(Nutrients furnished in diets nos. 12 and 17 at 1/5th these amounts)

Vitamin A acetate	(I.U.)	1333	Pyridoxine·HCl	(mg)	0.8
Vitamin D_3	(I.U.)	66.7	Cobalamine	(μg)	3.3
dl-α-tocopherol	(mg)	40	Folic acid	(mg)	3.3
Menadione sodium bisulfite	(mg)	0.13	Biotin	(μg)	70
Thiamine·HCl	(mg)	0.83	Choline	(mg)	50
Riboflavin	(mg)	1.67	Inositol	(mg)	33.3
Niacin	(mg)	10	Linoleic acid	(g)	1.3
Calcium pantothenate	(mg)	5.3	Short chain fatty acid mix*	(g)	1.3

* Short chain fatty acid mix: 30% tributyrin, 30% capric acid, 10% caproic acid, 10% tricaprylin, 20% lauric acid.

whatever appeared in animals on four of the superior diets (nos. 6, 7, 11, and 12) and on four diets we knew to be poorer (nos. 4, 5, 9, and 10); 47 of the 48 eyes involved were cataractous. Diets of intermediate quality yielded intermediate numbers of cataracts. In one of the two diets in which the galactose level was raised to 40% of the total calories, the supplemented semi-synthetic diet afforded some but not complete protection. Also, the increased level of whole milk in diet no. 14 afforded some protection in spite of the increased lactose challenge. When this diet was supplemented with a vitamin mixture, diet no. 13, the protection was almost complete. Each basal diet appeared to have some distinctive properties with respect to its ability to protect against cataracts. The diluted lab chow diet, no. 5, seemed to induce cataracts the most rapidly of all; even when the lab chow was at the 80% level, diets nos. 1 and 2, protection from cataract formation was not complete.

The results of the second experiment, in which animals were placed on good diets *after* cataracts had been produced on a poor diet, designed to determine if there would be regression, were not as clear-cut as the experiment involving prevention. The results on 26 cataracts are summarized in Table 4. Of the 26 cataracts observed, 16 showed an improvement in their "scores" of from 40 to 80%. In general the regressions were slow and incomplete, though improvement in many cases was clearly manifest.

DISCUSSION

It is difficult to discuss our experimental study and findings adequately and in proper perspective. On the one hand our

TABLE 4. *Cataract scores of individual rats on supplemented diets after induction of cataracts by galactose feeding*

Rat no.	3 Weeks			5 Weeks			10 Weeks			% Decrease in Score 3rd to 10th week
	Diam.	Dens.	Score	Diam.	Dens.	Score	Diam.	Dens.	Score	
1 R	4.0	4	16.0	3.6	4	14.4	3.0	4	12.0	25
L	3.0	4	12.0	1.2	4	4.8	1.4	4	5.6	53
2 R	3.6	4	14.4	3.6	4	14.4	1.6	4	6.4	56
L	3.4	4	13.6	3.4	4	13.6	2.0	4	8.0	41
3 R	3.0	4	12.0	1.2	4	4.8	1.4	4	5.6	53
L	3.4	4	13.6	1.2	4	4.8	1.8	4	7.2	47
4 R	3.6	4	14.4	3.6	4	14.4	1.4	4	5.6	61
L	3.6	4	14.4	3.6	4	14.4	1.8	4	7.2	50
5 R	2.8	3	8.4	3.0	1	3.0	2.6	1	2.6	69
L	2.8	4	11.2	2.8	2	5.6	2.8	2	5.6	50
6 R	2.8	3	8.4	2.2	3	6.6	2.0	4	8.0	5
L	3.0	4	12.0	3.0	4	12.0	2.0	4	8.0	33
7 R	3.2	4	12.8	2.6	4	10.4	1.4	4	5.6	56
L	3.2	4	12.8	3.4	4	13.6	1.4	4	5.6	56
8 R	3.6	4	14.4	3.2	4	12.8	2.2	4	8.8	39
L	3.4	4	13.6	1.6	4	6.4	1.8	4	7.2	47
9 R	2.6	3	7.8	1.8	4	7.2	1.4	4	5.6	28
L	2.8	4	11.2	1.2	4	4.8	2.2	4	8.8	21
10 R	2.8	4	11.2	3.0	1	3.0	1.8	1	1.8	84
L	3.0	4	12.0	3.0	4	12.0	1.4	4	7.6	37
11 R	3.6	4	14.4	1.2	4	4.8	1.6	4	6.4	56
L	2.8	4	11.2	1.6	4	6.4	2.0	4	8.0	29
12 R	4.0	4	16.0	3.6	4	14.4	3.6	4	14.4	10
L	4.0	4	16.0	3.6	4	14.4	2.0	4	8.0	50
13 R	2.8	4	11.2	3.2	4	12.8	2.6	3	7.6	32
L	2.6	4	10.4	2.6	4	10.4	2.6	1	2.6	81

R, L = right and left eyes, respectively. Diam. = estimated diameter of cataract in mm. Dens. = estimated density of cataract, with 1 = least and 4 = most dense. Score = product of Diam. and Dens.

strategy, once it is described, seems so simple, if not obvious, that it appears to require little comment. On the other hand, so far as galactose-induced cataracts are concerned, it is a new, untried strategy; if it had ever been tried at any time during the past 3 or 4 decades it would have been successful. The potential value of our findings rests on the probability that this same strategy, if broadly followed, may yield highly important unforeseen benefits in the realm of medical science.

Although our success in preventing galactose-induced cataracts in rats was complete on four diets for 9 weeks, this was not an "all or none" process. Other diets protected almost completely, and some yielded only very partial protection. If the galactose challenge had been less severe, it seems probable that diets of mediocre quality would have sufficed to give protection; if the challenge had been more severe, it might have required diets better than any we used to accomplish protection. These findings are completely in line with the nutritional principle (2, 7) that common food environments are consistently *suboptimal*, and hence are always subject to improvement. When, as suggested by van Heyningen's review (5), investigators have failed to prevent galactose-induced cataracts, it has been because they have failed to recognize this principle and have never tried seriously to improve to the limit the total environment of their experimental animals.

It is evident that from our study no one could derive a precise list of the nutrients involved in protecting against cataract, nor does our study rule out the possibility that for some or all individual animals, certain specific nutrients may be crucially limiting factors in the nutritional team. We have not proved by actual experiment that leaving out any one of the essentials would have resulted in failure to protect. Neither have we studied the possible effect of imbalance between nutrients. We have not ruled out the possibility that there is a glucose–galactose synergism involved in cataract production. Our simple experiment shows that when we attempted to furnish enough of all the essentials, success was attained. Many further experiments will be required to clear up numerous uncertainties.

If a physician were to treat an obscure malady by giving his patient several drugs at the same time, in the hope that one or another of the drugs might bring relief, this may be reprehensible, and would aptly be dubbed the "shotgun" approach. To extend this disapprobation to the administration of several *nutrients* simultaneously is to miss one of the most vital principles of nutritional science—the teamwork principle. Because of this teamwork principle, the administration of many nutrients at the same time is not only entirely logical but basically essential. When we do this we are following in the footsteps of nature. When human beings are fortunate enough to maintain health by consuming wholesome food, this is accomplished by reason of the fact that they consume regularly *every one* of the about 40 nutritional essentials. It is not following nature's strategy if we consume tryptophan on Monday, ascorbic acid on Tuesday, calcium on Wednesday, etc. We utilize in our bodies all nutritional elements simultaneously every day.

The careful discrimination between nutrient action and drug action is necessary if we are to avoid serious pitfalls. For example, the Food and Drug Administration is inclined to rule that drugs in order to be sold must be both "*safe*" and "*efficacious*." If we unfortunately and uncritically apply the same criteria to nutrients, we immediately condemn most nutients as unsuitable for sale, because while they are usually safe, they are, generally speaking, not efficacious when administered singly. For example, there is probably no single nutrient that would be at all "efficacious" in preventing cataracts in rats; the entire team of nutrients, on the other hand, is extremely efficacious.

Attacking specific diseased conditions *seriatim* with the purpose of ascertaining what nutrition can do to prevent or alleviate them is certainly not fashionable today in the area of medical science. We can hope that our unqualified success in preventing galactose-induced cataracts in rats, once a "long-term aim," may help make the nutritional strategy more fashionable.

Immediately our success in preventing cataracts in rats leads to the questions: Can the cataracts associated with diabetes be prevented by a sophisticated nutritional teamwork approach? Can the cataracts often associated with human senility be prevented by regularly providing potential victims with an excellently proportioned set of nutritional elements?

It may be presumed that the rats in our experiments which were completely protected from galactose-induced cataracts were able, by having all their nutritional needs adequately satisfied, to build and adapt enzyme systems to metabolize galactose in such a way as to obviate its damaging effects. If the crucial agent concerned in cataract production in rats is galactitol (8), its formation was probably minimized when the metabolic operations flowed smoothly in a normal manner. If galactitol is involved in the production of senile cataracts, its effects in humans can probably be minimized by furnishing all the raw materials needed for promoting its normal metabolism. If sorbitol (9) (or another polyalcohol) is involved in the production of diabetic cataracts, then its deleterious action can probably be minimized in diabetics by providing the cells and tissues with a complete complement for building effective metabolic machinery.

The results obtained in the curative experiment were definitely positive, but the regressions were slow and incomplete presumably because of the slow rate of metabolism in the lens of the eye. It seems possible that if the dietary challenge offered these rats had been less severe or if the change in diet had been instituted at the very first sign of cataract instead of waiting until the cataracts were well formed, the responses might have been more favorable.

Cataracts in rats was chosen by us as a diseased condition to attack merely by "pulling it out of the hat," as something that could be studied objectively and conveniently. There is little evidence on which to predict in advance how many other diseased conditions in rats will respond similarly to the nutritional teamwork approach—other eye maladies, atherosclerosis, carious teeth, delayed bone healing after fracture, production of malformed young, etc. Substantial evidence is available to suggest that this approach will prevent the production of malformed young (10), but the other diseased conditions have not been explored with due consideration of the total food environment and the teamwork principle.

In the arena of human disease prevention, our unqualified success with galactose-induced cataracts in rats suggests that added emphasis on sophisticated nutritional teamwork be encouraged for the prevention not only of human cataracts and other eye maladies but also diseases of obscure etiology such as multiple sclerosis and muscular dystrophy, also mental retardation, ischemic heart disease, dental diseases, allergies,

arthritis, premature senility, obesity, mental disease, alcoholism, and even cancer. To promise success in these numerous areas would be extravagant, but on the other hand, it can be stated that serious sophisticated trials of the teamwork approach—such as we have used to prevent cataracts in rats—have never been made in connection with any of the human diseases mentioned. Much of the nutritional exploration related to these areas can unfortunately be characterized as merely "dabbling," rather than dealing seriously with the *total* food environment.

1. Williams, R. J. (1971) *Nutrition Against Disease* (Pitman Publ. Co., New York), p. 212 *et seq.*
2. Williams, R. J., Heffley, J. D., Yew, M. L. S. & Bode, C. W. (1973) "A renaissance of nutritional science is imminent," *Perspect. Biol. Med.* **17**, 1–15.
3. Mitchell, H. S. & Dodge, W. M. (1935) "Cataract in rats fed on high lactose rations," *J. Nutr.* **9**, 37–49.
4. van Heyningen, R. (1971) "Galactose cataract: A review," *Exp. Eye Res.* **11**, 415–426.
5. Lerman, S. (1965) "Metabolic pathways in experimental sugar and radiation cataracts," *Physiol. Rev.* **45**, 98–122.
6. Williams, R. J., Heffley, J. D. & Bode, C. W. (1971) "The nutritive value of single foods," *Proc. Nat. Acad. Sci. USA* **68**, 2361–2364.
7. Williams, R. J. (1974) *Physicians Handbook of Nutritional Science* (C. C Thomas, Springfield, Mo.), in press.
8. Kinoshita, J. H., Merola, L. O. & Dirkmak, E. (1962) "Osmotic changes in experimental galactose cataracts," *Exp. Eye Res.* **1**, 405–410.
9. van Heyningen, R. (1959) "Formation of polyols by the lens of rats with 'sugar' cataracts," *Nature* **184**, 194–195.
10. Williams, R. J. (1971) *Nutrition Against Disease* (Pitman Publ. Co., New York), chap. 4.
11. Fox, M. R. S. & Briggs, G. M. (1960) "Salt mixtures for purified-type diets: III, An improved salt mixture for chicks," *J. Nutr.* **72**, 243.