THE EFFECT OF SUPPLEMENTING A RACHITOGENIC DIET WITH DESICCATED THYROID, IODINATED CASEIN, AND CASEIN

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THE EFFECT OF SUPPLEMENTING A RACHITOGENIC DIET WITH DESICCATED THYROID, IODINATED CASEIN, AND CASEIN

By

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A THESIS

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Introduction

In the determination of vitamin D the biological assay method has in general proven superior to the physical and chemical methods developed thus far.

The basis of the biological method involves the production of severe rickets in young rats by means of a suitable rachitogenic ration and subsequent feeding of the material to be tested to one group of rats while the reference group is fed a known amount of vitamin D by use of the U.S.P. reference standard. After a period from 7 to 14 days of vitamin D feeding, the animals are killed and the degree of rickets and resultant calcification determined by one or any combination of the following methods: "line" test, ash content of bone, test for increase of body weight, and radiographic analysis. The key to the biological assay method is the availability of a rachitogenic diet capable of producing a uniform and severe degree of rickets which necessarily implies fairly good growth.

At Michigan State College, a modified Steenbock rachitogenic ration is used which is somewhat goitrogenic as well as deficient in one of the essential amino acids, namely, lysine. Inasmuch as lack of uniformity in the growth of animals might be due to variations in thyroid activity, it was considered likely that the use of desiccated thyroid or iodinated casein would influence the growth of rats fed the rachitogenic diet and result in more uniform response.

It was the purpose of this investigation to determine if desiccated thyroid or iodinated protein might have some value as a component of a rachitogenic diet. A preliminary study was also made of the value of adding casein to a rachitogenic diet to increase the supply of lysine, one of the limiting amino acids.

Historical Review

In 1921 there appeared the first of a series of papers entitled "Studies on Experimental Rickets" originating from the Johns Hopkins University by McCollum and associates (1-9). McCollum (1) concluded from an initial series of investigations that "It might seem from a perusal of diets here in use that the cause of these diseases might lie in a deficiency of fat soluble A or calcium in the food or a disturbance in the metabolism of these factors". Shortly thereafter it was noted (2) that cod liver oil caused calcium salts to be deposited in the same fashion in which deposition occurs in spontaneous healing in rickets of humans. Thus, in the early days of the vitamins, "fat soluble A" was considered one substance, capable of curing both xerophthalmia and rickets. Hess, McCann, and Pappenheimer (9) fed young rats a diet consisting of casein 21%, rice starch 51%, salt mixture 5%, Crisco 17%, and yeast 60 mg. along with orange juice. The skeletons of these rats bore no lesions resembling rickets. In 1922 McCollum (7) bubbled oxygen through cod liver oil at 120° C. and found that the resultant oil was ineffective against xerophthalmia but was capable of curing rickets. Thus, vitamin A had been destroyed and the factor remaining was called vitamin D, the anti-rachitic factor. After numerous trials, the ration finally decided upon by McCollum for the production of rickets in rats, Ration 3143, (3) was composed of wheat 33%, maize 33%, gelatin 15%, wheat gluten 15%, NaCl 1% and $CaCO_3$ 3%. In 1922 a biological test (6) for determining the calcium-depositing power of various food substances based on the production of severe rickets in growing young rats by diet 3143 was announced.

However, McCollum's diet 3143 possessed certain shortcomings such as: (1) vitamin A was not present in sufficient quantity; (2) it produced a variable grade of rickets; and (3) it contained too much protein, 33%—especially gelatin which produced anorexia and at times diarrhea. In 1925 Steenbock and coworkers (10) developed an improved rachitogenic diet, 2965, which consisted of yellow corn, 76%, wheat gluten, 20%, $CaCO_3$, 3% and NaCl, 1%. This diet eliminated many of the disadvantages of McCollum's diet previously used. Moreover, the diet was cheaper and more easily prepared.

In order to produce rickets in rats, unlike other species where merely the absence of vitamin D is sufficient, they must be fed a ration containing calcium and phosphorus in an abnormal ration along with the absence of vitamin D. Brown, Shohl, etc. (11) have shown that the ratio of Ca-P and the salt level are interdependent and that at a given level of calcium or phosphorus, increasing the ratio of Ca-P intensified the degree of rickets whereas at a given ratio of Ca-P, increasing the level of salts diminished the degree of rickets. Satisfactory results were obtained with .25% phosphorus present in the ration and a Ca-P ratio of approximately 5:1. This is the case in either the Steenbock or McCollum ration.

Much has been written concerning the importance of the acid-base factor of the diet. Rickets has been produced by McCollum (3) with either $CaCO_3$ or $CaCl_2$, hence under a variety of conditions with regard to the acid-base balance of the diet. Shohl and Bennett (12, 13) were able to cure rickets by the addition of the same amount of phosphorus, whether in the form of alkaline, neutral, or acid salts. Shohl and Bennett (14) next demonstrated that the acid-base factor is important only in borderline cases of rickets with acid diets tending toward the production of rickets.

In 1934 Harris and Bunker (15) reported that variability in the production of experimental rickets was probably due to the corn component which they suspected contained some anti-rachitic factor. They also observed considerable variation in the phosphorus content of corn. This variation was so large that the Ca-P ratio of rachitogenic diets varied from 3.98:1 to 6.7:1. Ma in 1937 (16) stated that the sterols in corn may be activated by exposure of corn to sunlight thus reducing the rachitogenic properties of diets intended for the production of rickets. In 1935 Harris and Bunker (17) found that rachitogenic diets could be compounded more successfully from corn than from casein. This was attributed to the fact that the phosphorus of cereals exists mostly as phytin, which is not as well utilized as phosphorus of casein. Krieger and Steenbock (18) further confirmed this by observing that the utilization of phosphorus from phytic acid was enhanced by vitamin D but in no case was the utilization of phosphorus from phytin equal to that of inorganic phosphorus. Although calcium of calcium phytate is as readily available as that of $CaCO_3$ (19), this factor is unimportant since the amount of calcium in corn is about .05% and view of the large percentage $CaCO_3$ in rachitogenic diets this amount is insignificant.

Tripp and Holmes (20) demonstrated the importance of proper mixing of the ration. They were able to show that $CaCO_3$, wheat gluten, and the finer corn portions tend to settle towards the bottom of the container with the large corn particles remaining on top. Thus, a rat eating at the surface would get a different proportion of Ca-P than one eating the bottom part.

Ma (16) modified the Steenbock ration by substituting yellow table corn meal for ground whole corn. Inasmuch as this change caused a marked diminution in the amount of the B vitamins, 4% brewers yeast was added to provide an adequate supply of these nutrients.

With the knowledge of the amino acid requirements of the rat, Francis (21) tabulated the amount of the individual essential amino acids present in the Steenbock ration and found it to be deficient in lysine. The addition of .5% lysine increased the growth rate twice over the unsupplemented ration producing satisfactory rickets in 16 days in addition to reducing the incidence of respiratory infections. Similar results were obtained by Yang (22) who round that 1% lysine supplement did not show any greater effect than the .5%.

Rats fed the Steenbock ration are found to have thyroid enlargements with hyperplasia. This is to be expected, since the diet on the average has a content of 15 gammas iodine per kilo as determined by Levine, Remington and von Kolnitz (23). The daily intake of iodine necessary to yield a concentration of .1% iodine in the thyroid (dry basis) which is essential to normal thyroid functioning was found by the same workers (24) to be approximately 1 gamma per day. This same group (25) found that low iodine goiter is produced when the iodine content in the gland is .03% or less (dry basis) and this probably corresponds to an iodine intake from known sources of .3-.4 gammas per day. The presence (26) of 265 micrograms of iodine per kilo in an otherwise well balanced diet is sufficient to protect growing rats from iodine deficiency. Thompson (27) reported that the high concentration of calcium plus the iodine deficiency was an important factor possibly rendering the thyroid colloid stiffer and the thyroid membrane less permeable.

There is little reference in the literature to the use of desiccated thyroid and iodinated protein as a means of offsetting the goitrogenic effect of the Steenbock ration and stimulating the growth of young rats. In 1938 Smith and McLean (28) by feeding rats desiccated thyroid were unable to produce decalcification of adult rats or any evidence of lack of calcification in rapidly growing rats. On the other hand Mitschke (28) by the administration of thyroid extracts intensified the degree of rickets. However, desiccated thyroid is expensive and its potency variable. The method of iodinating casein by Reineke (29) provides a comparatively inexpensive product of high thyroid activity. This product was used to establish whether or not the rachitogenic diet used routinely in the assay of vitamin D milks at Michigan State College could be improved by eliminating its goitrogenic properties.

Experimental Procedure

Throughout the pre-rickets producing period the rats were maintained on a diet which provided for normal development in all respects except that the supply of vitamin D was limited so that the rats would develop severe rickets in 21 days.

For the rickets producing period a rachitogenic ration consisting of table corn meal, 72%, wheat gluten, 20%, yeast, 4%, and NaCl, 1%, was used as well as the following modifications:

Ration Number	Modifications
I	Basal (the above ration)
II	1 Kilo Basal + 5 grains desiccated thyroid
III	1 Kilo Basal + 10 grains desiccated thyroid
IV	1 Kilo Basal + 25 grains desiccated thyroid
V	Basal + .1% iodinated casein
VI	Basal + .05% iodinated casein
VII	Basal + .025% iodinated casein
VIII	Basal + .0125% iodinated casein
IX	Basal + .025% iodinated casein + 5% casein
X	Basal + 5% casein

Young albino rats weighing from 44 to 60 grams and 21-25 days old were assembled into groups of 2 or 3 and fed the rachitogenic diet or one of the above modifications for 21 days and water, ad libitum. They were then placed in separate cages one day prior to the beginning of the ten day assay period so as to adequately adjust themselves to their new surroundings. The animals received a supplement of homogenized vitamin D milk supplying 4 units of the vitamin. In each series some animals were included as negative controls. At the end of the assay period the animals were killed and the distal ends of the radii and ulnae removed and cleansed of adhering tissue. The bones were then permitted to remain at least overnight in 95% ethanol. After the wrist bones were separated, longitudinal median sections were made through the end of the bones with a sharp scalpel to expose a plane surface through the junction of the epiphysis and diaphysis. The bone sections were then rinsed in distilled water and placed in a 2% solution of silver nitrate for two minutes. The sectioned surfaces of the bone were exposed in distilled water to light from fluorescent lamps until the calcified areas had developed a clearly defined stain without discoloration of the uncalcified areas.

Records were made of the growth during the experimental period, the general appearance of the lines and the width of the metaphyses. These criteria were employed for determining the suitability of the various rations.

Data

Table I

Ration Number	Supplement to Basal	No. of Starting Rats	Ave. Initial Weight	Weekly Wts. 1st	2nd	3rd	Ave. Wt. Gained in 3 Weeks	Ave. Wt. Gained Daily
I	None	3	48	53.3	66.3	74.3	26.3	1.2
II	5 grains d. thyr.* per kg.	6	51.8	58.5	74.3	85.8	34.0	1.6
III	10 grains d. thyr. per kg.	6	51.3	57.8	75	83.5	32.2	1.5
IV	25 grains d. thyr. per kg.	5	51.8	57.2	72	81.8	30	1.4

*1/2 grain commercial desiccated thyroid tablets were used.

1. Experiment started Feb. 17, 1949--ended March 17, 1949.

   The temperature during this period averaged about 77° F.

2. During the assay period the following rats died:

   (a) One on ration II

   (b) Two on ration III

   (c) Three on ration IV

3. All rachitic metaphyses were of desirable width and character.

4. Line Test Results:

   (a) Rats on ration I and II produced uniform medium lines.

   (b) Rats on ration III and IV produced thin high lines.

Table II

Ration Number	Supplement to Basal	No. of Starting Rats	Ave. Initial Weight	Weekly Wts. 1st	2nd	3rd	Ave. Wt. Gained in 3 Weeks	Ave. Wt. Gained Daily
I	None	10	48.7	55.9	66.1	74.1	25.4	1.2
II	5 grains d. thyr. per kg.	5	49.2	55.4	67.4	82.6	33.4	1.6
III	10 grains d. thyr. per kg.	5	47.8	56.4	65.2	72.5	24.7	1.1
V	.1% iodinated casein	5	48.4	55.6	63.4	--	--	--
VI	.05% iodinated casein	13	48.0	51.1	59.6	65.2	17.2	.89
VII	.035% iodinated casein	8	46.7	51.6	59.8	72.1	25.4	1.2

1. Experiment started March 8, 1949--ended April 29, 1949. The figures above represent two similar series started at slightly different intervals. The temperature during this period averaged about 78° F.

2 (a) During the depletion period the following rats died:

   (1) One on ration III

   (2) Five on ration V

   (3) Five on ration VI

   (4) One on ration VII

  (b) During the assay period the following rats died:

   (1) Four on ration VI

3. All rachitic metaphyses were of desirable width and character.

4. Line Test Results:

   (a) Rats on ration I produced medium to thin lines.

   (b) Rats on ration II produced uniform medium lines.

   (c) Rats on ration III and VI produced thin high lines.

   (d) Rats on ration VII produced uniform medium lines.

Table III

Ration Number	Supplement to Basal	No. of Starting Rats	Ave. Initial Weight	Weekly Wts. 1st	2nd	3rd	Ave. Wt. Gainedin 3 Weeks	Ave.Wt. Gained Daily
I	None	13	48.1	48.0	55.7	62.4	14.3	.68
VII	.025% iodinated casein	29	47.3	48.2	56.4	63.2	15.9	.76
VIII	.0125% iodinated casein	12	48.7	49.8	58.1	62.0	13.3	.63

1. Experiment started May 5, 1949--ended July 9, 1949. The above figures represent two similar series started at slightly different intervals. The temperature during this period averaged about 85° F.
2. During the assay period the following rats died:
   (a) One on ration I
   (b) One on ration VIII
   (c) Five on ration VII
3. All rachitic metaphyses were of desirable width and character.
4. Line Test Results:
   (a) Rats on ration I produced a variety of faint, thin, broken lines. Several showed no calcification.
   (b) Rats on ration VIII produced thin lines.
   (c) Rats on ration VII produced uniform medium lines.

Table IV

Ration Number	Supplement to Basal	No. of Starting Rats	Ave. Initial Weight	Weekly Wts. 1st	2nd	3rd	Ave. Wt. Gained in 3 Weeks	Ave. Wt. Gained Daily
I	None	6	46.5	45.8	50.5	57.5	11.0	.52
IX	.025% iodinated casein + 5% casein	15	48.7	53.0	65.9	77.6	28.9	1.4
X	5% casein	8	47.2	55.0	70.5	78.2	31.0	1.5

1. Experiment started June 16, 1949--ended July 27, 1949. The above figures represent two similar series started at slightly different intervals. The temperature during this period averaged about 85° F.
2. During the assay period the following rats died:
   (a) One on ration I
   (b) Three on ration IX
   (c) Two on ration X
3. All rachitic metaphyses were of desirable width and character.
4. Line Test Results:
   (a) Rats on ration I produced thin lines.
   (b) Rats on ration IX produced uniform medium lines.
   (c) Rats on ration X produced lines varying from medium uniform to diffused.

Discussion

These investigations were conducted under a wide variation of environmental temperature. Therefore, the results obtained must be interpreted taking this factor into account since animal appetite and thyroid function are influenced by environmental temperature.

From the data it is evident that rations III, IV, V, and VI are unsuitable for the standard 21-day period. This may be attributed to an excessive intake of desiccated thyroid or iodinated casein. The detrimental effects assert themselves usually within 3-4 weeks as evidenced by the number of rats that died during the rickets producing and assay periods and by the high thin line of calcification, which is usually the result of insufficient food consumption.

The addition of 5 grains of desiccated thyroid to the basal ration produced the best growth as well as the most uniform lines, when compared with the rest of the respective series. This assumes some importance since the same comparative results were obtained at different times and at varying temperatures. Ration VII and I appear about equal in their ability to promote growth; however, the addition of .025% iodinated casein appears to definitely aid in calcification response. Each series of rats received Michigan State College homogenized vitamin D milk calculated to supply 4 U.S.P. units vitamin D. Some variation in the actual potency of vitamin D milks might, of course, be expected.

Apparently the sub-series containing rats fed .025% iodinated casein, .0125% iodinated casein as well as plain basal were fed milk of somewhat lower vitamin D content because the line test responses were generally smaller. Nevertheless, those receiving ration VII showed better responses.

The fact that rats on ration II seem to do better than rats on ration VII is quite interesting since apparently both represent optimum tolerable levels of desiccated thyroid and iodinated casein. Although rats on ration II and VII belong to different sub-series (but same series) and are therefore not entirely comparable, the possibility exists that the thyroid extract may differ somewhat in its overall physiological activity from that of the iodinated protein.

The results with ration VIII containing .0125% iodinated casein indicated that this amount of iodinated casein did not affect the animals with regard to rickets production and the line test.

In no case did the average gain in weight in 3 weeks of rats receiving either ration II or VII exceed the respective basal group by more than 8 grams. This may be attributed to the fact that the basal ration is deficient in lysine as well as available phosphorus, thus limiting the effect of either the iodinated casein or desiccated thyroid as growth stimulators. When rations IX and X were employed, the growth rate was nearly tripled over the corresponding basal fed group. The growth attained by the end of the first two weeks was sufficient to suggest that only a two-week period would be necessary for the preparation of rats for vitamin D assays. The results, therefore, compare favorably with those obtained with lysine. The line test results, using rations IX and X, further substantiate the effectiveness of iodinated casein in producing more uniform lines.

Summary

1. The addition of desiccated thyroid to a rachitogenic diet had a favorable effect on the growth rate of young rats. Five grains per kilo of the ration proved optimal and resulted in an average gain in weight in rats of 8 grams in 3 weeks over those receiving the unsupplemented diet.
2. In the case of iodinated casein 0.025% was found to be optimal. Better line test responses were consistently observed with this modification of the basal rachitogenic diet.
3. The addition of 5% casein to either unsupplemented or iodinated casein supplemented basal resulted in greatly improved weight comparable to those obtained with .5% lysine supplementation by Yang.

   The line tests in the group receiving the iodinated casein were again superior to the others.

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