VITAMINS A AND D: THEIR RELATION TO GROWTH AND RESISTANCE TO DISEASE

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Within the last twenty years, and especially during the last decade, there has accumulated an extensive literature on the subject of vitamins, which shows clearly that an adequate, though minute, amount of these accessory food factors in the diet is essential to the proper functioning of the animal organism. Of the vitamins so far known, two of the most important are the fat-soluble vitamins A and D.

VITAMIN A

Our knowledge regarding the functions of vitamin A has been gained largely as the result of animal experiment. It has been found that a deficiency of this vitamin interferes with the rate of growth in animals^{1 2 3}; produces a metaplasia and keratinization of mucous epithelia cells^{4 5 6 7 8 9}; and increases the susceptibility to local infections of the degenerated epithelia.^{4 8 9 10 11 12 13} No evidence of any effect upon general resistance to disease has been forthcoming.

It would be unwise to assume, however, that conclusions drawn from animal experimentation can be rigidly applied to human beings in whom deprivation of vitamins is conditioned by naturally arising dietary deficiencies. For humane reasons the complete withdrawal of all vitamin A from the diet is impossible. When compared with animal experiments, therefore, where it is the rule that the basal diet is complete and well balanced except for the absence of the vitamin to be tested, human experiments are complicated by the fact that the basal diet of many of the subjects is incomplete and imbalanced, and that the vitamins which are being investigated are only partially, if at all, deficient. Consequently it has been difficult to obtain clear-cut results in man.

Hess found no evidence of vitamin A supplements improving the rate of growth of children¹⁴; and only one case has been reported where the degenerative changes of epithelia occurred as in animals.^{7 15} Further, the evidence concerning the effects of vitamin supplements upon susceptibility to infection and resistance to established disease is conflicting, since a relation between vitamin A deficiency and infections has been found by some investigators,^{16 17 18 19 20 21 22 23} while it has not been observed by others.^{14 24 25 26 27}

VITAMIN D

It is now generally recognized that a deficiency of vitamin D interferes with the metabolism of calcium and phosphorus.^{28 29 30 31 32 33 34 35} When this fact is coupled with the observation that a slowing of the rate of growth of animals follows an upset of the calcium or phosphorus content of the blood,^{36 37 38} it seems highly probable that an optimum amount of vitamin D is necessary if maximum growth is to proceed. Experiments on vitamin deficiency support this view.^{13 36} Whether or not vitamin D plays any part in determining susceptibility to infection is as yet unproved, as the evidence of different observers is at variance.^{8 13 36 39}

AN EXPERIMENT UPON SCHOOL CHILDREN

In view of the uncertain state of our knowledge concerning the prophylactic and curative value of vitamin supplements in man, and having regard to the fact that large amounts of these substances are being prescribed

at considerable expense to the general community, it was felt that there was a definite need for a test of such preparations by a controlled experiment. Accordingly, for a period of six months during the winter and spring of the school session 1931-2, a concentrate of vitamins A and D was administered to 294 children of both sexes and of all ages from 5 to 15, attending the North School, Peterhead. These children were selected at random, and had as controls 281 contemporaries. It was shown by a census of the parents' occupations that the pupils of this school were drawn almost entirely from the lower working classes.

The purpose of the experiment was to study the effect of the addition of supplements of vitamins A and D to the average home diet of children of the poorer classes. The effects that were especially looked for were those upon growth, general nutrition, susceptibility to infection, and resistance to established disease.

For a period of six months from November 9th, 1931, to May 15th, 1932, each child in the treated group received one capsule of the vitamin concentrate twice daily—one in the morning and one in the afternoon of every day upon which it attended school. Each child in the control group was given instead, but at the same time, an arachis oil capsule, which was similar in taste but entirely deficient in vitamins. According to the statement of the manufacturers, one capsule of the vitamin concentrate contains 1,000 blue units (Carr-Price value) of vitamin A, and 1,200 international units of vitamin D. The children in the treated group were thus receiving the equivalent in vitamin A of over one ounce of cod-liver oil during each day that they attended school.

Children who consistently experienced difficulty or showed marked distaste when swallowing the capsules were eliminated during the first three weeks, and, before the experiment was concluded, others were eliminated because they were suffering from tuberculosis or other serious illness, or because they had left school, or because they were absent at the time of the second examination. In the last event, however, they were included in the observations recorded below regarding the incidence of disease. By all these eliminations the numbers in the experiment were reduced from 326 in the experimental group and 325 in the control group to 294 and 281 respectively.

MEASUREMENTS

Each child was physically examined at the beginning and at the end of the experiment by the writer, who did not know to which group the pupil belonged. It was found impracticable to weigh the children without clothing, and they were therefore weighed and measured in their indoor garments. In order that a fair comparison might be made between the findings at the two examinations, however, the number of garments was counted on each occasion, an average weight per garment was determined for each 2-year age group, and an allowance was made for any difference in the number of garments at the second examination. The height was measured without footwear to the nearest eighth of an inch, and the weight to the nearest eighth of a pound.

CLINICAL OBSERVATIONS

It was recognized, of course, that quantitative measurements are the most reliable of the observations that can be made at a physical examination, but a wealth of other valuable criteria of comparison of health and of resistance to disease would have been lost had the examination been restricted to them.

If the examiner is unaware which of his subjects belong to the experimental group and which to the control group, if he sets down in writing fixed standards by which

he can measure the degree of abnormality of each factor and to which he can refer before undertaking the second examination, if each individual is examined for the presence or absence of all the factors which are to be analysed, and, most important of all, if examinations from which comparisons are to be made are carried out by the same observer, then these "clinical" observations may be of the utmost value as data of comparison. In the present instance all these requirements were met, and the data in question were obtained by the use of certain standards which, though they might vary with each examiner, were reasonably constant when used by the same observer at both examinations. Observations based on these fixed standards were made upon the general nutrition and development of the child; its posture; the width of the subcostal angle and the breadth of the shoulders; the development of the breasts in females; the condition of the teeth; the presence or absence of enlargement of the tonsils and of the cervical lymphatic glands, of nasal catarrh, of external eye disease, of nail biting, or of anaemia, as determined by a clinical examination of the conjunctiva, lips, palate, and finger-nails; and the degree of cleanliness as measured by the presence or absence of head-nits or vermin and of flea-bites on the body. It will be noted that observations were made on certain factors upon which the vitamin concentrate could not be expected to have any effect. Such observations, however, were found to be of value in establishing the initial comparability of the groups.

RECORD OF ILLNESS

In order that an indication might be obtained of the effect, if any, of the vitamin supplements upon susceptibility to infection and resistance to established disease, a record of the number of days of illness from specified diseases observed in school or the cause of absence was kept by the teachers from January 5th to May 20th, 1932, in the case of every child. This record was kept on a form upon which a dated space was left for each school day, and illnesses were noted under appropriate headings.

The records of illness causing absence were compiled from medical certificates, or from information supplied by the attendance officer. Illnesses observed in school were the record of the class teacher's observations. The writer, however, visited the various classes on an average once a week, checked the observations of the teachers, demonstrated new conditions, and generally exercised reasonable supervision. In this way the degree of accuracy of the observations made was kept at a high level. The numbers observed as regards the incidence of sickness were 294 in the treated group and 288 in the control. These numbers differ slightly from those examined physically because some were absent at the time of the second examination.

INITIAL EQUALITY OF THE GROUPS

Space does not allow a detailed account of the methods by which the initial equality of the groups was proved. Suffice it to say that a careful comparison of the original heights and weights and of the data obtained from all the observations referred to under the heading "clinical observations" served clearly to establish the comparability of the groups at the beginning of the experiment.

COMPARISON OF THE FINDINGS OF THE TWO EXAMINATIONS

With the similarity of the groups at the beginning of the experiment satisfactorily determined, it is possible to proceed to a consideration of such of the data as will indicate if any significant difference between the two

groups existed at the close. A comparison of the gains in height and weight in the two groups during the period of the experiment will determine if there was any difference in the rate of growth, but, in order to make the comparison a fair one, the gains must be expressed as a percentage of the original measurements. This is done in Table I, from which it will be seen that the treated groups show a slight advantage in respect of the gains in both height and weight. If both sexes are taken together, the treated group shows an average gain in height and in weight of 2.3 and 5.3 per cent. respectively of their original measurements, compared with 2.1 and 4.9 per cent. respectively in the controls.

TABLE I.—Average Gains in Height and Weight at all Ages in the Respective Groups

Observations	Groups					
	Females		Males		Both Sexes	
	C	T	C	T	C	T
Number of children in groups at all ages	146	149	135	145	281	294
Height:						
Average at first examination (inches)	50.288	50.087	49.104	48.724	49.719	49.412
Average at second examination (inches)	51.360	51.235	50.101	49.818	50.755	50.534
Actual average gain in inches at second examination	1.072	1.148	0.997	1.094	1.036	1.122
Average gain expressed as percentage of average height at first examination	2.1	2.3	2.0	2.3	2.1	2.3
Weight:						
Average at first examination (pounds)	59.699	59.705	57.844	56.848	58.808	58.296
Average at second examination (pounds)	62.833	63.128	60.455	59.590	61.691	61.383
Actual average gain in pounds at second examination	3.134	3.423	2.611	2.742	2.883	3.087
Average gain expressed as percentage of average weight at first examination	5.2	5.7	4.5	4.8	4.9	5.3

C = Control. T = Treated.

The extent to which the gains in height and weight in the treated groups exceed those of the control group can also be expressed as a percentage of the control gains. This method shows that the treated group as a whole gained 8 per cent. more in height and 7 per cent. more in weight than did the control group.

An examination of any changes in the state of nutrition in the two groups is another observation which may fairly be regarded as an index of the rate of growth. This was done in two ways: first by comparing the numbers in the various nutritional categories (better than normal, normal, subnormal) in the groups as a whole at the first and second examinations; and secondly, by noting at the end of the experiment whether the nutrition of each individual had improved, deteriorated, or remained unchanged. By this means it was found that there was, in the case of both these observations, a slight balance in favour of the treated group. This accords with the findings regarding height and weight.

In summing up the results of a statistical analysis of the data, which he was kind enough to make, Dr. J. O. Irwin of the London School of Hygiene and Tropical Medicine reported that the balance in favour of the treated group was significant for height in males but not in females, and not significant for weight in either sex. In view of this report the value of the supplements in the promotion of growth must be regarded as, at best, slight.

In order to determine if any effect upon the resistance to local infection had been obtained the relative frequency of abnormal conditions of the tonsils, lymphatic glands, nose, eyes, and skin was studied in the various groups

TABLE II.—*Summary of the Results of the Different Observations upon the Susceptibility and Resistance of the Various Groups to Colds*

School or Absence	Observations	Females			Males			Both Sexes		
		C	T	T Excess	C	T	T Excess	C	T	T Excess
School	1. Average amount of illness in days	5.057	5.671	+0.614	7.212	5.970	-1.242	6.014	5.837	-0.207
	2. Percentage affected	36	45	+7	48	43	-5	42	43	+1
	3. Average number of separate illnesses	0.756	0.913	+0.157	1.236	1.022	-0.214	0.969	0.953	-0.006
	4. Average duration in days of each illness	6.7	6.2	-0.5	5.8	5.8	0	6.2	6.0	-0.2
Absence	1. Average amount of illness in days	1.263	1.316	+0.053	1.095	1.07	-0.025	1.188	1.190	+0.002
	2. Percentage affected	19	17	-2	17	20	+3	18	18	0
	3. Average number of separate illnesses	0.23	0.205	-0.025	0.157	0.216	+0.019	0.233	0.210	-0.023
	4. Average duration in days of each illness	4.8	6.4	+1.6	5.6	4.8	-0.8	5.1	5.7	+0.6

C = Control. T = Treated. School = Cold observed in school. Absence = Cold causing absence.
 - = Balance in favour of the vitamin supplement. + = Balance against the vitamin supplement.

at the close of the experiment. Here again, as in the case of nutrition, two methods of comparison were adopted. In the first place, the condition of the groups as a whole at the end of the experiment was compared with regard to the presence in any degree of the factor under review; and, in the second place, a comparison was made of the individual improvements and deteriorations. As a result no definite evidence was found of the vitamin supplements having been of use in the prophylaxis or treatment of any of the conditions studied by this means.

COMPARISON OF THE RECORDS OF ILLNESS

In order to determine from the records of illness if there is any evidence of difference in the resistance to disease of the two groups several methods may be adopted. A broad indication of any differences in the general resistance of the groups will be obtained from a comparison of the average number of days of illness from all, and from specified causes; the presence or absence of a diminished susceptibility to infection in the treated group will be indicated by a comparison of the percentage of cases in which illness from the various causes occurred, and by a comparison of the average number of *separate* illnesses in the groups; and, lastly, any effect upon the resistance to established disease will appear from a comparison of the average duration of each *separate* illness. All these methods appear to be of value, and were accordingly used in the case of all the diseases observed in school or causing absence.

When the average number of days of illness from all causes, except pulmonary tuberculosis, was compared in the groups no evidence of an increased resistance to disease was found in the treated group. Actually the treated boys and girls averaged one and a half more days of illness in school than the controls. As far as absence from school is concerned, however, the groups were equal, with an average of approximately four and a half days' illness.

In the same way, when the data regarding the incidence of the specified diseases, colds, sore throat, influenza, infectious diseases, skin disease, eye disease, and ear disease were examined in detail by the various methods described above, no definite evidence was forthcoming of diminished susceptibility to infection or increased resistance to established disease. Accordingly it is not proposed to include the tables showing the results of these methods of analysis.

It has been thought worth while, however, to marshal the evidence concerning colds in Table II. This has been done, first, because of the claims that are made for

vitamin A supplements as a prophylactic against colds, and, secondly, on the assumption—reasonable in the light of the experimental evidence—that if these supplements have any prophylactic or therapeutic value they will show it in the case of mild infections of mucous epithelia. Incidentally this procedure will serve to show how all the data were analysed. From Table II, then, it will be seen that no significant differences have been found in the groups as a result of any of the observations made. The vitamin supplements therefore had no prophylactic or therapeutic effect upon the common cold.

QUESTIONNAIRE TO PARENTS

At the conclusion of the experiment a questionnaire was sent to the parents of all children in the control and treated groups. They were asked to state their opinion of the effect of the capsules upon the health and the appetite of their children. In order to encourage them to give an unfavourable verdict if they thought it merited, they were informed that two forms of the preparation had been used and that their help was required to determine which was the better.

In approximately 80 per cent. of each group an improvement of both health and appetite was reported—surely a striking example of the power of suggestion upon the human mind, and a warning of the necessity of judging the value of such preparations by controlled experiments rather than by "impressions."

DIETARY SURVEY

The writer is indebted to Dr. J. B. Orr and Mr. W. Godden of the Rowett Research Institute for information concerning a survey of the diets of sixty-six Peterhead families, which they carried out during the course of the experiment.⁴⁰ The diet of these families may fairly be considered to be representative of that of the children attending the North School, Peterhead, as in each case at least one member of the family was a pupil of that school. From this information Table III has been compiled. In it the findings of the 1932 survey are compared with those of 1927 in largely the same families, and with the British Medical Association standards⁴¹ for calories, protein, carbohydrate, and fat, and McLester's standards⁴² for minerals. In addition, the percentages of the sixty-six families below the average and below the standards are shown.

It will be seen that there is a notable lowering of the amounts of all the constituents of the diet in 1932 as compared with 1927, when Orr and Clark⁴³ stated that it was more than probable there was a deficiency of some

of the vitamins, especially vitamins A and D. Further, in the case of all the constituents, more than half of the families are below the average, and the great majority are below the standards. Commenting upon the high calorie intake in 1927, the authors⁴³ considered that there was either an unnecessarily high consumption or excessive waste. This is explained, no doubt, by the fact that the herring fishing was very successful in 1926 and 1927. As Peterhead is chiefly a fishing town everyone shared in this prosperity; 1930 and 1931, on the other hand, were poor fishing years, and it is not surprising, therefore, to find the dietary giving evidence of decreased purchasing power, as indicated in Table III.

TABLE III.—Results of a Dietary Survey of Sixty-six Peterhead Families in 1932 compared with that made in 1927 and with Certain Standards.

Constituent of Food	Average Amount Purchased per Man Unit per Day (Grams)			1932 Survey	
	1927 Survey	1932 Survey	B.M.A. and McLester's Standards	Percentage of the Families Below the Average	Percentage of the Families Below the B.M.A. and McLester's Standards
Protein...	125.1	80.5	100.0	56	82
Carbohydrate	685.7	431.9	500.0	56	80
Fat ...	85.2	56.9	100.0	58	94
Calcium ...	1.19	0.683	0.75	55	68
Phosphorus ...	2.14	1.22	1.50	62	89
Iron ...	0.023	0.0115	0.015	55	86
Calories ...	4,120	2,629	3,400	53	85
Income in shillings	1.52	1.18	—	56	—

A study of the actual foodstuffs purchased affords valuable information concerning the vitamin content of the diet. The average amount of milk bought per man value per day was one-third of a pint. There was a marked lack of animal fats—only one-third of a pound out of every 100 lb. of food purchased being butter—and the consumption of animal foods was low. Vegetables and fruit were used very sparingly indeed. It seems probable, therefore, that, although no evidence of vitamin deficiency so gross as to produce xerophthalmia was found, the vitamin content of the diet did not amount to the optimum requirements. The observation that the addition of vitamins A and D to the diet produced a slight improvement in the rate of growth supports this conclusion.

AVERAGE DAILY ATTENDANCE

The average daily attendance, expressed as a percentage of the average daily roll, is the best index of the amount of illness occurring in a school. This figure for the period of the experiment has been compared with the average for the same months during the preceding five years. The figures are: 86.6 per cent. for 1931–2, and 86.4 per cent. for the preceding five years. The period of the experiment may be regarded, therefore, as occurring during an average year.

DISCUSSION

The results of the administration of vitamin supplements to children whose diet was considered to be deficient in them are disappointing. Not only has no conclusive evidence of any beneficial effect upon susceptibility to infection or resistance to established disease been demonstrated, but the effect upon growth compares unfavourably with that observed in the milk experiments of Orr⁴⁴ and Leighton and Clark⁴⁵ in 1927 and 1928, as shown in Table IV. The North School, Peterhead, was one of the schools chosen for these experiments, and the interval

between the first and final measurements was the same seven months of the year.

It will be seen, then, that the basal diet + vitamins A and D and other constituents of milk produced a material improvement in the rate of growth, whereas the basal diet + vitamins A and D *without* the other constituents of milk produced only a slight improvement. Therefore the supplement of vitamins A and D failed to produce substantial improvement because of a deficiency in the basal diet of some or of all of the other constituents of milk. Of these deficiencies perhaps the most important were those of first-class animal protein and of minerals. The protein content of the diet was drawn in

TABLE IV.—Comparison of the Increases of Height and Weight in the Various Groups in the 1927 and 1928 Milk Experiments^{44, 45} and in the Peterhead Vitamin Experiment.

Experiment	Group	Number in Group	Height Increase (All Ages) (Inches)	Weight Increase (All Ages) (Pounds)
1927 Milk experiment	Milk	551	1.470	3.617
	Non-milk	731	1.212	2.974
			= + 0.258 (i.e. 21.29%)	= + 0.643 (i.e. 21.62%)
1928 Milk experiment	Milk	567	1.4585	3.5776
	Non-milk	590	1.1810	2.4610
			= + 0.2775 (i.e. 23.50%)	= + 1.1166 (i.e. 45.37%)
1932 Vitamin experiment	Treated	294	1.122	3.087
	Controls	251	1.035	2.883
			= + 0.086 (i.e. 8%)	= + 0.204 (i.e. 7%)

+ = Balance in favour of the treatment.

large measure from starchy foods, and consequently was of poor biologic value. As for the mineral content of the diet, although the averages both for calcium and for phosphorus were only just below Sherman's standards⁴⁶ of 0.68 and 1.32 grams respectively in the 1932 survey, the fallacy must be avoided of regarding a satisfactory average established by a dietary survey as an indication that all members of the group investigated are receiving adequate amounts of the substance under review. Actually, in the case of calcium and phosphorus, 55 and 62 per cent. respectively of the families were below the average. The average figure, therefore, tends to create a false impression of the true state of affairs. It was by supplying deficiencies in those below the average and bringing their rate of growth up to that of their more fortunate fellows that the milk supplements effected the raising of the average rate of growth.

It appears clear, then, that the milk supplements succeeded where the vitamin addenda largely failed, because, in addition to correcting the vitamin deficiency, they made good the associated deficiencies which almost always go hand in hand with a shortage of vitamins. The correction of one partial deficiency in man, while other associated deficiencies remain uncorrected, can never produce the dramatic results that are obtained from the restoration to the otherwise complete diet of experimental animals of a factor which was previously entirely absent. That this applies to the question of susceptibility to disease as well as to growth is shown by McCarrison's work in India.⁴⁷ He found that rats fed on a completely balanced diet were practically free from disease, while animals living in the same environment, but on badly balanced diets, suffered the whole gamut of human ailments. He stated, further, that the most disease-producing of these diets was one of "white bread, margarine, tea, sugar, jam, preserved meat, and scanty, overcooked vegetables." The Peterhead dietary survey showed that

such a diet was extremely common. The correction of only one of its many errors could not then be expected to compensate for all its other deficiencies.

As the optimum requirements in man are not known it has been possible to produce only presumptive evidence that the dietary of the treated children was deficient in vitamins A and D. The diet, as a whole, however, was so bad that few people in this country can be faring worse. If these children were not suffering from a vitamin deficiency, therefore, the condition must be relatively uncommon. Whether the vitamin supplements failed to produce striking results for the reasons suggested—namely, the failure to correct associated deficiencies, or because no vitamin deficiency was present—the fact remains that little benefit resulted from the administration of vitamin concentrates to those members of the community who had been shown by an investigation of their diet to be among those most likely to receive benefit.

On biological grounds, then, there can be no comparison between the value of milk and that of vitamin concentrates as supplements to a defective basal diet. To this there is added the potent economic argument that not only does milk produce better results than vitamin concentrates, but it does so at no greater cost. The time has come when the public must be educated to realize that vitamin supplements do not constitute a nutritional short cut to health. A vitamin concentrate can correct only a vitamin deficiency; it has no magic power of assuming the functions and properties of other essential factors of the diet. The metabolism of food in the body is a chemical process, and if this process is to proceed to the best advantage the correct constituents must be present in sufficient quantity, and they must be present in approximately correct proportions.

SUMMARY

1. A dietary survey in Peterhead showed that the diet of many families of the poorest classes was grossly inadequate in several respects, and presumably deficient in vitamins A and D.

2. A concentrate of vitamins A and D was therefore administered for six months in daily doses equivalent in vitamin A to rather more than one ounce of high-grade cod-liver oil to 294 school children of the lower working classes in Peterhead; 281 contemporaries acted as controls.

3. The rate of growth of the treated children appeared to be only slightly better than that of the controls.

4. Susceptibility to infection and resistance to established disease were apparently unaffected by the treatment.

5. Evidence is produced to suggest that the cause of this failure lay in the fact that the vitamin supplements made good only one dietary deficiency and left uncorrected associated deficiencies of equally essential constituents of the diet.

6. The importance of a well-balanced dietary is therefore stressed, and the value of milk supplements, as a step in this direction, is compared favourably on both biological and economic grounds with that of vitamin addenda.

This experiment was made possible by the generosity of the manufacturers of the vitamin concentrate, who placed large quantities of their product at the disposal of Professor L. S. P. Davidson of Aberdeen University, by whom, in turn, the concentrate was made available for the Peterhead experiment. To him I am deeply indebted, also, for his never-failing interest and advice. In addition, I wish to thank Dr. Harry J. Rae, chief regional medical officer of health, Aberdeen, Aberdeenshire, and Kincardine, for his kindness in affording me every facility in carrying out the work, and Dr. J. B. Orr and Mr. W. Godden of the Rowett Research Institute, Bucksburn, for supplying me with valuable information and much helpful advice. I am especially grateful to Mr. W. G. Mair, head master of the North School, Peterhead, and his staff for their constant courtesy and helpfulness, without which the experiment could not have been carried out.

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The returns from universities and university colleges in receipt of Treasury grants for the academic year 1932-3 have now been issued by the University Grants Committee (H.M. Stationery Office, 1s. 3d.). Of the 50,155 full-time students to which this publication relates, medicine and dentistry claim 11,247; of these 9,835 were men and 1,412 women. Edinburgh and Glasgow Universities head the list with totals of 1,233 and 1,067 respectively. The schedule of degrees and diplomas obtained during the year and analysed according to faculties gives a total of 1,055 degrees and 1,183 diplomas under "medicine including dentistry" in Great Britain.