preparation capable of producing a satisfactory response on a total dose containing only 5.5 mg. of solids.

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THE PROPHYLAXIS OF RICKETS BY SINGLE MASSIVE DOSES OF VITAMIN D

BY

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In an earlier paper (Krestin, 1944) it was shown that rickets still presented a problem in infant entrants to Preston wartime nurseries, for, although severe and advanced degrees of this disease were extremely rare, an early or mild variety was found in 37% of all admissions under 2 years, while in the poorer parts of the town this figure was even higher. Furthermore, it was noted that the free distribution of cod-liver oil for the infants before their admission to the nurseries did not produce any obvious reduction in the incidence of this disorder. Similarly, in a recent report by the Ministry of Health (1944) describing a widespread survey including Great Britain and Ireland, it was found that 73% of the infants with radiologically active rickets had received cod-liver oil or other vitamin D preparation for some period before the investigation, and Corner (1944) found the incidence of the disease in hospital patients actually higher in those who had previously received vitamin D supplements than in the average series. Since the antirachitic value of cod-liver oil is now beyond doubt, and has been shown to be reliable when given regularly and in large enough doses in these nurseries (Krestin, 1945), it is evident that the disappointing results obtained by these mothers in their own homes were due to irregularity of administration and inadequacy of dosage.

For these reasons it seemed desirable to investigate the possibility of a method of preventing the disorder that could be used independently of the mother and yet not require the daily attendance of the child at a clinic or medical centre.

Previous Work

Although Vollmer in 1928 (quoted by Vollmer, 1939) showed that rats which had been fed on a rachitogenic diet could be protected against rickets by a single massive dose of vitamin D, this observation was not applied clinically until 1938, when Harnapp (1938a, 1938b, 1939), in Germany, found that infants under 18 months could be protected during the winter months by single oral doses of 7.5 or 10 mg. of either vitamin D₂ or D₃ dissolved in oil. These results were soon after confirmed in that country by Schwartz (1939), Rietschel *et al.* (1940), Hartenstein (1940), and Heisler (1940), most of whom favoured the view that, whereas 5 mg. was too small, 7.5 to 10 mg. was sufficient for the purpose, and that larger doses were unnecessary. Less constant results were obtained by Windorfer (1938) and Brockmann (1938). More recently Wolf (1943) and Rambar *et al.* (1943), in America, reported the results of using single doses of 15 mg. of "ertron," an electrically activated preparation of ergosterol; although in both cases the numbers of infants followed up for five months or more were small, the results obtained were very satisfactory.

Present Investigation and Results

This investigation concerns full-term infants and children between 2 months and 3 years of age, of average health, and showing no radiological or clinical evidence of rickets on admission to ten day and three residential wartime nurseries in Preston. All lived under similar conditions, received similar diet, and were under constant supervision. The period of observation began during the autumn of 1943, and lasted for 6 months throughout the following winter and early spring. After admission each child was clinically examined and then sent for radiographs of the lower ulnar epiphyses. A single dose of 7.5 mg. of calciferol—i.e., 300,000 i.u. of vitamin D₂ dissolved in 1 c.cm. of arachis oil—was then given by spoon after a milk feed, the amount having been measured in a graduated Record syringe. The oil was readily taken by all ages, and, except for vomiting in one small infant, was not followed by any gastro-intestinal disturbance or other unpleasant effects. Thereafter each child was clinically examined at regular intervals of 4 weeks or less, and at the end of 6 months another radiograph was taken of the wrist. Owing to the distance of the nurseries from the x-ray centre it was not possible, except in a few instances, to have radiographs taken at more frequent intervals. Biochemical examinations of the blood were not practicable. Throughout the period of observation no other vitamin D preparation was given, nor was any child in this series exposed to ultra-violet radiation.

About one-third of the infants had received some cod-liver oil before admission. The doses were small, and often irregularly given. As the subsequent results in these infants did not appear to differ from the results in those who had not previously received any vitamin D preparation, they are not tabulated separately.

At the same time and during a similar period of the previous year two other groups of infants and children living under exactly similar conditions and receiving the same diets were studied. One, a "control" group, received no vitamin D preparation; the other received daily doses of the Ministry of Food cod-liver oil. The results obtained in these two groups have been discussed elsewhere (Krestin, 1945), but the figures are included in the accompanying Table for comparison.

The diagnosis of rickets in these nurseries has been discussed in earlier papers. The radiographic changes at the lower ulnar epiphyses have been clearly described by Wimberger (1923), A. F. Hess (1930), and others, and so require no further discussion here. It should, however, be noted that in mild rickets of short duration obvious alterations in the appearance of the x-ray films may not occur, or may last for so short a time that they may be overlooked unless radiographs are taken at frequent intervals. Craniotabes—i.e., asymmetrical softening of the cranial bones in the region of the lambdoid suture—was found to be a reliable sign in infants older than 3 months, but was rarely found after the sixth month. After the fourth month the most reliable sign, when scurvy could be eliminated, was a definite enlargement of the costo-chondral junctions of the fourth to the tenth ribs. Moreover, this sign was of par-

Table showing Comparison of Results after Antirachitic Prophylaxis with Single Massive Doses of Vitamin D₂ and after Daily Doses of Cod-liver Oil, with a Control Group of Infants

Age Groups:	0 to 6 Months			6 to 12 Months			1 to 2 Years			2 to 3 Years		
	Number Examined	Developed Rickets	Remained Rickets-free	Number Examined	Developed Rickets	Remained Rickets-free	Number Examined	Developed Rickets	Remained Rickets-free	Number Examined	Developed Rickets	Remained Rickets-free
Single oral dose: 7.5 mg. D ₂ = 300,000 i.u. . .	16	2	14	27	1	26	50	0	50	44	0	44
Daily doses of M.O.F. cod-liver oil:												
1 dr. = 700-800 i.u. . .	18	12	6	—	—	—	—	—	—	—	—	—
2 dr. = 1,500 i.u. (approx.) . .	28	3	25	28	2	26	55	6	49	63	0	63
3 dr. = 2,100 i.u. (approx.) . .	—	—	—	15	0	15	11	1	10	—	—	—
4 dr. = 3,000 i.u. (approx.) . .	—	—	—	—	—	—	44	0	44	60	0	60
Controls (no vitamin D) . .	14	12	2	30	18	12	28	3	25	15	0	15

ticular value, since, once having appeared, it would last for weeks or months after all x-ray signs of activity had gone. Thus, the appearance of either of these clinical manifestations was accepted as evidence of rickets even with a normal x-ray picture. Similarly, even in the absence of clinical signs, the appearance of definite radiological changes was regarded as diagnostic.

The results obtained are shown in the Table. The most significant figures are those in the group under 1 year, which, as may be seen from the control series, shows the greatest liability to the disease. The figures in the 2-3-year age group are probably without significance, since the controls show that if a child living under the conditions obtaining in the nurseries can avoid the disease during the first two years of life it will probably remain free after that age even without special prophylactic treatment. Compared with infants receiving regular daily doses of cod-liver oil, the results of administration of a single massive dose of vitamin D₂ are satisfactory, the failures being 3 out of 43 infants under 12 months and 3 of the 93 infants under 2 years. Thus the claim of earlier workers in Germany and America appears to be substantiated.

Discussion

Mode of Action

Windorfer (1938) found that after a single large oral dose of vitamin D dissolved in a small amount of oil 93% was absorbed from the bowel. There is, so far, little evidence in the literature as to the exact fate of the vitamin after its absorption. By feeding large doses of this vitamin to rabbits Warkany (1936) and his colleagues (Warkany, Guest, and Grabill, 1942) were able to produce a rise in the blood level from the average normal of 50 i.u. to 2,700 i.u. in 24 hours, which was maintained for about 4 days before slowly returning to normal in 4 to 6 weeks. In human subjects they found that after stopping the daily administration of larger doses the serum level of vitamin D remained above normal for from 3 to 6 months. Further, Heymann (1936, 1937) showed that after large doses were given to rabbits the vitamin could be demonstrated in the tissues and organs for varying periods, and for as long as 12 weeks in the liver and plasma. Thus it would seem that after a single large dose the organism is able to draw on a store of this vitamin for some 8 to 12 weeks. By this time the growing animal has probably been able to lay down enough calcium at the metaphysis to last throughout the winter, though it may be advisable in the case of infants, particularly those under 1 year, to repeat the dose after 3 months if the first one was given in the autumn or winter—i.e., before the beginning of March.

Possible Disadvantages: Toxicity of Vitamin D

Except for one instance of an infant who vomited the dose and was then quite well, no ill effects of any kind were observed among those who received the single dose of 7.5 mg. This was equally true in a further series of infants with active rickets (not reported here) receiving single doses of 15 mg. (i.e., 600,000 i.u.). Further, subsequent radiographs of the non-rachitic infants did not show any noticeable increase of calcium deposition at the metaphysis. Similarly, complete freedom from unpleasant after-effects was noted by all the earlier workers referred to above.

A considerable amount of recent work has shown that most of the undesirable manifestations previously observed after relatively small doses of vitamin D were due to toxic substances produced by the over-irradiation of ergosterol. With more recent methods of preparation these substances are not produced, and the material supplied is almost pure calciferol. With preparations of this kind, Bills and Wirick (1930) found that amounts over 4,000 times the minimal antirachitic dose were required to produce even mild manifestations of toxicity in the case of rats. Catel and Pallaske (1931) and Pallaske (1932) could find no injurious effects at necropsy after very large amounts given to goats and other animals. In infants, J. H. Hess *et al.* (1930) found that daily amounts up to 50 times the ordinary prophylactic dose could be continued for months, and up to 250 times this dose for short periods, without ill effect. Steck *et al.* (1937), after extensive work with dogs and human subjects, concluded that 20,000 i.u. per kilogramme of body weight could be given daily for indefinite

periods with impunity, but with doses greater than this undesirable symptoms might follow. After amounts up to 1,000,000 i.u. given by mouth or by intramuscular injection to premature infants, Zelson (1940) failed to find evidence of damage to tissues at necropsies where death resulted from intercurrent infection. Rambar *et al.* (1943) failed to find any persistent rise in the blood levels of the calcium or phosphorus after single oral doses of 15 mg. (i.e., 600,000 i.u.). After the daily administration of from 20,000 to 40,000 i.u. for 6 months to a premature twin, however, Ross and Williams (1939) reported the appearance of anorexia, loss of weight, and vomiting, ending in death; at necropsy there were bronchopneumonia and extensive calcification of arteries, heart muscle, kidney, stomach, and lungs.

It may therefore be concluded that the amounts of vitamin D used in this study are well within the limits of safety, and that, where necessary, they could be repeated once or twice during a period of 6 months without ill effect. There is, however, some evidence that metastatic calcification may occur with much lower doses in the presence of renal disease. In such circumstances it would probably be advisable, for the present, to use the older routine of small daily doses.

Wolf (1943) states that erteron is less toxic than irradiated ergosterol. This substance is not at present available in this country.

Absence of Vitamin A from Preparation

As the preparation used in the single-dose method contained no vitamin A, these infants differed from those receiving daily cod-liver oil in that they were deprived of this added vitamin as well as of the daily supplements of oil. Although it was the general impression in the nurseries that these infants remained well and thrived satisfactorily, it was thought advisable to compare their progress as regards weight, height, and incidence of infection with the control and cod-liver-oil groups. This is shown in the diagrams. As growth is more rapid during the first year of infancy, separate diagrams are given for those under 1 year, and for those over 1 year but not exceeding 2 years, at the end of the six-months period of observation.

Weight.—It will be seen (Fig. 1) that in those over 1 year there is little difference in the average gain in weight in the three groups. Thus infants receiving no vitamin A or D or oil, and those receiving vitamin D only, seemed to thrive as well as those getting daily oil containing these vitamins. The infants

FIG. 1.—Average gain in weight after six months. A, Controls. B, After receiving single dose of vitamin D. C, After receiving daily doses of cod-liver oil. a, Under one year. b, Over one year. Figures within columns show number of infants.

under 1 year who received the daily oil appeared to gain less than the other two groups. This unexpected result may possibly be explained by diminished alimentary absorption following the daily administration of two doses of oil, since there seemed to be no reduction in the amount of feed taken by these infants.

Height.—Fig. 2 shows the average gains in height. It will be noted that neither the control nor the single-dose group show any disadvantage compared with those having the daily supplements.

Infection.—Records of all infections were kept on charts showing the duration of illness in days for each child. As the influence of age, immunity from previous attacks, and the opportunity for contact are doubtless predominating factors in the acute infectious or specific fevers, these are omitted from

consideration. For similar but somewhat different reasons, the incidence of gastro-intestinal and skin infections is also not discussed. It was thought that the average number of days of illness due to infection of the upper and lower respiratory

FIG. 2.—Average gain in height after six months.

tracts—i.e., nasopharyngeal, tracheo-bronchial, and pulmonary infections—would provide some guide as to the susceptibility of each group. Infection was recognized by the appearance of definite clinical manifestations, including a rise of rectal temperature to 99.6° F. or more.

The average number of days of illness for each group is shown in Fig. 3. It will be seen that there is a lack of con-

FIG. 3.—Average number of days of illness due to infection of the upper and lower respiratory tracts during period of six months.

sistency in the two age groups. In those under 1 year the cod-liver-oil group has a lower average than have the other two groups. In those over 1 year, the lowest average is found in the single-dose group. This difference cannot be explained, and is presumably due to chance.

Owing to the fact that many of the controls under 1 year developed manifestations of rickets and received treatment for this before the end of the six-months period of observation, the numbers on which the averages are based in this group are small, so that undue significance cannot be attached to them. Nevertheless, the other columns in the diagrams suggest that the infants who received the single oral dose of vitamin D were at no obvious disadvantage compared with those who received the daily cod-liver oil. This is not altogether surprising, for while retarded growth and increased liability to infection may result from gross vitamin-A deficiency produced under experimental conditions, there is no definite evidence that real benefit follows the addition of this vitamin to an already adequate diet in infants showing no signs of such deficiency. Obvious manifestations of vitamin-A deficiency are probably uncommon in infants and children living under moderately healthy conditions; none was noted in any of the entrants to these wartime nurseries, and they would not be expected to appear on the diets there given.

It should be mentioned that all infants, including the controls, received the Ministry of Food orange juice every day.

Advantages of the Method

These for the most part are obvious and require little discussion. The chief of them is that an infant can be given a single small dose of oil by a trained nurse at an out-patient

clinic, welfare or other medical centre, and then need not be seen again for two or three months. The method is thus largely independent of the mother. A very considerable quantity of oil is saved, which, besides being more economical, may be a factor of importance in wartime. In the case of residential or day institutions where large numbers of infants have to be cared for, the reduction in work is greatly appreciated by the staff. Further, this method is particularly suitable for feeble infants, for those liable to gastro-intestinal disturbances, or for those who for any reason are unable to take daily doses of oily preparations. Park (1940) has drawn attention to the danger of lipid pneumonia from aspiration of oil given frequently or in large quantities to weakly babies or those liable to vomiting.

Although this paper is concerned with healthy full-term infants, it is relevant to mention that where, ordinarily, larger amounts of vitamin D are required, as in premature babies, those recovering from marasmus or acute illness, or those who are taking thyroid, the dose with this method would require increasing and probably repeating. Thus a premature baby would probably need an initial dose of 15 mg. followed by one or two further doses of 7.5 mg. during the winter and spring months.

It is claimed by some workers (Hess and Lewis, 1933; Rietschel *et al.*, 1940; Hartenstein, 1940; and others) that for the prevention of rickets in infants vitamin D₃ is superior to D₂. The evidence for this at present, however, is not convincing. The available supply of vitamin D₃ in this country was insufficient for any large-scale investigation.

Summary and Conclusions

The prophylaxis of rickets by means of a single massive dose of vitamin D₃ given by mouth was investigated during a period of six months of the autumn, winter, and early spring in 137 infants under 3 years, and the results compared with controls who received no vitamin D preparation and infants who received daily doses of the Ministry of Food cod-liver oil.

Of 93 infants under 2 years who received one dose of 7.5 mg. (300,000 i.u.) 90 remained free from the disease throughout the period of observation.

A short review of the literature is given, and the possible disadvantages and advantages of this method are briefly discussed. The freedom from all ill effects is noted.

It is suggested that when a child first comes under observation in the late winter or spring—i.e., after the beginning of March—one dose of 7.5 mg. is probably sufficient. If first seen before this time, it would probably be wise to repeat the dose after 3 months.

Premature infants, those taking thyroid, and those growing rapidly after marasmus or an acute illness may require double the above doses, possibly repeated at shorter intervals.

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