The prevention and treatment of rickets

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THE PREVENTION AND TREATMENT
OF RICKETS

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UNIVERSITY OF NEBRASKA
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The number of antirachitic agents has grown so large within recent years that it has seemed worthwhile to review them, in an attempt to appraise their value in the prevention and cure of rickets. This I shall attempt to do in the following paper. I shall limit as far as possible discussions on the much-debated etiology of this important disease of childhood, confining the attention largely to a study of the action of and a comparative appraisal of the various antirachitic agents.
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INTRODUCTION

The discovery of the fourth vitamin, vitamin D, has been of the greatest importance to the medical profession as well as to mankind, because it has brought about the solution of the century-old problem of the cause and prevention of rickets. Today, because of this discovery, severe rickets in civilized countries at least, is coming to be a rare disease. The opinion has been expressed that within the next decade, or even sooner, the disease in all its forms may be almost completely eradicated; that it will become as rare as has infantile scurvy since the widespread use of orange juice.

To the English physiologist, Mellanby, belongs the credit of the discovery of the anti-rachitic factor or vitamin. To quote from his article (1): "An examination of the results obtained suggests that rickets is a deficiency disease which develops in consequence of the absence of some accessory food factor or factors...It therefore seems probable that the cause of rickets is a diminished intake of an anti-rachitic factor which is either fat-soluble A, or has a somewhat similar distribution to fat-soluble A." On diets consisting chiefly of cereal and small quantities of whole or skim milk, diets which are now recognized as deficient in vitamin D and also in calcium, there developed in Mellanby's puppies soft bones, bowed legs, and other typical deformities seen in rachitic children. More defin-
ite proof of the presence of true rickets was obtained from roentgenograms and from chemical analyses of the dogs' bones, which were found to have a decidedly low calcium content. When a few cubic centimeters of cod liver oil was added to the diet, rickets failed to appear. Comparatively large amounts of butter fat and suet prevented it to some degree, but lard, cottonseed, olive and linseed oils proved entirely ineffective. Here was positive proof that the cause of rickets was to be found in a definite deficiency in the diet and that the cure lay in the addition of certain specific foods to the ration.

Hopkins and Chick (2) state: "Evidence is accumulating that rickets is caused by a shortage not of fat as such, but of the "fat-soluble growth factor", which is contained in certain fats...Milk and butter are the best sources of the antirachitic (or fat-soluble) factor for young and growing children; margarines made from animal fats are also valuable; those made from vegetable oils are to be condemned." Hess and Unger (3), however, did not agree with this view, that the anti-rachitic and fat-soluble factors were synonymous.

In 1922 McCollum and his co-workers at Johns Hopkins Hospital (4) published definite proof of the existence of two separate and distinct fat-soluble vitamins. They found that cod liver oil oxidized for twelve to twenty hours does not cure xerophthalmia in rats, but that it does, however, cause the deposition of calcium in the bones of young rats
which are suffering from rickets. This shows that oxidation destroys fat-soluble A without destroying another substance which plays an important role in bone growth, which McCollum called vitamin D.

The exact method by which vitamin D exerts its influence on calcium and phosphorus metabolism is by no means clearly understood at the present time. Nevertheless, some of its effects on certain blood phases of mineral metabolism are well recognized. Among these are the retention of calcium and phosphorus in the blood, and the deposition of calcium and phosphorus in the bones. (5) Unquestionably, one of the effects of small or moderate amounts of the antirachitic factor is to increase the amount of calcium and phosphorus retained in the body on any given diet. The rachitic infant stores much less calcium and phosphorus in his body than does the normal child. Since both calcium and phosphorus are excreted through the kidney, it is difficult, if not impossible, to say whether the increased retention is due to an increased absorption of mineral or to a decreased excretion. A third possible factor might be the deposition of greater amounts of calcium and phosphorus in the bones of the infant. Clouse (5) believes that in all probability the vitamin does not exert its influence in any one direction, but to some extent in all three directions. Even non-rachitic babies show a seasonal variation in blood phosphorus which corresponds to differences in the amount of sunlight they receive. Conceivably, vitamin D might bring
about increases in blood calcium and phosphorus either by increasing the absorption of minerals from the intestine or by decreasing excretion through the kidney or intestine, or both. Evidently vitamin D increases the capacity of the blood to hold phosphorus, possibly by raising the level at which it begins to be excreted.

Certain investigators believe that the relation of calcium to phosphorus in the blood, or the calcium times the phosphorus product, is more important from the standpoint of normal calcification of the bone than is the individual concentration of either one alone. When the calcium times the phosphorus product of such solutions is thirty or less, calcium is not deposited in the tissue. When the product is forty or more, calcification is regularly obtained in vitro in about nine hours. In the absence of vitamin D, bone is abnormal both in chemical composition and in histologic structure. Rachitic bones of children and animals have a total ash content and a calcium and phosphorus content considerably below the non-rachitic. Normal bones, for example, contain from 55 to 60% of ash, but in rickets the ash content sinks to 30% or lower.

The mode of healing at the cartilage-shaft junction induced by the ultraviolet ray (sunlight) is exactly analogous to that which occurs after the administration of cod liver oil, as determined by Howland and Park. The time relations are also similar. Huldschinsky found that the ultra-violet ray produced definite evidences of healing at
the end of four weeks and at the end of two months almost complete healing. Howland and Park found that cod liver oil first gave rise to evidences of healing at the junctions of the cartilage and shaft of the long bones three weeks after the administration was begun and that at the end of about two months the calcification of the diseased ends of the shafts seemed to be complete. Neither cod liver oil nor light meets the defects in the composition of the diet directly by supplying to the body either calcium or phosphorus but meets them indirectly by so raising the potential of cellular activity as to secure the most efficient utilization possible of those substances available in the body which are directly or indirectly concerned with ossification and calcification. (7)

Howland and Kramer (8) in 1920, have shown that the serum of infants suffering from active rickets contains a diminished amount of inorganic phosphate and that during the process of healing following the administration of cod liver oil, the phosphate content gradually rises to the normal level. The calcium content was not necessarily affected; sometimes it also was slightly reduced. Hess and Gutman (9) and Hess and Unger (10) confirmed these observations. Hess and Lundagen (11) furthermore demonstrated a seasonal tide in the inorganic phosphate of the blood parallel to the severity of the rickets. Von Meyenburg (12) and György (13) (cited by Steenbock, Hart, Jones and Black (14)) also reported a decrease in inorganic phosphate. In rickety rats Kramer and
Howland (10) and Gutman and Franz (16) have reported marked changes in the inorganic phosphates of the blood. Park (17) in his review of the etiology of rickets says "The first detectable signs of rickets are probably a diminution of the inorganic phosphorus or calcium of the blood." Hess and Lundagen (11), however, report in some case of rickets no blood changes are demonstrable, and Hess and Unger (10) state definitely that while lowering of inorganic phosphorus generally results, it is not a specific for the disease. Steenbock, Hart, Jones and Black (14) find that while a reduction of inorganic phosphate need not necessarily precede the incidence of severe rickets, sooner or later in the course of the disease, such a reduction results.

Deficient calcification results in abnormal histologic structure and in a characteristic roentgen picture. Histologically the absence of calcification may be detected in either one of two ways—by means of the now famous line test, first suggested by McCollum and Shipley, or by the microscopic examination of partially decalcified bone, stained with hematoxylin. The principle underlying the line test is that when bone sections are soaked in dilute solution of silver nitrate, silver phosphate is formed in the areas where calcification has taken place, and this silver salt, when exposed to intense light, is reduced to black silver. A distinct dark line of decalcification appears at the ends of normal bones, no line at all in severe rickets, and a more or less sharp line in cases of healing rickets, accord-
ing to the degree of recovery. From the width and character of the line formed under standard conditions, the relative quantity of the anti-rachitic effect is judged. Evidence of imperfect calcification is also found in roentgenograms of the ends of the long bones. In children the ends of the bones, normally convex in outline, develop a frayed appearance, and finally become cupped or concave instead of convex. In severe rickets in rats the uncalcified area or metaphysis between the diaphysis and the epiphysis, normally a thin sharply defined line, widens into a broad and irregular band. The roentgen method has the great advantage of allowing the investigator to follow the progress of healing in one and the same animal during life, which, of course, is impossible with the line test.

Vitamin A, which is closely associated with vitamin D in cod liver oil, has received less scientific attention. The reasons for this perhaps are that, unlike vitamin D, it is widely distributed in foods, animal and vegetable, and also because the manifestations of a deficiency are less striking. Experiments on animals which have been fed on a diet containing little, if any, vitamin A indicate that it plays an important part in the maintenance of health and vigor. Its complete withdrawal causes marked nutritional disturbances characterized by an arrest in growth and terminating finally in death. Furthermore, there is cornification of the epithelium of all mucous membranes of the body.
Xerophthalmia or keratomalacia is one form of this degenerative change. There may also be a lowering of resistance to infections. Vitamin A deficiency is most likely to manifest its serious effects on health and vigor in infants and young children, since it is a growth-promoting vitamin, and therefore an important nutritional factor. Although rickets is chiefly characterized by faulty bone development, there are frequently evidences of impairment of the general nutrition. Therefore, the combined use of vitamin D and vitamin A in high concentration will improve the general health as well as induce normal ossification. Owing to the better state of nutrition the incidence of complications may also be reduced.

From their investigations, DeSanctis and Craig (19, 19, 20) conclude: "If rickets is solely a problem of vitamin D deficiency, why is it necessary to give so much more in its pure form (viosterol D only) than when cod liver oil is given?" They believe that rickets is not due to a deficiency of vitamin D alone, but that vitamin A and possibly other factors play an important part in this disease. They found that viosterol in 100 X, 250 X and 500 X (7,300 to 36,000 vitamin D units, no A units) gives only slight protection, while the protection is greatly increased by the addition of carotene to 500 X viosterol (36,000 D units and 1,750 A units), giving almost 90 per cent protection. (20)
For a number of years there had existed a more or less vague opinion that the incidence of rickets was in some way connected with sunshine, fresh air, and other hygienic factors in the child's environment. However, it was not until June, 1919, that Huldschinsky (21) (cited by Steenbock, Hart and Jones (22)), a German physician working in Berlin during and directly after the World War, showed conclusively that light is an important factor in the cure of rickets. By means of the quartz mercury vapor lamp he cured four very severe cases of rickets in children 2½ to 4½ years old. The criterion on which he relied was the evidence furnished by the x-ray of calcium deposition at the ends of the long bones. He found that there were definite signs of calcium deposition after four weeks of treatment and that at the end of eight weeks it was almost complete. Animal experimentation carried out by Hess, Unger and Pappenheimer (23) and Shipley, Park, Powers, McCollum and Simmonds (7) have confirmed these clinical observations of the curative process of heliotherapy.

As noted by Shipley, and his associates (7), in May, 1920, Huldschinsky (24) again reported the curative effects of treatment with the ultra-violet ray in rickets in a series of thirty children, aged between 1½ and 6½ years, who exhibited all clinical manifestations of the disease. In all, healing was accomplished after 22 to 26 treatments covering a period of two months. In April, 1920, Putzig (25)
corroborated the findings of Huldschinsky. He obtained cures by means of the quartz lamp in premature infants suffering from rickets. In July, 1920, Riedel (26) further confirmed Huldschinsky's findings in a series of 100 children suffering from rickets. He relied on treatment with sunlight in some of his cases, supplementing with the quartz lamp ray only on sunless days.

Raczynski (27) "took two puppies of the same litter, both of which were being suckled by the mother, and kept one in absolute darkness and the other, throughout the day, in sunlight. At the end of a six-weeks' period, both were killed. An analysis of their bodies showed that the one which had been reared in the sunlight contained over 50% more calcium and 25% more phosphorus than the other, but that on the contrary, it contained less than half the quantity of chlorin." (Quoted from Hess and Unger (28))

These chemical analyses were in harmony with the chemical results reported by Hess and Unger in 1921 (29), whereby they verified the reported therapeutic value of light. They exposed infants for one-half to several hours daily to sunlight, varying the period of treatment according to the intensity of the sun and sensitiveness of the skin. They found that in every instance there was marked improvement in the rickets, as evidenced by the calcification of the epiphyses noted by means of the roentgen ray, in one instance the results being noticed thirteen days after heliotherapy was begun. They also noted that the alteration resembled
that which follows the administration of cod liver oil. These same authors (30) concluded that "the remarkable seasonal incidence of rickets is due to the seasonal variation of sunlight; that many cases of rickets are due to defective hygiene rather than to dietary errors (although diet is also an etiologic factor in this disorder), that sunlight should be used to prevent and to cure infantile rickets."

It was shown by Hess (31) that a filter of ordinary window glass, five millimeters in thickness, interposed between the sun and the experimental animals, filtered out the potent rays and thus no protection was afforded. The proposition was advanced that the longest waves of value in relation to rickets lie in the neighborhood of 300 millimeters. Pacini (32) in a consideration of this subject, has expressed the same opinion. Shipley (33) believes that very short ultraviolet rays, those about 210 millimeters in length, probably have the greatest antirachitic effect. Hess and Weinstock (34) state: "waves 324 millimeters in length have little or no value in protecting against rickets, and that waves of 302 millimeters are of great value in this respect...This renders light that has passed through ordinary window glass of no therapeutic value in this disorder...It should be borne in mind that the shorter the light waves in this region, the more irritating they are, so that it is probable that there is a therapeutic limit also in this direction."

Water has been found to transmit the activating rays,
thus demonstrating how cod liver oil may possibly acquire its activity. (35)

Light therapy usually improves the child's activity, muscle tone, and general contentment, in addition to bringing about normal calcium metabolism; whereas cod liver oil administration brings about normal calcium metabolism, but has much less effect on the general health. Conversely, improvement of the general health is not necessarily accompanied by healing of the bone lesions. (36)

The full value of sun baths is obtained only when the sun's rays reach the skin without the intervention of clothing or window glass. If the baby is fortunate enough to have been borne between the first of March and the first of September, sunbaths are started outdoors before the end of the first month of life. If the baby is born in the winter months, the sunbath frequently must be given indoors inside an open sunny window. When outdoor sunbaths are given, the hands and face are exposed first for ten or fifteen minutes only. After the first few days other parts of the body, at first the arms and a little later the legs, are in turn exposed to the sun. The period of exposure is increased two or three minutes daily. The increase for infants with dark skins may be more rapid than for infants with fair skins. As the weather gets warmer, the arms and legs and in time the whole body may be exposed together. As the baby becomes accustomed to the sunbath, the period is lengthened to one hour twice daily. Care must be taken to increase the length
of the sunbath gradually, so as not to burn the skin. Sufficient exposure to produce slight reddening will gradually tan the skin. Pigmentation is the outward evidence that the ultra-violet rays of the sunlight are effective. It is important, too, in the intense heat of July and August, that the sunbaths should be given before ten o'clock in the morning and after three o'clock in the afternoon. The baby's head at this season should be protected from the sun between these hours. Graduated outdoor sunbaths, such as are here described, may be given to any baby three or four weeks old, who is born in the spring and summer.

In northern climates it is possible to give outdoor sunbaths to healthy infants even in the winter. Feeble and premature infants cannot, of course, be exposed outdoors in winter. It is well-known that the temperature on a cold day may be 40 or 50 degrees higher in the direct sunlight than it is in the shade. The baby born in the fall or winter may be given outdoor sunbaths except on days when the temperature is below freezing. Many mothers, however, prefer to give indoor sunbaths to young babies. These may be satisfactorily given in front of an open sunny window, preferably facing southeast to get the morning sun. The room should be warmed and the doors closed to avoid drafts. The baby must lie directly in the path of the sunlight. These indoor winter sunbaths should preferably be given between ten and one o'clock when the ultra-violet content of the sunlight is most intense. Increase in the amount of skin surface
exposed and the length of exposure should be gradual; but, in time, the face, arms and legs may be slightly tanned, even in winter. It may not be possible to expose the whole body. Babies who are given indoor sunbaths in winter may begin outdoor sunbaths early in the spring, so that they will be well tanned by the end of April. (37)
Artificial Ultraviolet light:

In 1922 Hume (38) and also Goldblatt and Soames (39) of the Lister Institute, made the interesting observation that the growth of rats, when placed on a ration deficient in what they supposed represented only vitamin A, could be prolonged by exposing them to the radiations of the quartz mercury vapor lamp. Later, Goldblatt and Soames (40) also showed that livers taken from rats which had been exposed to such radiations were able to induce growth in rats, while livers taken from non-irradiated rats were inactive. Steenbock and Black (41) state: "By irradiation with the quartz mercury vapor lamp, rat rations can be activated, making them growth-promoting and bone-calcifying, to the same degree as when the rats are irradiated directly...liver from irradiated rats is growth-promoting while liver from non-irradiated rats is inactive. The same was found true of lung and muscle tissue. Inactive muscle, exposed, after removal from the body, to the radiations of the lamp was found to have become activated, being both growth-promoting and bone-calcifying."

In 1924 it was shown independently by Hess (42, 43) and by Steenbock (44,45) that various foods, such as oils, milk and cereals can be endowed with specific anti-rachitic properties merely by subjecting them to ultra-violet radiations. To quote from Hess (43): "It occurred to us to ascertain whether the treatment of inert substances with ultra-violet
rays could endow them with anti-rachitic properties. With this end in view we irradiated various fluids with the mercury vapor quartz lamp. To summarize the results of these experiments it may be stated that it was found that cotton seed oil when rayed for an hour at a distance of one foot had acquired anti-rachitic potency. Linseed oil gave similar results. Fluids containing radium had no effect, orally or subcutaneously. Neither hydrogen peroxide nor ozonated water possessed any protective action. Irradiated mineral oil gave a negative result. Steenbock (44) at about the same time, says: "Proceeding on the assumption that failure of growth in our basal synthetic rations without the effect of illumination was due to a condition fundamentally the same as rickets, experiments were initiated in which our basal synthetic ration of purified food materials was illuminated and then fed to rats. Here also illumination of the ration caused it to become growth-promoting and, in addition, it was found that the ash content of the bones of rats receiving such a ration was increased percentagely over that of rats receiving the non-irradiated ration. Later it was also found that irradiation of fats, otherwise inactive in preventing rickets, caused them to become active and that rations which ordinarily produced wide rachitic metaphysis in the shaft bones of rats became anti-rachitic and promptly effected a rapid and complete healing of the lesion." "Evidence dependent upon histological methods shows that a ration which induced rickets in the rat can be made definitely anti-
rachitic by the simple expedient of exposing it to ultra-violet light." (45)

Hess (46,47) next proceeded to investigate whether there was a difference in the anti-rachitic effect of vegetables and plants grown in the dark and those grown in the light and subjected to irradiations from a mercury lamp. Wheat was grown in the laboratory both in darkness and in light with irradiation given daily for one hour. The wheat was then fed to rats, in daily amounts of 10 grams, in addition to the routine rachitic diet. The rats receiving the wheat grown in darkness (etiolated) developed rickets while those ingesting the irradiated wheat were protected. Similar results were obtained with lettuce.

Vegetable oil was found to retain its protective power for a period of at least six months. Exposure to the mercury vapor lamp for a period of two minutes or less resulted in its activation. Fractionization showed the active principle to be present only in the non-saponifiable moiety of the irradiated oil. It was reported independently in 1925 by Steenbock and Daniels (48), Rosenheim and Webster (49), and Hess, Weinstock and Helman (50) that irradiated sterols possess anti-rachitic properties. Steenbock and his associates (35, 51) state that the anti-rachitic activation "appears to be localized in the unsaponifiable lipoidal constituents as the sterols and closely related compounds. Cholesterol purified first by numerous crystallizations and then as a benzoate and finally as an acetate can be activated.
Phytosterols cannot always be activated."

Cholesterol, it seemed, then, was the primary substance which in some way was changed during the process of irradiation and, with this metamorphosis, assumed antirachitic properties. Cholesterol, it may be stated, is an optically active unsaturated sterol, whose structural formula, while not definitely settled, is probably represented by: (52)

Of particular interest is the presence of the hydroxyl group and the double bond between the two carbon atoms. The presence of both of these has been shown to be necessary for activation by irradiation. Thus, compounds in which the double bond is saturated by hydrogenation, i.e., dihydrosterol, cannot be activated. (50)

It was found by Hess and Windaus (53) that cholesterol which has been purified by means of bromination failed to develop antirachitic properties as the result of ultraviolet irradiation. Rosenheim and Webster (54, 55, 56) reported similar results. They felt, then, that there was some contaminating substance closely associated with cholesterol to which the latter owes its activity. It was found that when this contaminating substance was separated and irradiated, it had a potency at least five hundred times
that of irradiated cholesterol. In the meantime, Hess and Windaus (57), experimenting with a large number of cholesterol derivatives, found that only ergosterol was capable of being rendered anti-rachitic by irradiation.

As may be suspected, the contaminating substance intimately associated with cholesterol are one and the same. It seems at present that ergosterol is the only substance capable of assuming anti-rachitic properties during the process of irradiation. All substances owe their power of becoming anti-rachitic following irradiation to the contaminating presence, in minute quantities, of ergosterol, which apparently is the precursor of vitamin D.

Ergosterol is a chemically pure substance which the French chemist Tanret first separated in a crude form from the fat of rye ergot in 1889. Later, in 1908, he succeeded in getting out the pure crystalline body. It is closely related to and occurs in cholesterol in the proportion of 1/20,000 to 1/50,000. (58) Ergosterol contains three unsaturated double bonds and may probably be represented by the formula: (52)
This sterol is present in small amounts in most fats. It is richest in the fat of ergot and yeast and present to a lesser degree in the crude oil from cottonseed, peanut and corn. It is found in minute amount in mushrooms, cereal grains, animal tissue (liver) and egg yolk. The unique feature about this sterol is that it appears to be the only one of the many present in these fats which has the property, when irradiated by certain bands of the ultra-violet spectrum, of changing its chemical constitution and acquiring an entirely new physiologic or pharmacologic property. Thus, before exposure to the ultra-violet light, pure ergosterol is absolutely inert, so far as the prevention or cure of rickets and allied conditions is concerned; but irradiation creates in it an antirachitic property similar to that possessed by cod liver oil. The product has none of the vitamin A.

Exactly what happens during the process of irradiation is not yet definitely known. Oxidative changes are ruled out by the fact that irradiation is equally successful in producing anti-rachitic potency in an atmosphere of nitrogen. Probably no chemical change per se takes place as following irradiation, the melting point, optical rotation, and composition according to analysis remain unaltered. (59)

Windaus (60) (cited by Pfannensteil (58)) states that ergosterol loses its characteristic absorption and likewise its precipitability by digitonin as the result of ultra-violet irradiation, and acquires anti-rachitic properties. Hess and Weinstock (61), by means of spectral absorption
tests, demonstrated that a clinical change took place in cholesterol which had been endowed with anti-rachitic potency by ultra-violet irradiation. A series of tests (50) with selective filters showed that the radiations which render cholesterol active biologically are similar in their wavelengths to those which have been found to protect animals against rickets when they are directly exposed to the rays. This activated cholesterol absorbs ultra-violet radiations to a less degree than does ordinary cholesterol, an effect which is intensified with increasing degrees of irradiation. If, however, irradiation is prolonged for many hours, the activated cholesterol becomes less transparent than even non-irradiated cholesterol.

As is well known, the epidermal portion of the skin contains a large amount of cholesterol situated in its deeper layers, in close approximation to the prickle cells. It would seem quite possible that the cholesterol in the skin is normally activated by ultra-violet irradiation and rendered anti-rachitic—that the solar rays and similar artificial radiations are able to bring about this conversion. This point of view regards the superficial skin as an organ which reacts to particular light waves (the epidermal organ) rather than as a mere protective covering. It should be pointed out, however, in connection with this hypothesis that neither cod liver oil nor its concentrated extract has been found to be efficacious when injected subcutaneously into rachitic animals. Furthermore, the suggested mechanism
presupposes not only the formation of active cholesterol within the skin but its further transport by way of the circulation. (50, 62)

Activated ergosterol has anti-rachitic power 20,000 times as great as that of cod liver oil, that is, 1 milligram is the equivalent of 20 grams of cod liver oil. (63) It can be activated in a medium of nitrogen, absolute alcohol, petroleum ether, liquid petrolatum, and in vacuum when radiated for one-half hour with a magnesium spark or quartz mercury vapor lamp. Its greatest activity comes after 12 hours or irradiation. Further radiation decreases its activity so that after 30 hours of exposure to ultraviolet rays it is no longer anti-rachitic. (63)

In an early report (1928) on clinical experience with irradiated ergosterol, Hess and Lewis (64) summarize their results as follows: "in all cases this new therapeutic agent has been found to be reliable in the prevention as well as in the cure of rickets, that its action has been remarkably rapid, all signs of rickets disappearing more quickly than has been accomplished heretofore with cod liver oil, its concentrate or with direct irradiation. The beading of the ribs became distinctly less marked, calcification of the epiphyses was soon evident by the roentgen rays, and craniotabes quickly disappeared. Our experience can be summarized by the statement that this drug (irradiated ergosterol) never failed in rickets; that, even in many cases in which cod liver oil had not brought about healing,
irradiated ergosterol initiated a rapid cure... Apart from the clinical application, the most interesting question raised by irradiated ergosterol is in regard to the mechanism by which it raises the calcium and phosphorus, more particularly the former, to normal or even supernormal levels. Naturally, our attention first turned to the parathyroid glands in connection with the increase of calcium. As is well known, the extract prepared by Collip from parathyroids brings about a marked increase of calcium in man and in animals. When this preparation is discontinued, the calcium rapidly falls to normal... It seemed as if the irradiated ergosterol either was stored or stimulated the parathyroids or other glands which regulate calcium metabolism. Preliminary studies lead us to believe that the second interpretation probably is the correct one—that irradiated ergosterol acts as a stimulus for the parathyroid glands... one ounce of average irradiated ergosterol is the equivalent of from two to six tons of cod liver oil. Evidently there is no longer a question of being able to give sufficient of the anti-rachitic factor... Irradiated ergosterol is by far the most potent of the anti-rachitic agents. It is an absolute specific. Cod liver oil in the amount in which it can be given is a specific of limited dependability—only moderately effective for the average infant, uncertain in action for the rapidly growing infant, and ineffective for the premature... As yet, however, we have not sufficient clinical experience to define its proper dosage. The amounts now recommended
and employed are unnecessarily high, as shown by the fact that they induce an excess of calcium and inorganic phosphorus in the blood of the normal as well as in the rachitic infant—hypermineralization."

According to May (65), "Nearly every newborn infant probably is endowed with the amount of calcium and phosphorus in its body necessary to maintain a satisfactory balance until such time as adequate amounts of these elements are received through its mother's milk. This is especially true of the full-term infant. Also, the artificially fed baby may do well for many weeks without requiring an extra supply of vitamin D to keep up a normal calcium and phosphorus balance. On the other hand, the premature infant may be more susceptible to the development of a negative calcium-phosphorus balance on account of difficulty in ingesting enough milk, even by gavage, during the first few weeks of life.

"It is an accepted fact that premature infants are prone to develop rickets. They possess other physical inadequacies which directly or indirectly cause a high death rate in the first few weeks of life. In respect to the high incidence of rickets, it does not seem to be entirely due to the infant's inability to take sufficient milk, nor has it been established that a depletion of calcium and phosphorus necessarily occurs when the milk intake is subnormal..."

"Cod liver oil in doses sufficient to prevent rickets in premature infants is not well tolerated because of its
large content of fat. Viosterol, however, has supplied a medicament-containing vitamin D without an appreciable amount of fat which may be fed to premature infants without upsetting digestion, and thus prevent rickets from developing. Moreover, the physical well-being of the premature infant is greatly improved as observed clinically. There is a definite increase in the weight as compared with untreated infants; also, there is an increased appetite, greater resistance to infection and, finally, the percentage of deaths of premature infants is reduced when an adequate daily dose of viosterol is started within 24 hours after birth. The dose of viosterol should be from 45 to 60 drops daily after the first 10 days. This dose should be continued for 8 or 10 weeks, after which period it may be gradually reduced to 20 or 30 drops daily." (65)

Standardization—It has been deemed advisable and necessary, as a precautionary measure, to dilute all concentrated solutions of irradiated ergosterol with oil to such a degree of vitamin D potency as to render them safe and convenient for clinical use. The licensor of the patent specifies that each licensee should adjust the vitamin D strength of the product to the same potency. In order to make the conditions more uniform, the licensees must dilute their preparations of Viosterol to conform to the definite standard solutions made under control of the Alumni Foundation of the University of Wisconsin. Further, as an aid in this direction, the Council on Pharmacy and Chemistry of the
American Medical Association proposed (66) the name Viosterol in oil, 100 D, to designate such standardized oil solutions of irradiated ergosterol. This concentration has, by common consent, since been increased to 250 D.

The adoption of a unit of measure that will express differences in anti-rachitic potency in numerical terms if possible is highly important, particularly for the standardization of cod liver oil and irradiated ergosterol which are to be used medicinally. In the United States the Council on Pharmacy and Chemistry of the American Medical Association has accepted the rat unit proposed by the Wisconsin Alumni Research Foundation (Steenbock) for the standardization of irradiated ergosterol. (b) This unit is defined as "that amount of vitamin D which, when uniformly distributed into the standard vitamin D deficient diet—ration 2365, J. Biol. Chem. 64: 263, 1925—will produce a narrow and continuous line of calcium deposits on the metaphysis of the distal end of the radii and ulnae of standard rachitic rats." In this instance the line test and the Steenbock diet are taken as standards.

"Viosterol (irradiated ergosterol) is standardized by comparison with a 'potent cod liver oil' which is defined as one that contains 13.33 rat units per gram, or one rat unit in every 75 milligrams of oil. This 75 milligrams of oil, it should be noted, does not constitute the minimum daily dose, but is the total quantity of oil to be given during the entire period of the experiment, from 6 to 10
days, the exact length of the period depending on the food consumption of the individual rat. Viosterol preparations as now accepted by the Council on Pharmacy and Chemistry have a potency of 250 D, that is 250 times the vitamin D potency of the standard cod liver oil defined by Steenbock. Cod liver oil which has viosterol added to it has a potency of 10 D."

**Toxic symptoms**—The history of toxic symptoms produced by overdoses of irradiated ergosterol dates back to 1927, when Pfannensteil (67) reported toxic symptoms in the rabbit. Shortly afterward, Kreitmair and Moll (68) of the research laboratories of E. Merck and Company in Germany (cited by 69 and 70), and later others (71, 72) reported similar symptoms in animals. Klein (71) found that massive doses of irradiated ergosterol fed to albino rats caused anorexia and loss of weight with impairment of the general physical condition and the rate of growth. The blood calcium concentration was 50% higher than that of the control animals and those fed cod liver oil, while the phosphorus remained approximately the same. The protein concentration of the serum of the animals given ergosterol was less than that of the animals given cod liver oil, while the albumin-globulin ratio was higher than that of the animals fed cod liver oil. Green and Millanby (73) substantiated the frequent occurrence of calculi in rats on diets deficient in vitamin A. Later, Bills and Wireck (74) published an investigation of about
1200 rats, and concluded that activated ergosterol administered to rats in doses 100 times greater than the minimum anti-rachitic level showed no effect on general appearance, growth, reproduction, or resistance to respiratory infections. 1000 times overdosage was just perceptibly harmful, 4000 times overdosage definitely injurious, and 40,000 times overdosage strongly toxic.

Hess and Lewis (64), Hess, Lewis and Rivkin (75), György (76), Bamberger and Spranger (77) (latter two cited by (69)), and others have reported toxic symptoms in infants. The following toxic symptoms have been reported: hypercalceemia, loss of weight, vomiting, cachexia, fever, dehydration, stupor, diarrhea, albumin and casts in the urine.

Dixon and Hoyle (78), Hoyle and Buckland (79) and Hess, Poucher, Dale, and Klein (69), however, were unable to verify all the toxic symptoms reported. In fact, the last group did not observe any toxic symptoms whatever in their group of infants. They state: "We do not wish to conclude from this that toxic symptoms cannot be produced by large enough doses of viosterol in oil. This investigation does show, however, the large factor of safety in the administration of larger doses of viosterol to infants, at least over limited periods of time." (69)

In a similar vein, Underhill (72) states that "the deleterious effects described are produced by doses so enormous that the clinician need not fear the production of toxic effects from the administration of therapeutic doses of ergosterol properly irradiated...It would seem to be about as wise to restrict the use of irradi-
iated ergosterol from fear of harmful effects as to give up
the use of common salt because of its unpleasant effects
when taken in excess." However, the lack of vitamin A
must be remembered in feeding infants products such as
irradiated ergosterol.
Irradiated foods--Steenbock and Daniels (48) exposed several food materials, such as wheat, corn, rolled oats, patent wheat flour, cornstarch, meat, milk and egg yolk, to ultra-violet light, and found that they can be endowed with rickets-preventing properties. Hess and Weinstock (50) rendered dry milk, flour and spinach anti-rachitic by exposing them to radiations from the quartz mercury vapor lamp.

The foods that have been successfully irradiated include a long list: numerous oils and fats--olive, cottonseed, linseed, corn and coconut oils, lard, oleomargarine and butter; cereal products--refined wheat flour, whole wheat flour, shredded wheat, cream of wheat, oatmeal and even cornstarch; meat; milk, whole or dry; various vegetables, yeast, orange juice, chocolate and ice cream. The potency of egg yolk has been increased from ten to twenty times and that of butter fat from fourteen to twenty times by irradiation. Sugar is almost the only natural food for which attempted irradiation has been unsuccessful.

Steenbock, in 1924, patented the process of the irradiation of foods and medicinals by ultra-violet rays. The patent has, however, been assigned to an organization formed for the purpose of receiving it, the Wisconsin Alumni Research Foundation. The process is usually carried out by exposing the material in a thin layer on a moving belt which passes under a battery of mercury vapor quartz or carbon arc lamps. Solid material may be allowed to fall once or twice
to lower belts to secure a partial turning over of the particles, and liquids, instead of passing over a belt below the light, may be allowed to fall in a thin film around or in front of an ultraviolet generator. Long exposures, of one hour or more, may develop disagreeable tastes and odors in the food and may also result in an appreciable reduction in the content of other vitamins, especially vitamins A and C. Maximum potency can, however, be developed in very short exposures, with no effect whatever on the flavor or the appearance of the food. In the case of milk, irradiated for a few seconds, there is no change in flavor of the milk and the other vitamins are not affected.

Antirachitic potency developed in foods by irradiation appears to be a very stable property. Steenbock reports that irradiated cereals held at temperatures as high as 60 C. for sixteen months showed no decrease in potency. Ordinary processes of cooking also do not have any effect on the potency of irradiated cereals, although the vitamin may be destroyed by commercial baking if the temperature is allowed to go too high. (70)

A number of irradiated cereals manufactured under the Steenbock patent are now on the market. These cereals, as they are marketed, are not highly potent, certainly not potent enough, in the amounts usually eaten by the average child, to prevent or cure rickets. The value of such weak activation might be questioned by many, but in the words of Tisdall and Brown, "the chief value of irradiated cereals
is that irradiation changes them from rickets-producing foods to rickets-preventing foods. As three teaspoonfuls of cod liver oil each day during the winter months does not furnish any great excess of vitamin D over the amount necessary to prevent rickets in the average infant or young child, any means that can remove the rickets-producing tendency of cereals is of value." Cereal should not be taken in such quantity as to replace important and essential foods. In the case of bread and vegetables the extent of the irradiation in terms of value in comparison to cod liver oil is indicated on the labels.

Considerable work has been done on the feeding of irradiated yeast, both directly to children, and to cattle, thus obtaining what is called "yeast milk", which is then fed to the children. Coward (80) reports an early study on irradiated yeast. "A group of rats were made rachitic and irradiated yeast was then given as a percentage of the diet to certain rats, while others were given a daily dose of the international standard preparation of vitamin D for 10 days. It was concluded by comparing the healing produced in the different bones by the different diets that "yeast may be activated antirachitically by exposure to strong sunlight, and that different samples of dried yeast may differ greatly in the extent to which they may be activated."
**Vitamin D milk**

Cow's milk, the chief dietary substance of artificially-fed infants, has been endowed with a number of virtues by a kind Providence, but it does exhibit a few deficiencies; one of these is a relative lack of the anti-rachitic factor, vitamin D. Consequently, rickets has always been an extremely common condition in infancy and childhood and even in recent times, in spite of our newer knowledge of nutrition and increasing number of anti-rachitic medicinal agents, has been and is fairly prevalent, due either to the failure to offer anti-rachitic substances to babies or to the offering of insufficient amounts of these substances. Thus, a milk in which the vitamin D content is sufficiently high to afford complete protection against rickets is, a priori, distinctly advantageous, inasmuch as it represents an automatic form of prophylactic therapy.

Efforts to augment the natural vitamin D content of cow's milk have thus far included:

I. Direct irradiation of the milk.

II. Feeding of vitamin D concentrate to cows.

III. Irradiation of cows.

IV. Direct addition of vitamin D concentrates to the milk. (85)

Obviously, in this matter many problems—medical, public health and commercial—present themselves; notably, these are the existence and degree of antirachitic potency conferred on the milk, the method of expressing potency in international, Steenbock or other units, the relative biologic merit of the
various processes, the effect on other properties of the milk, the practicability and cost of commercial production, and the possibility and feasibility of routine assay and public health control. However, to establish the existence and degree of antirachitic potency for infants of any given "fortified" milk is surely the first and sine qua non requirement in this ever enlarging domain. (81)

I Direct irradiation of the milk:

Steenbock and Daniels (48) and Hess and Weinstock (50) were successful in rendering milk anti-rachitic by exposing it to ultra-violet light, as shown by laboratory experimentation upon rats. Cowell (82) was probably the first to give a clinical report on the feeding of irradiated milk to infants. Three young children, from 1½ to 2½ years of age, with active rickets, were the first human subjects. They were given a diet whose only anti-rachitic value lay in the daily ingestion of a pint of milk. The two infants who received irradiated milk (exposed for 20 minutes at a distance of three feet from a mercury vapor lamp) showed definite improvement at the end of four weeks. The third infant, who acted as a control and received non-irradiated milk, showed no change. Kramer (83) followed shortly thereafter with another more careful clinical analysis. In a series of eight patients with active rickets, the administration of irradiated milk produced healing in every case. This was demonstrable at the end of the third week and was marked at the end of the
fourth week. The phosphorus content of the blood was raised, reaching a normal level about the fourth week of treatment. György (84), according to Friedman (85), gave the first German report on the efficacy of irradiated milk in the treatment of rickets. He reported marked improvement in 16 of 18 patients with florid rickets, judging by clinical, blood and x-ray findings.

With the clinical value of this type of milk definitely established, further advances in this country have consisted chiefly in improving methods of irradiation. The present method of irradiation consists of uniformly exposing the milk in the form of a moving film which receives rays from carbon arc lamps at constantly changing angles of incidence, varying from 0 to 90 degrees. The thickness of the film of milk is about 0.4 millimeters, and the time of exposure does not exceed 16 seconds. Each cubic centimeter of milk receives about $2\frac{1}{2}$ million ergs of radiant energy. The resulting formation of vitamin D represents a large percentage of the maximum obtainable, yet the exposure is so short as not to cause detectable changes in taste or smell or vitamin A content. (85) If we would obtain a product which is reliable and constant, it is necessary, as emphasized in an investigation by Supplee, Dorcas and Hess (86), to carry out the irradiation under fully controlled conditions.

Irradiated milk may be said to be possessed of two inherent advantages. First, milk is the essential food for all infants, the indispensable and basal article of diet through-
out the rachitic age, and furthermore in that, owing to its unequaled content of calcium and phosphorus, it is outstanding in connection with calcification. There does not seem to be any danger of giving excessive doses to the growing child. Irradiated milk also has the advantage of being inexpensive. It is probably true that the use of this therapeutic method does not provide a constant intake of vitamin D. Assays of milk carried out in the winter, however, have shown no significant variations in potency. In respect to the antirachitic factor, which is furnished in largest measure by the rays of the sun and varies greatly from hour to hour, season to season and locality to locality, our daily quota is eminently capricious. This criticism of the product is, therefore, quite irrelevant. Nor is there the slightest basis for believing that, in the course of "flash irradiation" by a carbon arc, any harmful products are elaborated. On the other hand, there are definite limitations to the adoption of irradiated fluid milk. It is clear that it is adapted for use in cities and cannot be prepared for rural communities. In a city such as New York, where approximately 500,000 quarts of grade A milk is used daily and where four-fifths of the milk of this grade is pasteurized in the city, there is an especially favorable opportunity to combine pasteurization and irradiation of milk for babies and children. It may be added that dry milk, milk dried by the roller process, has been found to be very effective in protecting against or curing rickets and that this product maintains its potency for a period of many
months. Irradiation could well be extended to evaporated milk which is given to babies on a large scale in small and distant communities where the need of antirachitic therapy is not realized and its application would be difficult. (87)

II Feeding of vitamin D concentrate to cows:

In 1924 Lesne and Vigliano (88), as cited by Friedman (85), added 500 grams of cod liver oil daily to a cow's feed. When tested experimentally, the milk produced showed increased anti-rachitic potency, exhibiting good curative and protective powers against rickets. Other investigators, however, failed to demonstrate any increase in the vitamin D content of cow's milk by the addition of cod liver oil to the feed, which may well be explained by the fact that such large doses as are necessary decrease markedly the fat moiety of the milk in which the anti-rachitic factor lies.

Similar experiments were being conducted about the same time on humans. Hess fed cod liver oil to both pregnant and lactating women in an attempt to supply additional vitamin D to the young. The results were disappointing and Hess and Weinstock (42) concluded that "cod liver oil, when given to the mother during pregnancy, cannot be relied on to protect the offspring from rickets". However, they also state that the diet of the mother during the period of pregnancy or lactation has some effect on the development of rickets in the young, and that cod liver oil did confer subsequent protection when fed to the young during the latter half of the lactating
period directly and not through the medium of the mother's milk, demonstrating the essential difference between direct and indirect nutrition. Welseh (89) performed a similar experiment on a group of lactating colored mothers and thought that while the administration of cod liver oil to the lactating mother is not a satisfactory method of preventing rickets in the young, a certain amount of additional anti-rachitic substance does pass into the milk, effecting a rise in the serum calcium-phosphorus product in the infant, and lessening x-ray evidences of the disease.

Wachtel (90) was the first to feed irradiated yeast to cows and thereby markedly increase the vitamin D content of the milk produced. His work was closely followed by the investigations of Steenbock and his coworkers (91), who stated that the feeding of a standardized irradiated yeast might be considered as a practical measure for the production of a milk of standard anti-rachitic potency. Hess, Lewis, MacLeod and Thomas (92) report favorable results on a group of 102 infants, many of them colored or Italians, who were given milk from cows fed 100,000 and 300,000 units of ergosterol and 30,000 and 60,000 units of irradiated yeast. They also fed viosterol and found that the irradiated yeast induced a more potent milk than the viosterol, evident both by biologic assay on rats and by clinical tests of a preventive and curative nature. The chief advantage of this method is that it functions automatically; the specific factor is incorporated in the diet of the infant, relieving the physician of depend-
ence on the cooperation of the mother.

The feeding of "yeast milk" is a measure that is especially applicable to the certified farm where the ration of the cows is thoroughly controlled and one can be certain that a potent yeast is fed in proper amount and, more particularly, where frequent biologic assays of the milk can be carried out. It would seem, however, that it is hardly applicable for the general supply of large communities, especially for great cities which require many thousands of farms to meet their demands. (33) Hess and Lewis (87) report the feeding of yeast milk for the second year to a number of infants, with excellent results.

III Irradiation of Cows:

The direct irradiation of animals again involves special apparatus. Once installed, however, the actual process of irradiating an animal for 15 minutes a day does not seem too involved. Close supervision, as required in supplementary feeding, does not seem necessary. We have again, however, the same objection as with yeast milk, namely, the difficulty in following closely the potency of a milk whose vitamin D content, in this case, is dependent on irradiation operations carried on over widely scattered areas. The method resulted, according to Mitchell (94), in a milk having an anti-rachitic potency of only 22 units of vitamin D per quart, which is only about four times that of ordinary milk. Whether this will be sufficiently protective under all types of circumstances re-
mains to be corroborated. Attempts to raise the vitamin D content of breast milk by irradiation of the lactating mother have also proved successful, as reported by Hess (95), Gerstenberger (96), and others. However, Gerstenberger (96) states that the degree of healing at the end of 60 days of feeding was not quite as marked as is that usually observed by them after treatment of the infant itself with actinic rays or after the giving of food mixtures containing 2.2 or 3.5 cubic centimeters of cod liver oil per liter.

IV Direct-addition of vitamin D concentrates to the milk:

This, the latest, method of increasing the vitamin D potency of cow's milk, has been reported by Zucker (97). He suggested 150 units of vitamin D per quart, or the equivalent of three teaspoonfuls of cod liver oil, for any except very young infants, who would automatically receive smaller amounts in proportion to food intake.

Investigations by Barnes (98) with the use of the concentrate in infants has shown it to be a highly effective anti-rachitic agent, effecting, in rachitic infants, a return to normal of the serum calcium and phosphorus and the x-ray findings within two weeks. 150 units of vitamin D per quart has been selected as the amount which has seemed from clinical experience with cod liver oil to be a good prophylactic standard. In this method the chances of error are minimal as the whole procedure involves only the addition of a standardized, previously assayed concentrate.
While the procedure is probably more expensive than direct irradiation of milk, the price nevertheless is less than that of ordinary milk plus cod liver oil.

Wilson (39) made a clinical study of the rickets-preventing efficacy of milk fortified with 150 Steenbock units of vitamin D per quart in the form of a cod liver oil concentrate. Thirty-three infants receiving only irradiated milk as the source of vitamin D were observed over periods of from three to six months. Of these, fourteen remained normal, seventeen developed slight rickets during the period of observation and two a moderate degree of rickets. The infants who developed slight rickets grew somewhat faster than did those who remained normal; they nevertheless did not receive on the average more milk daily or more vitamin D. Moreover, the two infants who developed moderate rickets not only took less milk daily than did the group as a whole but also grew considerably faster. Coincident with a slowing in the rate of growth and an increase in the amount of milk consumed by these two infants, there occurred an increase in the number of units of vitamin D taken daily per hundred grams of weekly gain in weight and, as a result, healing of the rachitic process took place. Since the amount of vitamin D necessary to prevent rickets is probably dependent to a great extent on rate of growth and since the growth of young infants does not necessarily conform to the amount of milk consumed daily, it is clear that infants who gain rapidly on relatively small amounts of milk will not receive an adequate amount of vitamin
D from a fortified milk unless the amount of vitamin incorporated per quart is such that protection will be afforded, when considerably less than a quart is consumed. If, therefore, milk is to be relied on for the sole supply of vitamin D during the period of most rapid growth, it would appear that the minimum amount likely to be consumed during the first four months of life—approximately a pint—should contain an amount of vitamin D adequate to protect the normal rapidly growing infant. It would appear that the addition to one quart of milk of 150 Steenbock units of the vitamin D concentrate used did not furnish enough vitamin D to prevent the development of a moderate degree of rickets in two out of the thirty-three infants studied by Wilson (99).
History--

Cod liver oil is the liquid liver fat of the large sea-cod, Gadus Callarias, a deep-water fish occurring in the North Atlantic and in immediately adjoining sections of the Arctic Ocean.

It is probable that from time immemorial cod liver oil has been used by the Norwegian and Iceland fisherfolk as a sovereign remedy against many diseases and ailments. In 930 A.D. mention is made in Egils Saga of codfishing off the coast of Norway. It is related that cod liver oil was first exported from Norway to England as far back as about the year 1000 A.D. However, it was not until about 100 years ago that it won the recognition of the medical world, when physicians confirmed the fact that cod liver oil possessed remarkable properties.

Most of the cod liver oil used for medicinal purposes today comes either from Norway or from Newfoundland. It is only within comparatively recent years that medicinal cod liver oil has been produced in America. Many people still believe, therefore, that the American-made oil is inferior to that imported from Norway and other foreign countries where the industry has been established a long time. As a matter of fact, there is now little difference in the oils obtained from the various sources.
Production—

It is now believed as a result of recent investigations that marine algae which are found abundantly in waters inhabited by the cod fish are capable of synthesizing carotene through the action of sunlight upon the chlorophyll present in the plant. These plants or algae constitute the food of thousands of small marine animals known as plankton, which in turn convert the carotene of the algae into vitamin A in the process of digestion. Fish like herring, caplin, etc., which feed on the plankton are eaten by the cod and other large fish so that the carotene synthesized by the algae is converted to vitamin A in passing through the smaller to the larger fish by digestion and finally concentrated in the cod liver, though the manner in which this takes place has not yet been satisfactorily explained. It is possible that here, too, some unknown method of direct synthesis takes place.

Cod liver oil was originally produced in a very primitive way and history relates that many impurities were existent in these early oils. It was not until about 75 years ago that rational methods were employed—a pure cod liver oil produced and taste and odor improved without loss of therapeutic results.

Formerly, cod liver oil both here and abroad, was made by the "santried" or "rotting" process. The fish were cleaned, and the livers thrown into a cask. There they were left to rot and the putrefactive organisms developed in
the livers themselves. The weakening of the liver tissues under these influences, released the oil which floated to the surface, while the livers themselves becoming a foul mass, sank to the bottom of the container. The oil resulting, when skimmed from the surface, was dark in color, strongly acid, of a nauseating odor and taste, and contained many products of decomposition. Unfortunately, the memory of oil made in this manner is still retained by many who were forced to take it during childhood. The cod liver oil of today is a very different thing.

The catch of the codfish is made just before the spawning season when the cod livers are most filled with vitamins and fats before the starvation period and at a time when the prevailing low temperature insures soundness of product. The livers, which weigh approximately three-quarters of a pound and contain about 50% of oil, are removed from the cod the same day the fish are caught, thoroughly washed, the gall bladders and blubber removed. The livers are then placed in double-walled vessels through which steam is passed for about twenty minutes, until the liver tissue has softened and the oil is freed. Steam heating does not injure the efficiency of vitamins or cause them to lose their potency as does exposure to air. The crude oil is skimmed off and placed in tanks to allow the water to settle, remaining there from 12 to 14 hours. The oil is then chilled to a minus 8 degrees Centigrade or 17.6 degrees Fahrenheit, after which it is pumped from the freezing tank through a number of filter
presses which are placed in a refrigerated room where the 
temperature is minus two degrees Centigrade. The chilling 
removes fats of a high melting point which might solidify 
during storage. The upper surface of the oil is often 
covered with a blanket of carbon dioxide or nitrogen gas to 
protect it from possible changes due to atmospheric contact. 
The barrels in which the oil is shipped are lined with tin, 
to prevent the oil from taking up odors from the wood as 
well as to insure more thorough protection from loss. 
Various tests are run for physical characteristics and 
vitamin A and D potency before bottling. In the bottling 
of the oil special precautions must be taken against oxida-
tion, replacing the air above the oil in the bottle by car-
bon dioxide.

**Characteristics**—

A high grade of medicinal oil is light yellow and does 
not have any objectionable taste or odor aside from a slight 
fishy smell when the oil is held in the mouth. If exposed 
to light and air, however, it quickly becomes rancid, and a 
disagreeable taste and odor develop. Its vitamin content is 
also diminished, particularly its content of vitamin A. There-
fore, it is important that the oil be protected from unneces-
sary exposure to air or sunlight.

The commercial product represents a mixture of oils ob-
tained from vast numbers of livers. Therefore, there is not 
as much variation in potency of various samples as might be 
suspected.
There is no direct relation between the depth of color of a medicinal cod liver oil and its vitamin content and biological assay, rather than color, must be depended upon as the criterion of vitamin potency. Pale yellow color as a result of careful preparation, storage and preservation is a desirable feature of medicinal oil since the pale yellow oil is generally considered the more elegant product. However, pleasant taste and odor and high vitamin potency must also be possessed by such a product and products made pale by chemical, adsorbent or light treatments at the expense of taste, odor or potency must be guarded against. An oil possessing some color out of satisfactory taste, odor and vitamin potency is more to be desired than a pale oil of poor taste and odor and low vitamin potency, or a "white" oil of low potency. Pale oil has been repeatedly observed to darken with age, with no change in vitamin content. (100)

The viscosity or consistency of cod liver oil calls for important consideration because a more viscous oil would be less readily swallowed. At least one producer of medicinal grades of cod liver oil assures prospective users that his product is uniform in consistency. However, in an investigation conducted by Ewe (100), no material difference was found in the viscosities of various market brands of medicinal cod liver oil when compared at 25 degrees Centigrade. Oxidation is a well-known factor operating to increase the viscosity of cod liver oil. It is a familiar fact that when cod liver oil is exposed to the air it becomes progressively more
viscous and finally forms a gelatinous mass. The stearin content has no effect on the viscosity, at room temperature, but at much lower temperatures and especially around congealing temperatures the proportion of stearin very greatly affects the viscosity, varying directly. The viscosity is very materially influenced by the temperature, high temperatures reducing the viscosity and low temperatures greatly increasing it. When it is desired to minimize the influence of viscosity upon the taking of cod liver oil it is well to direct that the dose be taken from a small bottle of the oil kept at room temperature, the main supply being preserved in the refrigerator or other cool place.

**Dosage:**

With a view to obtaining an expression in regard to the amount of cod liver oil that must be administered under ordinary conditions, an inquiry was formulated and sent to nineteen leading pediatricians, by the Council of Pharmacy and Chemistry of the American Medical Association. (101) The inquiry was "What dosage of cod liver oil of high potency, taking into consideration the relationship to the age of the patients, do you recommend as a prophylactic? (It will add to the value of your reply if you will state the vitamin A and D potency of the oil on which your answer is based, together with reference to the method used for determining this potency.)" Most of the pediatricians seemed to agree on a dosage of three teaspoonfuls daily as amply sufficient
to prevent and cure clinically evident rickets. A few, however, although habitually employing this dosage in their practice, believe that occasionally a case of mild clinical rickets may develop even with this amount in the average white child. In contrast to the practice of physicians of former years, most of the men begin the administration of cod liver oil at a time when the growth begins to accelerate—if not within two weeks, then at least before the end of the first months—reaching the maximum dosage usually during the third and rarely later than the fourth month, thus usually aborting the rickets in its earliest incipience and hence obviating the use of large doses later. There appears to be general agreement that it is only during the first two or three months of most rapid growth that the child requires its maximum dosage of cod liver oil, which may be continued as an ample dosage on up to two years of age. This is in general agreement with the results of animal experimentation. Thus, Steenbock (35) reports: "a comparatively low level of anti-rachitic over a long period of time is to be preferred to a high level over a short period." The dosage recommended for premature infants is recorded elsewhere.

From the point of view of race, a special exception is made to the general rule of dosage of cod liver oil in the case of Negro infants, on account of their marked predisposition to rickets, due probably (according to Shelling) to differences in the character of the diet, the rate of growth, and the pigmentation of the skin. Hess and Unger (102)
published an interesting report on the "prophylactic therapy for rickets in a negro community", in 1917. They were able to prevent the development of rickets in more than four-fifths of the infants to whom they fed cod liver oil for six months, and in more than one-half of those who were given it for four months. Of 16 infants who did not receive oil, 15 showed signs of rickets, though all of them lived in the very same families or under similar conditions. They found that cod liver oil was a more potent factor than breast feeding in warding off rickets, and almost all the colored babies developed rickets, even though they were nursed. Though the administration of the average dosage for white infants of three teaspoonfuls, if properly supervised, may adequately protect even these Negro infants, 4 or 5 teaspoonfuls should be given if well tolerated by the digestive system; otherwise cod liver oil fortified with viosterol should be given. (101)

Due allowance must also be made for various other factors, which are very important at times and must be always borne in mind. These factors include those of age, rate of growth, race, diet, sunlight and climate, intercurrent infections, potency of the standard oils, etc. Bearing in mind the contention of A. F. Heas (92) that "no anti-rachitic agent is able absolutely to prevent rickets if the disorder is judged by the most delicate clinical criteria", the foregoing (101) dosage of three teaspoonfuls (12 cubic centimeters; 3 fluid-ounces) daily, thus empirically and experimentally arrived at, may tentatively be set as the standard optimum dosage of cod liver oil for the average infant at three months of
age. This standard of three teaspoonfuls may sometimes be more than is required. It will rarely be an inadequate amount, and in the majority of cases it represents the best standard that can be established at present."

**Administration:**

The importance of teaching the mother how to give the cod liver oil to the baby cannot be overemphasized. Success in the administration of cod liver oil to babies depends on two things: the method used, and the ability of the physician or nurse to convince the mother of the value of the cod liver oil. A good method of administration is as follows:

1. With the baby lying across the lap, the nurse or mother pours out the proper dose in a spoon held in her right hand. With her left hand she opens the baby's mouth by pressing the cheeks together between her thumb and fingers. The oil may then be poured little by little into the baby's mouth. If the mouth is not held open until the oil entirely disappears, the baby will spit out what is left. When this happens the mother very frequently reports that the baby has vomited the oil. It is frequent for infants to spit out oil not yet swallowed, but in only a few instances does the infant actually vomit it. Attempts to disguise the taste of the oil for very young babies are unnecessary. If by the fifth or sixth month the baby begins to object to the cod liver oil, it may be given with orange juice. Some babies may be taught to take it through a large rubber nipple or from a bottle. In
the latter case, more oil than is desired for a single dose must be put into the bottle to allow for that which will adhere to the glass. The addition of a little molasses or honey to the spoonful of cod liver oil will sometimes disguise the flavor for older children. There are several flavored cod liver oils on the market. Most babies and little children can be taught to take the pure oil, if it is looked on with favor by the mother and no unpleasant associations are attached to it. Many children who are given cod liver oil from the earliest months of infancy like it and even "cry for it." Others have to be taught to take it.

Concentrates:--

A concentrate that would retain the virtues of cod liver oil and at the same time permit the giving of a small dose of the substance would be welcomed by infants, parents and physicians alike. Clouse (70) in her extensive treatise on vitamin D, passed over the use of concentrates with the statement that generally cod liver oil can be given, or, if there is need of a concentrate, viosterol should be used. Barnes (33), however, states that in private practice there are too many infants in whom definite rickets develops in spite of the fact that adequate doses of cod liver oil have been prescribed. Babies do not all take cod liver oil willingly in teaspoonful doses, and some do not tolerate the fat in the quantities used if cod liver oil is given.

During 1927, the department of agriculture investigated
a number of extracts and concentrates of cod liver oil and found that many were almost devoid of vitamin A and only a few contained any material amount of vitamin D, though claims were made that these vitamins were present in abundance. (103) At present, however, concentrates which represent a potency by animal assays, of several hundred times that of the original cod liver oil can be prepared. Such concentrates are marketed in oil solutions and capsules, as well as in tablets. Marcus (104) has thrown considerable doubt on the stability of the latter, having shown that vitamin A is unstable in the presence of finely divided solids. This may account for the finding of DeSanctis and Craig (19) that the cod liver oil concentrate in tablet form which they tested gave almost the same protection as cod liver oil while the concentrate in oil solution did not. Cod liver oil in liquid form in a dosage of three teaspoonfuls a day prevented rickets in 97 per cent of one hundred cases studied, while the cod liver oil concentrate in tablet form—three tablets a day—prevented rickets in 92 per cent of 143 cases. Cod liver oil concentrate in liquid form, 10 drops daily, prevented rickets in 73.5 per cent of 89 cases. A further comparison of the various antirachitics as studied by these authors is given on page 8.

Barnes (98) gives the following report on the feeding of a cod liver oil concentrate. "42 rachitic infants were divided into three groups of 13, 14, and 15, respectively, and they were given each day 6, 12, and 18 drops, respectively, of a
corn oil solution of cod liver oil concentrate of such a potency that they received, according to groups, 4,000 units of vitamin D and 10,000 units of vitamin A; 8000 units of vitamin D and 20,000 units of vitamin A; and 12,000 units of vitamin D and 30,000 units of vitamin A. Healing was very rapid in all cases and was borne out by the return of the blood calcium and phosphorus to normal within an average period of two weeks or less and a rapid increase in strength and activity on the part of the child. Roentgenograms showed rapid calcification, this roentgen evidence paralleling the improvement in the blood picture. The medication was well taken and caused no dietary disturbances. The healing was due to the cod liver oil concentrate, and not due to a loss of weight or a stationary weight, as is shown by the progressive gain all children showed. That it was not due to the effect of the sun's rays was evident by the fact that patients with active rickets who showed no healing were continuously coming to the clinic up to the time the experiment was concluded. This cod liver oil concentrate retains its active anti-rachitic effectiveness as measured in rat units of vitamin D, and, in the dosage levels studied, is remarkably effective in curing rickets in infants."
HALIBUT LIVER OIL

The halibut and its oil;--

The announcement and sale of halibut liver oil early in 1932 (105) caused considerable furore in both the medical and scientific world.

The halibut or hippocampus hippocampus, Linnaeus, is a flatfish, formerly common off Cape Cod, and now found chiefly in the Pacific waters off Oregon, Washington, British Columbia and Alaska, in Davis Straits west of Greenland, in the North Sea, and off Norway. The halibut grows to great age and very large size, rare ones running up to 700 pounds, though most of the commercial sizes are under 100 pounds. The commercial age-group of halibut may be eight to twenty-five years, which is, on the average, perhaps four times the average age of cod. The food of the halibut consists in large measure of the whole cod and other fishes including liver and liver oil which is already highly concentrated. The halibut therefore has the advantage not only of a food already very rich in vitamins, but many years in which to accumulate them, producing an oil which, by natural processes, is a concentrate of a concentrate. The potency varies not only with the age of the fish, but also with the amount of oil present in the liver. This depends, in turn, on the season of the year.

The world supply of halibut liver oil is not as large as that of cod liver oil. The percentage of oil in halibut
livers is less than a third that of cod. This accounts for the relatively greater cost of halibut liver oil. The greater potency in large measure makes up for the much smaller volume, however.

**Vitamins A and D:**

Halibut liver oil approaches very nearly the ideal natural concentrate of vitamins A and D. An elastic gelatin capsule, the size of a garden pea, of halibut liver oil is equal in vitamin A to three to four teaspoonsfuls of U.S.P. cod liver oil. One drop of halibut liver oil may contain as much vitamin A as a pound of creamery butter and much more vitamin D.

The ready acceptance of halibut liver oil by the medical profession has been due in part at least to this richness in the two vitamins A and D, the fact that it could be administered in dosage volume measurable in drops rather than teaspoonsfuls, and the fact that it could be dosed in forms which avoided the taste of the oil in the mouth. Halibut liver oil contains enormously greater quantities of vitamin A than the familiar cod-liver oil. It is now possible for clinicians everywhere to administer abundant quantities of vitamins A and D in very small bulk and in pleasant form. The problem of ensuring an adequate supply of these vitamins to both children and adults has thus been made simple and its administration remarkably easy and convenient. A few drops of haliver oil added to infants' daily formulas,
or given to small children by spoon, or mixed with food, is readily accepted and ensures against any deficiency of vitamins A and D. Older children and adults, to whom any oil may be distasteful, can receive adequate dosage in the form of small, flexible, tasteless capsules. There is seldom any complaint of unpleasant eructations such as have made cod liver oil unpleasant for most people.

May and Wygant (106) state that the liver of the halibut is capable of concentrating and storing the fat-soluble vitamins, vitamin A being resident in a higher concentration than D and both vitamins A and D, volume for volume of extracted liver, being 100 times and 20 times greater, respectively, than contained in high grade cod liver oil.

A comparison of the vitamin A and D assays of halibut liver and cod liver oils was made by two independent laboratories (Parke-Davis and Company, and Abbott Laboratories) (107), using the same methods on the same oil samples. The vitamin A potency per gram of oil ranged from 37,500 to 62,500 units with an average for the thirty samples of 49,583 units. Compared with the standard 500 gram-unit cod liver oil, the halibut liver oil was from 75 to 125 times more potent than cod liver oil. This shows that halibut-liver oil is an extremely potent source of vitamin A. The antirachitic vitamin D potency per gram of oil varied from 2000 to 3333 daily units, averaging 2479 units. This is much greater than for cod liver oil. In fact, as a natural source of vitamin D, halibut liver oil occupies a very high place. From the
standpoint of physical constants, the specific gravity and saponification number of halibut liver oil were essentially the same as for cod liver oil. The free fatty acid value and non-saponifiable residue were higher in the halibut-liver oil than in the cod liver oil. The iodine number of the halibut liver was lower, however, indicating that halibut liver oil contains less unsaturated fatty acid, and therefore may be expected to oxidize less easily than cod liver oil. Tolerance tests on rats gave evidence that halibut liver oil produced no undesirable effects. Rats fed as much as 10,000 times the daily vitamin A and 400 times the daily vitamin D requirements to correct the induced deficient symptoms, grew rapidly and developed no apparent indications of any pathology. The level of blood phosphorus and serum calcium remained at normal. The excess of vitamin A was stored to a large degree in the liver as a nutritional reserve.

Fortified halibut liver oil:--

Halibut liver oil has been fortified with viosterol. Referring to the choice which the clinician may make between halibut liver oil with viosterol and halibut liver oil plain, it may be remarked that for administration in most cases of deficiency of vitamin A or vitamin D, or both, the product fortified with viosterol is the natural choice, since this preparation not only provides large amounts of vitamin A, but has vitamin D value equal to viosterol, and the consistent use of this preparation ensures against the possibil-
ity of any deficiency in either of these vitamins. In the treatment of cases in which vitamin D is specifically indicated, it is obvious that halibut liver oil with viosterol is preferable to haliver oil plain, because of the greater vitamin D activity of the former preparation. The plain haliver oil is indicated where there is a clinical demand for a concentrated preparation of vitamin A which does not have the unusually high vitamin D activity possessed by haliver oil with viosterol.
CONCLUSION

The various anti-rachitic agents have been studied from several points of view, and compared with the other supposedly "equally good" antirachitics. I shall not attempt to summarize the material at this time, but leave the reader to his own judgment and experience as to the best means of preventing and treating the disease which we have considered—rickets.

However, a word might be said at this point as to the lay treatment of the disease. The present high pressure commercial campaign by food manufacturers, pharmaceutical houses, manufacturers of irradiating apparatus and milk dealers to sell vitamin D directly to the public is to be condemned. Uncontrolled administration of vitamin D is not without attendant dangers. The campaign encourages self-medication, whose evils are already widespread enough. That some of the products have their place is granted, but that place is not in the hands of the public, who too often feel that "if some is good, more is better". We are sadly in need of adequate and universal standardization and supervision of vitamin D-containing food products and the direct sale and advertising of such products to the public should not be permitted. (108) The warning as to the end-results is best given in the words of Act (109), whose sane judgment has a universally high regard: "It is true that we are thoughtlessly permitting or advocating the use of vitamin
D-containing remedies and foods in large doses. It may take twenty or thirty years, possibly not, to appraise the harm which may have been done."
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