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Use of vitamins in pediatrics

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THE USE OF VITAMINS IN PEDIATRICS

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INTRODUCTION

There is probably no problem that causes the senior medical student more concern than the prescribing and ordering of drugs and medicines. There are so many of them, their dosages vary so greatly, and it is so important that the dosage be correct in most of them that the student takes his pen in hand with much hesitancy and moves as though walking on hallowed ground when he writes his first few prescriptions. Not the least of these worries is the use of vitamins, as any physician who has been practicing dur-

ing the past fifteen or twenty years can corroborate. Is the dosage he is prescribing sufficient? Or is it too large and liable to cause ill effects? Or, another important consideration, is the vitamin he is prescribing going to be of any value in the treatment of the particular problem with which he is confronted? It was with these questions in mind that I began my survey of the vitamins and this paper is concerned with answering them as well as our present knowledge of this new field will permit.

The advances made in vitamin logy have been so rapid, both in their discovery and the isolation of new products, and in the almost daily reports of further applications of the old, that an exhaustive survey of their pediatric possibilities is beyond the scope of a single study. Again, out of theinnumerable articles published in the last decade, relatively few can be selected as representing therapeutic applications based on sufficiently numerous and extended clinical experiences. Only too many of these new substances have been advanced as cure-alls and specifics for various conditions, to be found on more careful analysis to be premature or unreliable.

For the same reason we cannot expect to expl re the effects of deprivation of these substances on rodents or immature chicks since there are marked species differences in nutritive requirements, the rat, for example, has no difficulty in synthesizing vitamin C. Futhermore, a deficiency of the same factor may give totally different symptoms in different animal species; a lack of vitamin E in the rat affects primarily the reproductive system, in the rabbit it produces muscular dystrophy and in the chick osteomalacia.

One cannot assume that the many deficiencies known in experimental animals will necessarily have counter-parts in man. Human deficiencies also differ from those of experimental animals, in that human diets, when def-ective at all, are likely to be lacking several factors; the disease pictures are, therefore, more difficult to separate. We shall, consequently, leave these matters strictly in the hands of the investigators in the field of biological chemistry until such time as adequate clinical usage has demonstrated their practical use-fulness in the armamentarium of the practicioner, and will largely confine ourselves to the discussion of these vitamins, the usefulness of which has been substantiated

to at least some degree by the test of time, and touch only briefly on the less tried products and their uses.

It is for this reason that we will restrict our study to the six vitamins with recognized therapeutic efficiency, namely vitamins A, C, D, E, K and the established members of the B group and shall omit consideration of such newcomers as vitamins P, T and F, which have as yet to prove their identity or usefulness.

In recent years, emphasis on vitamins has been principally in the field of preventative medicine. While the normal, healthy child may obtain vitamins from a properly selected diet in spite of the severe processing and high degree of refinement given modern prepared foods, inadequate intake or impaired absorbtion of important nutritional factors will ultimately pro-duce deficiency states. In this country, deficiency diseases occur not so much because our children lack sufficient amount of food, but because that which is provided tends to exist as highly concentrated, "purified and improved" forms such as white flour, sugar, purified oils, and foods "ready to serve." This limits the amount of food taken in the natural state, and it is in the natural state that foods are richest in vita-

mins and minerals.

Undoubtedly the recent commercial interest in the exploitation of the vitamin-conscious parent by advertising "Vita Flakes" as being twice as rich as "ordinary cereals" in vitamin X, will aid to a certain extent in offsetting these refining processes. But the amount of the crystalline substance which they put back into the cereal is usually far less than that which they took out. It is an interesting commentary on our present mode of existence to see the insistence of consumer and manufacturer alike on an extreme degree of refinement, and an equally intent and expensive campaign to restore the very substances discarded in the process.

In considering the problems arising from deficiency of these specific substances we cannot afford to omit the developing infant in utero. It is still impossible to estimate what temporary or permanent stigmata are implanted in the newborn as a result of a lack as early as conception itself. Certainly we do know that during pregnancy the vitamin store of the mother is depleted in favor of the fetus and must be met in order to assure an adequacy for both mother and child.

Chapter I

VITAMIN A

Vitamin A is the "fat-soluble" vitamin which was discovered by McCollum and Davis when they observed that young animals sickened and failed to grow unless butter-fat or some other product carrying this then unknown factor was added to their diet of purified foodstuffs. It is now known that this vitamin occupies an important place in pediatric practice, being essential not only to growth but also to the child's health and well-being

The most significant function of this vitamin is its influence in maintaining the structural integrity of epithelial cells. Without it, epithelial structures everywhere, wherever their location or function, all undergo the same highly characteristic change. This takes place through a process of metaplasia in which normal epithelial cells are replaced by stratified keratinized epithelium. The diseases of infancy and childhood dependent on a lack of this substance include many dermatoses, diseases of the respiratory tract, infections of the middle ear, intestinal disorders, as well as by drying of the conjuctiva, with failure

of the paraocular glands leading to xerophthalmia.

Vitamin A deficiency may develop on a basis of inadequate intake, impaired intestinal absorbtion, or defects in its utilization. The newborn infant is particularly susceptible to a faulty intake, for he is born with very low stores, the concentration of the vitamin in the liver at birth being less than one-tenth of that found in the adult. Another possible cause of defective vitamin A intake is the exclusive uses of canned foods due to the slow deterioration which occurs on standing. This should be borne in mind in the case of infants fed on evaporated or dried milk.

Defective absorbtion undoubtedly contributes to the susceptibility of the premature infant congenital atresia of the bile ducts may likewise lead to vitamin A deficiency, and it has been observed several times in chronic dysentery and in patients with the celiac syndrome and cretinism. Lastly, a factor which may cause serious interference with the absorbtion of the vegetable precursors of vitamin A is the habitual use of mineral oil.

This particular need for vitamin A during

infancy is emphasized by Cowgill[1] who estimates that from birth the infant should recieve not less than 2000 units, which requirement is met with about 750 c.c. of breast milk. He emphasizes the importance, however, of supplementing the feedings with cod liver oil or some other appropriate concentrate, especially when cow's milk, which is poorer in this respect than human milk, forms a material part of the diet.

It has been held that the average diet of art-ificially fed infants is inadequate in respect t vitamin A. As night blindness is conceded to be a very early manifestation of vitamin A deficiency, preceeding retardation of growth, susceptibility to infections and xerophthalmia, Lewis and Haig[2] devised an appara-tus and developed a technique by means of which night blindness or dark adaptation could be estimated even in children less than one year of age. They reported their observations of the minimum light threshold after complete dark adaptation on 53 infants ranging

1. G.R. Cowgill, "The Vitamin Requirements of Man." J.Am. Dietet. XXIII, 195, 1937.

2. J.M. Lewis and C.J. Haig, "Vitamin A Requirements in Infancy as Determined by Dark Adaptation." J. Pediat. XV, 812, 1931.

in age from 1½ to 13 months. These infants were divided into four groups: Group 1 consisted of 26 infants recieving the average infants diet; Group 2 consisted of 9 infants recieving a diet supplemented by large quantities of vitamin A (17,000 units) in the form of halibut liver oil; Group 3 consisted of 4 infants receiving a diet containing approximately one-fourth the vitamin A content of the average diet; and Group 4 consisted of 14 infants receiving about one-twelfth the vitamin A content of the average diet. These diets were given for periods varying from 3 to 10 months. The results of the dark adaptation tests were within normal limits in all four groups of infants. Those in the low vitamin A group gained weight just as well and were no more susceptible to infection than those in the high vitamin A group. These observations indicated that 135 to 200 units of vitamin A, or approximately 25 units per kilogram of body weight, covered the minimum vitamin A requirements of these infants. Since the average diet contains 12 times as many units of vitamin A as were contained in the low vitamin A diet used in this study, it appears that there is a large margin of safety in the infants' diet In respect to its vitamin A content and these studies

would seem to indicate that it is unnecessary to supplement this element in the average diet of infants.

This work, however, is not concerned with early infancy, that is, the first few weeks but other studies also would seem to indicate that prophylactic supple-ments are desirable only in very early infancy and in conditions likely to interfere with intestinal absorb-tion, especially liver disease and chronic diarrheas.

In arranging the diets of older children it is not difficult to meet the minimal requirements of vitamin A, but it is possible that a great many children fail to receive the optimal amount. If the child takes a pint of milk daily, two eggs, two liberal helpings of butter and a helping of carrots and some green vegetables, with a little cheese and a helping of liver occasionally, he will be safe as far as vitamin A is concerned.

Although there may be considerable latitude in vitamin A requirements of normal children, Breese and McCoord[3] have recorded a series of cases of celiac disease, which showed a subnormal absorbtion of vitamin

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3. B.B. Breese, Jr., and A.B. McCoord, "Vitamin A Absorbtion in Celiac Disease." J. Pediat. XV, 183, 1939.

A. Even when given a large amount of vitamin A by mouth these patients did not show an increase in the blood vitamin A content equal to that of a group of children with other diseases. This inability of the patient with celiac disease to absorb vitamin A was usually associated with a flat sugar tolerance curve, increased per cent of fat in the stools and low carotenoid pigments in the blood. This inability to absorb vitamin A normally, although characteristic of celiac disease, does occur in other diseases and therefore is not pathognomonic of celiac disease.

In the treatment of such cases the usual therapeutic dose of vitamin A (ten drops of halibut liver oil or percomorph liver oil 3 times a day, providing 50,000 to 60,000 international units) should be doubled or trebled.

An interesting study of the effects of avitamin-osis A on the blood picture was made by Ahmann and Overstreet[4] on a group who had been living on restricted diets for periods that varied from a few months to many years. The children had lost the alertness of health

4. C.F. Ahmann and M.R. Overstreet. "Effects of Avitaminosis A on the Human Blood Picture." Am. J. Physiol. CXXVI, 254, 1939.

and were listless and inattentive, but conjunctivitis was the most outstanding defect of this group. In a few cases the ocular condition had progressed so far that there was actual involvement of the cornea and the conjunctiva appeared salty. The skin had become dry and desquamated. These flaky areas were particularly noticeable on the back of the forearm, the upper arm, near the tips of the shoulder, on the calves and across the chest. Many of the children had no subcutaneous fat, so that the skin on the face was shrivled and dry. The hair was also dry, had lost its normal gloss and appeared bleached and lifeless. It is in such cases that the therapeutic specificity of the vitamin is manifested.

Sandels et al[5] in her extensive work on the value of vitamin A in the treatment of follicular conjunctivitis of children of school age has shown that this deficiency condition is rapidly cured by the administration of vitamin A and at the same time throws doubt on the question of massive doses. The children who

5. M.R. Sandels, H.D. Cate, K.P. Wilkinson and L.J. Groves, "Follicular Conjunctivitis in School child-ren as Expression of Deficiency - Vitamin A." Am. J. Dis. Child. LXII, 101-114, (July) 1941.

received 13,000 U.S.P. units improved at approximately the same rate as did those receiving as high as 38,000 units, a time factor so operating which limits the rate of healing and which is not increased proportionately by excessive doses.

Lehman and Rapaport[6] in a study of the cutaneous manifestations of vitamin A deficiencies in childhood suggest that keratosis pilaris, lichen pilaris, lichen spinulosis, ichthyosis follicularis and other synonyms are merely descriptive terms for the cutaneous manifestations of vitamin A deficiency and may be expected to respond to specific treatment.

The intensiveness of research on this vitamin in the field of pediatrics is demonstrated in Straumjford's[7] report presenting evidence to show that vernix caseosa may be a manifestation of vitamin A deficiency in the newborn and that it represents disturbances in corni-fication analogous to the skin changes accompanying

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6. E. Lehman and H.G. Rapaport, "Cutaneous Mani-festations of Vitamin A Deficiency in Children." CXIM, 386, 1940. J.A.M.A.

7. J.F. Straumfjord, "Vernix Caseosa: Manif-estation of Vitamin A Deficiency." West J. Surg. XLVIII, 341, 1940.

Keratomalacia and other signs of vitamin A deficiency. In support of this theory is presented an experimental study in which twenty-five women received 50,000 to 100,000 units of vitamin A through six months of pregnancy. Twenty-one had babies with little or no vernix; only four had babies with moderate or much. Of thirty-one women who received no additional vitamin A, twenty-three had babies with moderate or much vernix.

In regard to the use of vitamin A in preventing or ameliorating colds, or other common upper respiratory tract infections, the evidence reviewed by the American Medical Association[8] indicates that severe deficiency of vitamin A lowers resistance to infection but that the administration of vitamin A during the course of an infection probably has no beneficial effect on the outcome unless a severe deficiency is present. There is evidence that moderate deficiency of vitamin A may also increase the duration or severity of respiratory infections; that an adequate intake of vitamin A may lessen the severity and duration of

8. American Medical Association. "The Vitamins: A Symposium." 1939.

infection in cases of moderate deficiency. It seems at the present time that many factors are of equal or greater importance, and no substantial justification exists for calling vitamin A the "Anit-infective Vitamin."

From this study it seems that the newborn infant during the first few weeks of life probably requires more vitamin A than it does later on; approximately 2000 units daily. 135 to 200 units, or about 25 units per kilogram of body weight, being the minimal dosage after the first few weeks of life. This amount is easily btained from a normal diet. In celiac disease the infant should recieve 100,000 to 150,000 units daily, probably because of poor absorbtion. Deficiency states seem to require a certain minimal healing time and doses of 13,000 units daily cleared up cases of folli-cular conjunctivitis as rapidly as doses of 38,000 units daily.

Chapter II

VITAMINS OF THE B GROUP

The field of investigation concerning the vita-mins of the B group is still in a state of flux. Almost daily new factors and filtrates, new this and that preventing substances are isolated from the original complex. In order to preserve clarity we shall avoid such nomenclature as B_1, B_2, etc., but shall speak of these factors individually and as distinct entities, only when they are represented by definite chemical compounds.

For this reason we will discuss in detail only thos vitamins which have been subjected to at least a moderate period of clinical use and which have some definite therapeutic applications, namely thiamin, riboflavin and nicotinic acid and speak only in passing of those members not yet of determined value in infancy and childhood, such as biotin, choline, pyridoxine, inositol and pantothenic and para-amine benzoic acids.

The vitamins of the B group, closely related in nature, have been shown to be related in function as well. At least three of its members - thiamin, riboflavin and niocin - are known to act as the functional group of enzymes concerned in various stages

of carbohydrate combustion, and there is evidence that pyridoxine and other factors, whose importance has to date been largely demonstrated only in the rat, may play similar roles. The fact that the combustion of fat apparently does not require the presence of thiamin accounts for the well-known B-sparing action of this foodstuff. Protein, on the other hand, requires the presence of various B factors. A deficiency of one single factor may cause failure to thrive and grow. Interruption of the chain of metabolic processes at different points, however, causes different metabolic products to accumulate, these different perversions of metabolism being responsible for the various deficiency syndromes.

In general when considering the vitamins of this group it is well to consider that children with a deficiency of the vitamin B complex rarely present the classical picture of pellagra, ariboflavinosis or beri-beri. From the work of Spies[1] and others it is evident that in practice these syndromes frequently

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1. T.D. Spies, S.P. Vilter, and W.F. Ashe, "Pellagra, Beri-beri and Riboflavin Deficiency in Human Beings." J.A.M.A., CXIII, 931, 1939.

coexist and that diagnosis of one necessitates a thorough search for others.

While adequate amounts of all the vitamins are recognized to be essential to normal growth and health in infancy and childhood. The B group is thought to be the one least likely to be supplied in sufficient amounts particularly in infancy. Vitamins A, C and D are now prescribed for most bottle-fed babies, but of vitamin B the infant receives only the small amount present in the milk formula and to a small degree from the orange juice which is given for its vitamin C content. Breast milk has been shown to contain even less thiamin than cow's milk so that there may develop evidences of thiamin deficiencies in both breast and bottle-fed infants. In discussing the relation of B deficiency to infant mortality it must be remembered that of all the disturbances responsible for infant mortality during the first year, few cause greater apprehension than diarrhea and enteritis because 20-30% of infants die of gastro-intestinal diseases of vague etiology. Because the maternal diet and the artificial feeding of infants can never be controlled completely and rigidly, particularly from the standpoint of depleting vitamin reserves, there is a considerable likelihood of these gastro-intestinal disturbances being the result

of a vitamin deficiency.

The influence of vitamin B complex on growth and constipation was studied by Joslin and Helms.[2] Their finding indicate a definitely increased growth in infants in length, in development of the chest and in weight as the result of an increased amount of vitamin B given in the diet during the first year of life. Constipation was relieved in each instance of the 35% of this series which manifested the symptom. Of their control group the 20% who manifested constipation did not show a disappearance of this symptom upon the use of the usual laxatives such as mineral oil, milk of magnesia and the like. In another group of nursing infants who had failed to gain in weight because of insufficient breast milk, vitamin B was added to the diet of the mothers. Of these 57% were able to continue nursing their babies for periods varying from 2 to 6 months. Of this group of infants 50% were constipated. The addition of vitamin B to the diets of the mothers cleared up all but 5% of these

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2. C.L. Joslin and S.H. Helms, "The Vitamin B Complex: A Clinical and Experimental Study with special reference to Growth and Constipation." Pediat., LIV, 533, 1937.

cases. In 100 older children it was found that 27 had anorexia, while 40 were constipated. These were all fed a pr per diet and given a special cereal rich in vitamin B. The appetite in each case was improved and the constipation was corrected.

Litchfield[3] et al., in a study of the value of the administration of vitamin B to prematures have shown that infants receiving yeast extract showed gains in weight much sooner than those not receiving this preparation. Of the group of prematures receiving yeast extract, 55% began to gain during the first week of life, whereas less than 8% of the control group showed a gain during the first week. Ninety-five per-cent of those receiving yeast extract showed gains at the age of 2½ weeks, whereas only approxi-mately 48% of the control group showed gains at the end of this period. Again infants with birth weights under 1,500 gm. who were given yeast extract attained four or five times their birth weight at the age of 3 months, as compared with those not given yeast extract,

3. C. Litchfield et al. "Effect of Yeast Extract (Vitamin B Complex) on Growth and Development of Pre-mature infants." Am. Dis. Child ., LVII, 546, 1939.

who only doubled or tripled their weight at this age. Of those having birth weights over 1,500 gm. twice as many of those given yeast extract tripled their weight as those without the extract, and many of those given the yeast extract quadrupled their weight. Three infants of their series given yeast extract showed a gain of five times their birth weight at 3 months. In their entire study there were no instances of gastro-intestinal disturbances accompanying the administration

of this substance.

In general, the work at present suggests that the result of adding thiamin to the diet of infants and children is an increase in appetite, and in assimilation and utilization of food, thus producing an increase in weight and height. Infants and children up to 2 years of age gain 70 per cent more if supplied with additional thiamin.

A total of 20 patients with severe, moderately severe, and mild cases of Sydenhams chorea were treated by Stone[4] with vitamin B complex and artificial fever

4. S. Stone, "Treatment of Sydenhams Chorea by Fever and Vitamin B Therapy." New Eng. J. Med. CCXXIII, 489, 1940.

therapy. He found the results of the treatment to be be excellent. Artificial fever episodes were produced every three or four days and the patients were given in addition, thiamin chloride intravenously and vitamin B complex orally after each fever treatment. The action of fever therapy on chorea is probably not specific, but the influence of the vitamin is more direct. He feels that these patients for various reasons do not eat the general all-inclusive diet necessary to avoid vitamin B complex deficiency and that the situation is apparently analogous to that found in the alcoholic avitamin sis.

Hay[5] in his series of cases on the treatment of pink disease (acr dynia) with intramuscular injections of thiamin has obtained satisfactory results in a large percentage of the children treated. He concludes that "whatever may be the true explanation of the part vitamin B_1 plays in this interesting disease, it would seem wise t continue to administer it intramuscularly in the hope of relieving some cases, and preventing

5. J.D. Hay, "Pink Disease Treated by Intramuscular Vitamin B_1: A Report f Eight Cases." Practicioner, CXLVI, 264, (April), 1941.

others from becoming severe. It would also seem advisable to give the ther fractions of vitamin B." But some authors believe vitamin B to be of no value in the treatment of acrodynia. Possibly there is a vitamin B deficiency that closely resembles acrodynia.

The child needs relatively more thiamin than the adult and an acute illness may reveal a latent deficiency.[6] Eighteen cases of postdiphteritic paralysis of the diaphragm and pharynx were treated with thiamin by Frey.[7] Of these, 11 were cured by injection of large doses of thiamin; in 5, the paralysis was relieved but the child died from other causes, and not because the treatment failed. A small dose of thiamin given after serum treatment, failed tp prevent the onset of paralysis. Larger doses given in this way were more effective. It seemed that thiamin was use-ful in cases of paralysis of the diaphragm and pharynx though its effects on other types of postdiphtheritis paralysis were less satisfactory.

In a recent study of endemic riboflavin deficiency in infants and children conducted in the

6. Editorial, "Vitamin B and Postdiphtheritic Neuritis." Brit. M.J., II, 325, 1940.

7. L. Frey, "Vitamin B_1 and Postdiphtheritic Diaphragmatic Paralysis." Ztschr. f. Kinderh. LXI, 730, 1940.

southern part of the United States by Spies[8] et al. it was found that the clinical symptoms of this defic-iency correspond closely with those occuring in the adult such as cheilosis, conjunctivitis, etc.. The children suffering from this deficiency were usually underweight, underdeveloped for their age. Many of them were apathetic and indifferent and had made poor progre ss in school. Frequently they complained of their mouths being sore and of their eyes burning and itching. The symptoms waxed and waned with the seasons and with changes in the quality of the dietary but they appear-ed most frequently during the spring and summer. In-creased exercise and infections seemed to precipitate the appearance of lesions in the borderline cases. The response of these children with riboflavin deficiency to the synthetic preparation or to substances rich in riboflavin was gratifying. The cheilosis healed rapidly, the ocular symptoms disappeared, and the general health of the children improved. In treatment they found that the average case responds.

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8. Spies, T.D., W.B. Bean, S.P. Vilter and H. Huff, "Endemic Riboflavin Deficiency in Infancy and Childhood." Am. J. Med. Sc., CC, 697, 1940.

satisfactorily to the oral administration of 1 mgm. of riboflavin three times a day or one ounce of brewer's yeast or liver extract daily.

The role played by niocin in infancy and childhood is well portrayed in the report of a study made in Alabama by Spies, Walker and Woods[9] of 800 pellagrins and extended to include the families of these patients.

A diagnosis of pellagra was made in 194 children and six infants, and each case the diagnosis was confirmed by therapeutic tests. They examined the children of pellagrous parents repeatedly, with particular attention directed towards the diet of the mother during pregnancy and lactation and of the child after birth, towards the physical and mental development of the child, and towards the presence or absence of lesions diagnostic of pellagra. It was often found that the diet of the mother was inadequate during pregnancy and lactation and that, as a result, the quality of her breast milk was poor and supply often insufficient for the child's needs so that the

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9. T.D. Spies, A.A. Walker, and A.W. Woods, "Pellagra in Infancy and Childhood. J.A.M.A., CXIII, 1481, 1939.

nursing infant had to be weaned soon after birth and was given some sort of food, which in many cases, was inadequate for its nutritional needs. As they grew older, the majority of these children had poor appetites and usually ate very irregularly. Most of them perferred carbohydrate foods and often refused most of the other foods. Analysis of the dietaries of such children showed that in most cases their diets were unbalanced and failed to supply in adequate amounts the foods essential for proper nutrition. Usually these children were underweight and underdeveloped for their age and appeared to be undernourished and in ill-health. They were said to be irritable, easily frightened and fretful and cried a great deal. They were listless, tired and apprehensive and they did not manifest the normal interests of childhood. Those of such age found it difficult to concentrate and, as a rule, made poor progress in school. Although they seemed too tired to play, they could not rest. They did not sleep well at night but instead tossed about and frequently awoke crying. Many complained of soreness of the tongue and lips and of burning and pain in the stomach. Usually they suffered from constipation but they might have attacks of diarrhea during the spring and summer. The response of niacin-

containing preparations was as dramatic as it is in adults. Lesions characteristic of the disease were seldom seen in infancy but frequently appeared early in childhood.

The dosage of vitamin B is quite variable. Deficiency states will respond to one ounce of brewer's yeast or liver extract daily. It should be emphasized however that the requirement may be increased consider-ably by long continued febrile conditions.

Chapter III
VITAMIN C

Infantile scurvy is the commonest form of vitamin C deficiency seen in the United States. It is characterized clinically by swelling and tenderness of the thighs, disinclination to move, irritability, fretfulness, pallor and a worried expression; pathologi-cally by a tendency to hemorrhages throughout the body and especially in the bones. Though scurvy may appear at any age during infancy and childhood, it is seen more frequently in infants than in older children and adults because of the necessarily restricted character of the diet. It is because of this fact that the greatest incidence of avitaminosis C is between the seventh and tenth months of life, rarely before the fifth. In a preliminary survey made by Jackson and Park[1] in Balt-imore, evidences of scurvy were found in the bones of 12% of the infants coming to autopsy between the ages of three and nineteen months.

The disease is considerably more common in

1. H. Jackson and Park, "Congenital Scurvy." J. Pediat., VII, 741, 1935.

bottle-fed infants because of destruction of a portion or all of the vitamin by heat. Less often scurvy may occur in breast-fed infants due to a maternal deficiency of vitamin C or in infants who because of eczema or some ther ailment have been kept too long on a highly restricted diet.

According to various reports, such as that of Abt and Farmer[2] intestinal dysfunctions, such as enteritis, colitis, and celiac disease, tend to diminish the absorbtive power of the intestinal mucosa with a consequent predisposition to avitaminosis C.

The determination of the ascorbic acid content of the blood, spinal fluid and urine is a recent diagnostic advance and one which coupled with the X-ray has made possible the detection of even very early scorbutic tendencies. By the use of these estimations Wortis, Liebman and Wortis found that no specific level of vitamin C at any given moment in the blood, spinal

2. A.F. Abt and C.J. Farmer, "Ascorbic Acid Absorbtion in Infantile Diarrhea." Journ. Pediat. XVIII, 756 (June), 1941.

3. H. Wortis, J. Liebman, and E. Wortis, Vitamin C in the Blood, Spinal Fluid and Urine." J.A.M.A., 110, 1896, 1938.

fluid or urine was necessarily associated with the clinical manifestations of scurvy. They found that a blood level of vitamin C above 0.7 mg. per 100 c.c. was almost invariably associated with a normal spinal fluid content and a normal urinary excretion test for vitamin C. A blood content of vitamin C below 0.4 mg. per 100 c.c. was associated with a subnormal spinal fluid content and a subnormal urinary excretion test. In these ranges the blood was an accurate index of the state of the vitamin C nutrition. In the intermediate subnormal range for blood of from 0.4 mg. to 1.69 mg. per 100 c.c. all available tests should be used and the clinical evaluation of the patient should be a large factor in diagnosis.

Absolute depletion of ascorbic acid in the urine and lowering of the levels in the plasma from 0.15 to 0 mg. per 100 c.c. were found by Ingalls[4] in a study of 7 infants who were proved to have scurvy. Increase in the ascorbic acid in the urine and elevation of the levels in the plasma depended on the dose

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4. Ingalls, T.H., "Studies on the Urinary Excretion and Blood Concentration of Ascorbic Acid in Infantile Scurvy." Journ. Pediat., X, 577, 1937.

employed in treatment. The greater the dose the more rapid the replenishment of the vitamin. These results suggested that there are zones in the excretion of ascorbic acid in the urine which are generally characteristic of frank scurvy, of symptomatic scurvy and of suboptimal and of optimal intake of vitamin C. It appeared that recovery from frank scurvy depended on the quantitative replenishment of ascorbic acid in the tissues through stages of absolute and then relative depletion until an average depot had been attained.

From studies of large groups of infants in an effort to determine the minimal vitamin C requirements it appears that the condition that has usually been considered as latent scurvy is actually definite mild scurvy. Such a distinction puts an entirely different interpretation on the evaluation and classification of symptoms and causes of scurvy. It seems that scurvy is a definite pathological entity but does not become evident or retard development until the absence of the specific physiologic functions of the vitamin is manifest. A condition of chronic scurvy may exist for several months, with spontaneous clearing and recurrence accompanied by its resultant retarding effects on cellular function and physiologic processes of tissues. The

symptoms of severe manifest scurvy comprising the classic entity of Barl ws disease, develop through a combination of factors, which include continued low utilization of vitamin C and diminished cellular metabolism in interrelated functions of the tissues as a result of infection, allergy or glandular heritage. There is a distinct variability in individual susceptibility which is determined by prenatal as well as postnatal factors.

Prophylaxis of infantile scurvy is essential in all infants even partially dependent n boiled, pasteurized, dried or evaporated milk, and some supplementation in an artificial or preferably a natural form should be instituted as early as the first or second month. Orange juice is the most convenient source; one teaspoonful daily, increased as soon as permitted by the digestive abilities. The minimum protective dose has been stated to be about one tablespoonful a day, though this probably far short of the optimal, and a dose of two or more tablespoonfuls per day is desirable.

The treatment of a child who has developed scurvy is usually a simple matter. Orange juice should be given in doses of four ounces or more a day. The only difficult cases will be those in which gastro-

symptoms of severe manifest scurvy comprising the classic entity of Barl ws disease, develop through a combination of factors, which include continued low utilization of vitamin C and diminished cellular metabolism in interrelated functions of the tissues as a result of infection, allergy or glandular heritage. There is a distinct variability in individual susceptibility which is determined by prenatal as well as postnatal factors.

Prophylaxis of infantile scurvy is essential in all infants even partially dependent n boiled, pasteurized, dried or evaporated milk, and some supplementation in an artificial or preferably a natural form should be instituted as early as the first or second month. Orange juice is the most convenient source; one teaspoonful daily, increased as soon as permitted by the digestive abilities. The minimum protective dose has been stated to be about one tablespoonful a day, though this probably far short of the optimal, and a dose of two or more tablespoonfuls per day is desirable.

The treatment of a child who has developed scurvy is usually a simple matter. Orange juice should be given in doses of four ounces or more a day. The only difficult cases will be those in which gastro-

diarrhea abates and the liquid steels change to formed steels. These facts point to a failure of absorbtion of ascorbic acid from the intestinal tract during infantile diarrhea, rather than to an increased destruction by bacteria in the intestinal tract. This failure of the oral absorbtion would pr bably not be clinically significant in the acute diarrheas of short duration but in protracted or chronic diarrhea in infancy the need for the parenteral administration of ascorbic acid as a protection against the development of scurvy would seem to be indicated.

The value of vitamin C in the promotion of wound healing while of considerably greater interest to the surgeon than the pediatrician is, nevertheless, deserving of consideration in poorly healing wounds in children. Kenny and Rapaport[8] for instance, report an interesting case in which the administration of crystalline vitamin C was of value in the stimulation of wound healing in the incision of an infant operated upon for pyloric

8. A.S. Kenny, and M. Rapaport, "Studies in the Use of Crystalline Vitamin C (Ascorbic Acid) in the Prophylaxis and Treatment of Infantile Scurvy and Some Other Disorders of Infancy and Childhood." Journ. Pediat., XIV, 161 (Febr.) 1939.

stenosis in whom there was no evidence of healing prior to its administration.

Following the isolation of vitamin C in crystalline form there was a great impetus for investigations of its therapeutic value in hemorrhagic diseases and hemorrhage in other diseases. At first, numerous reports appeared claiming good results from the use of vitamin C in symptomatic purpura, thrombopenic purpura, Schonlein's and Henachs purpuras, and he hilia. Favorable claims also were made for many diseases of infancy and childhood as leukemia, acute hemorrhagic nephritis and others. It has since become evident that these early enthusiastic claims could not be substantiated.

Vitamin C deficiency has recently been considered as playing some part in the etiology of certain infectious diseases, such as acute rheumatic fever. Rinehart[9] studied a group of children including their dietary histories, assay of their social environment, capillary resistance tests, routine examinations and periodic

9. J.F. Rinehart, "Studies Relating Vitamin C Deficiency to Rheumatic Fever and Rheumatoid arthritis; Experimental, Clinical and General Considerations." Ann. Int. Med., IX, 586, 1935.

follow-up. It was found that most of these rheumatic children were on the borderline of nutritional inadequacy. Many were severely deficient in vitamin C intake, particularly during the winter months. In many instances the economic status precluded adequate food. In other instances racial habits or idiocyncrasies led to low consumption of foods containing vitamin C. The capillary resistance tests revealed in general low levels particularly in those cases manifesting evidence of recent rheumatic activity. Many children were found to have edematous puffy gums. The patients were instructed to provide generous amounts of vitamin C in the diet. Usually a definite daily dietary of orange juice was prescribed. The author reports that altogether there was satisfactory increase in weight, general clinical improvement and absence of recurrence. The levels of capillary resistance were invariably elevated.

Favorable reports have also appeared for the use of vitamin C along with other treatment in pneumonia and pertussis. Negative results have been reported in poliomyelitis, and the results are inconclusive in diphtheria.

It is evident that vitamin C is not a specific

agent in the treatment of any of these diseases. It should not be forgotten, however, that the importance of an ample diet has long been recommended in the treatment of febrile conditions, and such patients have, perhaps, and increased requirement for all of the vitamins.

In concluding our study of vitamin C it can be said that the best source is probably orange juice. Four ounces per day will cause a rapid recovery in a case of scurvy. If they are unable to take this, 100 mg. of the crystalline substance can be given daily by mouth. Some reports indicate that a single intravenous administration of 100 to 400 mgm. will give results equal to a weeks consumption of orange juice.

Chapter IV

VITAMIN D

Vitamin D has long been the subject of much study and of many contributions to the literature. Although its use as a prophlactic accessory to the dietary of infants is widespread, many papers are published relative to the effects of its lack, or its use or of its relationship to other phases of the humen organism.

As has been shown to be true of many f the vitamins, what was formerly called vitamin D has been demonstrated to be not a single entity but a complex which includes ten or twelve members. Of these, we are formally concerned with only two, vitamin D_2 and D_3. The designation, vitamin D_1, is a misnomer, having been employed for only a short time to identify a preparation subsequently found to be a mixture.

Vitamin D_2, or calcifer l, is produced by the activation of ergosterol; it is the necsterol vitamin, the vitamin of plant origin. Vitamin D_3 results from the activation of cholesterol and is technically known as irradiated 7-dihydrocholesterol.

No other vitamin occupies a more important

place among the nutritional accessories which serve to prevent nutritional disease than vitamin D. Moreover, it is equally useful in the cure of rickets, which is caused by the failure to include sufficient of this vitamin in the diet of the growing infant. For this reason it has always been spoken of as the anti-rachitic vitamin.

For many years cod liver oil was regarded as the principal source of this vitamin, but recent studies have demonstrated that oils from the livers of other fish are superior in that i was difficult to supply a sufficient amount of the former without giving doses that were not easily retained by young babies. Especially was this so in prematures in which anti-rachitic measures are of even greater importance than they are in full-term babies.

So far as our present knowledge has progressed, preparations containing vitamin D are used chiefly for the prevention and cure of rickets in growing children. To a lesser extent, they are useful in the prevention and treatment of infantile tetany.

For the effective use of vitamin D in the prevention of rickets, it should always be remembered that the period of greatest susceptibility to rickets

is in the first few months of life. Moreover, the rate of growth is a very definite and important factor in determining the vitamin D requirements. The severity of rickets increases with increasing rates of growth. Consequently, the more rapidly the infant grows, the greater the need for vitamin D, if defective development of the bony structure is to be prevented. All infants require some source of vitamin D beginning at about the second or third week of life. Many are especially susceptible to the development of rickets. This may be explained in a large measure on an inadequate diet of the mother during pregnancy. All prematures are especially susceptible to rickets and as a consequence require at least twice the dosage of vitamin D than the normal infant needs.

In selecting the source of vitamin D for normal and premature infants, a standardized cod liver oil or one of the several concentrates may be used. Obviously, if cod liver oil is used, the bulk of the dosage necessary to supply adequate unitage will be much greater than that of the concentrates. In order adequately to protect an average normal infant with cod liver oil, it is desirable to begin with one-half a teaspoonful during the second week of life and rapidly increase this to two or three teaspoonfuls each day

if the recognized number of units is to be obtained. Obviously, this is bulky and will not be retained at all by the premature baby with a stomach frequently of from one-half to one ounce capacity. There certainly would be little room for the feed so important for existence to the premature. Cod liver oil is frequently not well tolerated by normal infants in the early weeks of life. In addition, it must not be overlooked that cod liver oil, like the liquid petrolatum forming the base of many nose drops, is capable of causing lipoid pneumonia if it is aspirated through the larynx into the lungs. This is especially likely to happen when vomiting occurs. Standardized cod liver oil is still favored by a number of pediatricians, and its use continues in older children. In fact, many children like the taste of it. In very young babies, in prematures, the rational procedure seems to be to utilize one of the concentrated fish liver oils, because the same unitage can be given for the young baby in concentrated dosage. If it is so decided to use these concentrated fish liver oils, from 15 to 30 drops are sufficient for premature babies, while from 8 to 10 drops will protect the full term child against rickets. The therapeutic dose, however in either type of baby should never be

less than 20 drops a day. Some advocate as much as 30 - 40 drops. Even more than this can be given without fear of causing evidence of excessive calcification to which the name hypervitaminosis has been given. This was caused when irradiated ergosterol was first put on the market in Germany under the name of Vigantol and was characterized by the deposition of calcium in various tissues of organs of the body as a result of the hypercalcemia caused by overdosage with this newly created vitamin D concentrate.

Strong et al[1] from the results obtained in their study conclude that irradiated evaporated milk containing 3.8 Steenbock units to the ounce, is an inexpensive, pleasant tasting, convenient source of vitamin D, which is almost universally available and which, when fed to the average, normal infant in the average or below average home, will protect about 9 out of 10 infants from rickets. They feel that it offers a source of vitamin D in an amount sufficient to reduce greatly the incidence of severe rickets.

1. R.A. Strong, E.F. Haef, and I.M. Harper, "The Antirachitic Properties of Irradiated Evaporated Milk Fed to Normal Babies Under Home Conditions." Journ. Pediat., VII, 21-36, (July) 1935.

among patients whose parents either have not been educated to the necessity of antirachitic supplements to the feed of all babies or who cannot afford them. Their impression is, however, that the irradiation of evaporated milk as yet should not be relied on exclusively to provide protection to all infants throughout the first year. It should be supplemented with additional vitamin D units from one of the conventional sources, particularly in the early months of life, when the intake of irradiated, evaporated milk may be insufficient to provide the unitage necessary to protect the infant. Obviously, when irradiated evaporated milk is used, the necessary amount of additional antirachitic factors will be considerably less than when infants are fed a milk in which the vitamin D potency has not been thus enriched.

Concerning the laudations of the various commercial firms over the superiority of their vario us vitamin D preparations, irradiated milks, etc., and the benefits to be gained from concentration and large doses, Drake[2] reports that no evidence can be found to

2. T.G.H. Drake, "Comparison of the Antirachitic Effects on Human Beings of Vitamin D from Different Sources." Am. J. Dis. Child., LIII, 754, 1937.

support any difference in the antirachitic effectiveness of vitamin D whether administered in the form of cod liver oil, of a mixture of fish liver oils of high potency (percomorph liver oil), or irradiated cholesterol of irradiated fresh milk or of irradiated evaporated milk. He observed no difference in the antirachitic value between the daily administration of 150 U.S.P. units of vitamin D in the form of one of these substances and that of 270 U.S.P. units of vitamin D in the form of viosterol. The administration of this vitamin in amounts as low as 95 U.S.P. units daily prevented the development of rickets of a moderate or marked degree in every case. No evidence was obtained that this extremely small amount was less effective in preventing rickets, as measured by roentgenograms, than were the large amounts usually administered, and that rapid healing of rickets of a moderate or marked degree, resulted from the daily administration of as little as 300 and 500 U.S.P. units.

According to Bakwin[3] the only form of tetany

3. H. Bakwin, "Pathogenesis of Tetany in the Newborn." Am. J. Dis. Child., LIV, 1211, 1937.

known to occur in infants after the neonatal period is that due to a deficiency of vitamin D or sunlight. On the other hand though the newborn infant has no appreciable reserve of vitamin D as shown by Teverud and Ender, the failure of vitamin D supplements to prevent the drop in serum calcium content following the ingestion of phosphate seems to be evidence against the point of view that this form of tetany is related to a deficiency of vitamin D.

The requirements for ingested vitamin D has been assumed to decline after infancy, although little experimental evidence for this supposition exists. Belief in this idea is reflected in the widespread lack of use of vitamin D preparation in childhood compared to the almost universal use in infancy. The assumption of a lesser need may be bases on the absence of rickets in childhood and on the presumption that older children get more sunshine than infants. Whether or not the fault is with vitamin D, there is abundant evidence that present customs of diet in this country

4. K.U. Teverud, and F. Ender, "The Vitamin A and D Content of the Liver of New-Born Infants." Acta. Paediat. XVIII, 174, 1936.

are not fully adequate for optimal skeletal and dental development. This is attested by the prevalence of dental caries and, in late childhood, the finding of osteoporosis. As a cause of these abnormalities a deficiency of intake of calcium, vitamin D or both substances is probably more common with the American type of diet than an intake deficient in phosphorous. At least some of these defects may be caused by inadequacy of vitamin D.

The criteria of adequacy of intake of vitamin D are fewer for children than for infants. Prevention of rickets is of no value and studies of calcium and phosphorous in the blood are of little assistance. The rate of growth might be useful, but too few studies are available in which this criterion was used when vitamin D was the only factor varied.

A criterion which has a considerable degree of usefulneww is the prevention and arrest of dental caries. Numerous observations have shown that vitamin D is an important factor in this regard.

Boyd, Drain and their co-workers[5] observed

5. J.D. Boyd, C.L. Drain, and M.V. Nelson, "Dietary Control of Dental Caries." Am. J. Dis. Child. XXXVIII, 721 (October) 1929.

rapid arrest of dental caries in children given a well rounded diet which included a quart of milk and about 350 units of vitamin D daily, the latter in the form of cod liver oil. In a recent intensive study of four children with dental decay these authors[6] n ted the effect of diets otherwise adequate but with the vitamin D intakes graduated; 0, 155 and 600 units daily were given successively to the same children. The ingestion of a good diet without added vitamin D brought about appreciable lessening of the activity of the caries during the first few weeks of the study in the fall months with the children spending much time outdoors. subsequently for a period of five months, during which the children recieved a diet of high protective value aside from its vitamin D content and through both the periods of no added vitamin D and of the 155 units addition, the caries was stationary with minimal but definite activity. It was not until the higher amount of 600 units of vitamin D had been given for nine weeks that the caries became definitely arrested.

6. J.D. Boyd, C.L. Drain, and G. Stearns, "Nature of Diet in Its Relationship to Control of Dental Caries." Proc. Soc. Exper. Biol. and Med. XXXVI, 645, (June) 1937.

The results with 600 units daily showed no advantage of this amount over the 350 units daily intake of previous experiments.

One may conclude from the various dental studies that the greatest freedom from dental caries is observed in groups of childr n receiving an adequate diet containing ample quantities of milk and 350 or more units of vitamin D daily. If the diet is suboptimal, the addition of vitamin D lessens the severity but does not prevent dental caries. Similarly, a diet otherwise adequate but lacking in vitamin D may decrease the incidence but does not prevent entirely the development of tooth decay nor provide for complete arrest of caries already present.

In support of the single massive dose method of vitamin D therapy, Bredsky et al[7] have reported in their studies of prophylaxis of dental caries in children, that a group of children receiving 600,000 U.S.P. units in the form of crystalline vitamin D_2 developed cavities at the rate of only 0.17 cavities per child

7. R.H. Bredsky, B. Schick, and H. Vollmer, "Prevention of Dental Caries by Massive Doses of Vitamin D." Am. J. Dis. Child., LXII, 1183, 1941.

while the control group acquired new cavities at the rate of 1.180 per child during the observation period.

Despite our studious avoidance of work based on animals and of questionable practical significance, it is extremely interesting in regard to vitamin D to mention in passing the work being conducted by Teemey[8] on the relation of the avitaminosis to susceptibility to poliomyelitis. He finds that the ingestion of vitamin D protects the monkey from the poliomyelitis when the virus is subsequently introduced by way of the gastrointestinal tract and that the lack of this vitamin increases susceptibility. He feels that the lack of vitamin D in infancy may leave a poorly insulinated myelin nerve sheath which can be affected by various conditions more easily than are nerves of subjects who have had adequate doses of vitamin D.

In conclusion we can say that the requirement for vitamin D begins in the 2nd. or 3rd week of life, and is greater in times of rapid growth. The premature

8. J.A. Teemey, "Ingestion of Vitamins A, B, C, and D on Poliomyelitis." Am. J. Dis. Child., LIII, 1202, 1937.

infant needs larger dosages than the full term. If cod liver oil is used the infant should be given one-half a teaspoonful per day at first and the dosage should rapidly be increased to 2 or 3 teaspoonfuls. Concentrates are much easier to give, especially to the premature whose stomach is so small. The premature will require 15-30 drops of percomorph oil daily, the full term baby 8-10 drops. In the treatment of rickets dosages of 20-40 drops daily should be used and larger doses are safe.

Chapter V

VITAMIN E

The first observation on the need of vitamin E for normal muscle metabolism was made by Evans and Burr[1] in 1928, when they permitted rats low in vitamin E to suckle and rear their young. Towards the end of the lactation period, they noticed that the majority of the apparently healthy young rats developed a mysterious malady, of which the main characteristic was a muscular paralysis and inability to right themselves when placed on their backs. One-third of the affected animals died, a small group recovered without sequellae, and about one-half continued to exhibit some evidence of paralysis even after recovery. The recovered animals usually belonged to the group most mildly affected. Feeding vitamin E to the mother prevented the disease; also the administration directly to the young was just as effective.

Although no definite disease conditions have been associated in the past with an insufficient amount

1. H.M. Evans, and G.O. Burr, "Development of Paralysis in the Suckling Young of Mothers Deprived of Vitamin E." J. Biol. Chem., LXXVI, 273, 1928.

of vitamin E in the diet, the similarity of the symptoms described in the animal dystrophic groups as compared with the findings in human beings prompted the investigation of the value of vitamin E in the treatment of muscular dystrophies and related conditions in children and adults. The assumption that vitamin E was not specific for muscular dystrophies and that the action was also as that of a stimulant to muscle metabolism, especially in the young, prompted also its rise in a number of other conditions where disturbance of muscle function was one of the prominent symptoms.

While at the present time the exact part played by this vitamin in the human dietary still remains to be determined, most of the present evidence suggests that the protective influence of vitamin E is required especially during early periods of growth, although its absence from the diet will also produce neuromuscular damage in the older subjects. The variety of changes ascribed to vitamin E deficiency would indicate that, like vitamin B complex, it is composed of many fractions, each with effective action in its own sphere.

As long as the newborn infant depends for its supply of vitamin E mainly on the reserves stored during its intrauterine existence and acquired through

placental transmission, it is plausible to assume that the anlage for such cases of muscle dystrophy has been laid down during pregnancy through dietary deficiency of the mother, for the supply of vitamin E received through maternal milk is limited and has apparently little protective value. The prematurely born infant especially will be apt to suffer because vitamin E deficiency in the mother is in itself an occasional cause of premature birth.

The extent of the deficiency, the age at which it occurs, and the lack of other vitamins may explain why, in some cases, nervous symptoms predominate, while in others the brunt of the damage seems to be borne by the muscular system. Thus, extreme deprivation of vitamin E in the offspring through maternal inability to absorb or transmit vitamin E through the placenta to the fetus may result in myatonias. The improvement occasionally seen without treatment in such cases is possibly due to improvement in diet during infancy and childhood. Less severe intrauterine deficiencies may result in cases of pseudohypertrophic muscular dystrophy. Milder forms of deprivation may become apparent in the frequently seen states of muscular hypotonia, generally poorly developed musculature, retarded growth, and slowness in

beginning to walk in cases where other causes have been ruled out.

Bicknell[2] believes that many of these diseases of the neuromuscular system may be due to relative or absolute deficiencies of vitamin E, either through dietary lack, impaired intestinal absorbtion or if the demands of the muscular and nervous systems were higher than normal, either from a hereditary disposition or from toxic influences. He feels that many obscure lesions of these systems might be explained in this way. The muscular dystrophies and amyatrophic lateral sclerosis for instance, would be interpreted as the same deficiency disease having one form in children and another in adults. In the group of myopathies of childhood he found the results of treatment with vitamin E to be remarkable; every patient except one improved who was treated for more than six weeks with one-half ounce of whole wheat germ, twice daily.

However, the instances of thorough clinical applications of this vitamin in infancy and childhood

2. F. Bicknell, "Vitamin E in Treatment of Muscular Dystrophies and Nervous Diseases." Lancet, I, 10, 1940.

are as yet too isolated and unconfirmed to merit its enthusiastic acceptance by the practicioner, and a final verdict as to its ultimate usefulness must be held in abeyance at this time.

Chapter VI

VITAMIN K.

The recent phenomenal progress in the knowledge of the antehemorrhagic factor, called vitamin K by Dam and Schønheyder,[1] and its influence on the prothrombin activation of the blood have brought into clear relief the etiologic relationship in which this vitamin stands to the formerly obscure bleeding tendency frequently encountered in the neonatal period.

The low prothrombin level of the blood as determined by the micro prothrombin method by Kato and Poncher[2] in newborn infants satisfactorily explains the pathogenesis of hemorrhagic disease of the newborn. This may be expressed clinically as hemorrhage into the gastrointestinal tract (melena, hematemesis) or bleeding from the cord or genito-urinary tract. While in many cases of intracranial hemorrhage birth trauma is the

1. H. Dam, and F. Schønheyder, "A Deficiency Disease in Chicks Resembling Scurvy." Biochem. J. XVIII, 1355, 1934.

2. K. Kato, and H. Poncher, "The Prothrombin in the Blood of Newborn, Mature and Immature Infants." J.A.M.A., CXIV, 749 1940.

precipitating factor, the severity of the bleeding may be induced by a lowering of the prothrombin level of the infants blood.

Quick and Grossman,[3] from their study of the prothrombin concentration of the blood of newborn infants conclude that at birth the prothrombin in the baby's blood is relatively high but often drops precipitously during the first days of life and then, strangely, is restored spontaneously. The frequency with which the prothrombin falls in normal infants makes it highly probable that all infants are in danger of hemorrhage during the first few days of life. In the recognized neonatal hemorrhagic disease it is likely that the fundamental cause is a delay in the spontaneous restoration of the prothrombin level. Consequently, if an infant should bleed accidentally the small loss of blood may be sufficient to reduce the already low prothrombin level to a point at which hemorrhage becomes difficult to control and a vicious circle is initiated. The cause of the prothrombin deficiency seems to be an

3. A.J. Quick, and A.M. Grossman, "Nature of Hemorrhagic Disease of the Newborn: Delayed Restoration of the Prothrombin Level." Am. J. Med. Scien., CXCIX, 1 (Jan.), 1940.

inadequate storage of prothrombin or vitamin K in the fetus. Presumably as soon as the baby is born the physiologic demands promptly exhaust the available prothrombin. As there is apparently a reserve neither of vitamin K nor of prothrombin, a marked decrease of the latter occurs. The condition is due to a lack of vitamin K, for the prothrombin can be restored promptly to normal by giving the baby an oral concentrate of this vitamin and the serious fall in concentration can be prevented.

Since the drop in prothrombin is a manifestation of vitamin K deficiency, the rise must be due to a supply of this vitamin which was not present at birth and since the feed intake during the first few days is scarcely sufficient another source must be responsible. Bacteria readily synthesize vitamin K and while at birth the intestinal contents of the baby are sterile, in a short time, especially if the baby is put to the breast early, bacteria are introduced and an intestinal flora is established. The time relation between the beginning of bacterial activity and the restoration of the prothrombin level makes it appear likely that the available vitamin K is of bacterial origin. The practice of putting the baby to the breast early may serve the

primary purpose of introducing harmless but useful bacteria into the alimentary tract and thus be a factor in diminishing the incidence of certain postnatal hemorrhagic tendencies.

The plasma prothrombin of the newborn infant can be significantly raised by feeding vitamin K concentrate to mothers either for a prolonged period prior to delivery or during labor. Sage[3] and his co-workers concluded that the time when this vitamin was administered to the mother by the intra-veneus route was inmaterial. Whether it was given 24 hours or 5 minutes before delivery the prothrombin time of the cord blood was practically identical. They used 1 mgm. of synkamin in a single dose. The same result but to a lesser degree, can be obtained by the feeding of vitamin K to the newborn infant. When it is considered that 20-40% of neonatal deaths are associated with cerebral hemorrhage and that the low plasma prothrombin level may often be a factor in these hemorrhages, vitamin K should be a definite therapeutic weapon in the armamentarium of the pediatrician.

It has been demonstrated that the administration

3. Behlender, G.P., Rosenbaum, W.M. and Sage, E.C., "Ante-partum Use of Vitamin K in the Prevention of Prothrombin Deficiency in the Newborn." J.A.M.A., 116, April 1941.

of vitamin K, either to the mother at some time before delivery or to the newborn is especially indicated in cases of maternal toxemia; in cases of difficult or instrumental delivery; where breast feeding is not possible, where any cerebral symptoms develop during the first few days of life; in cases of hemorrhagic diathesis, icterus gravis neonatorum, hydrops congenitus and anemia neonatorum, and where an operation is necessary on the newborn.

Grossman[5] has recently reviewed the uses of vitamin K in infancy and childhood. He stated that aside from its pre- or postnatal use in the newborn, vitamin K therapy is also indicated in those conditions of hemorrhage or potential hemorrhage in which there is a definite hypoprothrombinemia. Prothrombin metabolism is interfered with when:

1. Vitamin K is inadequate in the diet.
2. Bile is not present in the upper intestinal tract.
3. Fat digestion is impaired.
4. Normal mucosa of the upper intestinal tract is destroyed.

Liver function is impaired.

5. A.M. Grossman, "Vitamin K for the Pediatrician." J. Pediat., XVI, 239, 1940.

On these grounds the author is of the opinion that all cases in which there is congenital obstruction to the outflow of bile will present low prothrombin concentrations and should be given vitamin K to prevent a hemorrhagic diathesis. All cases of prolonged vomiting, especially hypertrophic pyloric stenosis will be in jeopardy of hemorrhage, and any surgery attempted during the first week of life should include a preoperative course of treatment with vitamin K.

But the use of this vitamin is still rather new and in our survey of the literature on this subject did not find any conclusive work on the minimal requirements. However, judging from the work of Sage et al,[6] it seems probable that a single injection of synkamin would probably increase the prothrombin content of the blood as much as repeated doses would in the course of a day or two.

6. Bohlender, G.P., Rosenbaum, W.M. and Sage, E.C., op. cit..

Chapter VII

SUMMARY

The vitamins are of importance throughout infancy and childhood. Their position as a growth factor should be reemphasized. They are specific for the prophylaxis and cure of several not uncommon disorders encountered by the general practicioner and pediatrician; their use as a valuable adjunct in many other diseases has been firmly established.

It is less the normal breast-fed infant started early on a jucicious regimen of solid foods that is in danger of a vitamin deficiency or is in serious need of the routine benefits of fish-liver oils and orange juices. Rather, it is the premature, the bottle-fed, the infants and children of parents in the lower economic strata and these debilitated by enteric or other infections that are predisposed to the avitaminoses. Of like importance, and as frequently encountered as the conditions produced by inadequacy of the extrinsic supply, are those dependent on the impaired absorption or utilization engendered by a disordered metabolism.

Despite voluminous literature on the subject, there has as yet been no clear demonstration that the

administration of the vitamins far in excess of bodily needs produces greater resistance to disease than the ingestion of quantities just sufficient to meet normal metabolic requirements.

Diagnosis and treatment of the deficiency states is obviously a medical problem and requires specific therapy. Pills purporting to contain multiple letter combinations of vitamins do not suffice. Specific nutritional biochemicals, together with adequate supporting therapy and a suitable diet, are necessary for effective treatment of vitamin deficiency syndromes in infancy and childhood.

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