The discovery of vitamin K, its biological functions and therapeutical application

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The discovery of vitamin K arose from some studies on the cholesterol metabolism of chicks carried out during the years 1928-1930 in the Biochemical Institute of the University of Copenhagen. It was then already known that rats, mice, and dogs can synthesize cholesterol but some experiments had been published which seemed to show that chicks could not thrive on a diet from which the sterols had been removed by extraction. When these experiments were published by Gardner and Lander in 1914, the role of fat-soluble vitamins was not very well recognized, and I therefore found it interesting to repeat them using artificial, practically sterol-free diets to which vitamins A and D were added in the form of sterol-free concentrates made from cod-liver oil, or of small amounts of cod-liver oil of known cholesterol content. Chicks were reared on such diets for different lengths of time from the day of hatching, and the amount of cholesterol in their excretions and their body was determined and compared with the cholesterol content in newly hatched chicks from the same litter. It was thereby found that a considerable part of the cholesterol which the newly hatched chick has taken over from the egg yolk disappears during the first 2 or 3 weeks, whereafter cholesterol is formed in increasing amount as the body weight increases. Chicks therefore are able to synthesize cholesterol, just as well as are rats, mice, and dogs, and they are also able to break it down.

More interesting than this finding was, however, an unexpected symptom which showed up in some of the chicks which were kept on the diet for more than 2 or 3 weeks. They got hemorrhages under the skin, in muscles or other organs, and blood occasionally taken out for examination showed delayed coagulation.

The lack or low content of cholesterol in the diet could not be the cause of the hemorrhages, since the experiments showed that chicks can synthesize cholesterol. Furthermore the hemorrhages also appeared in chicks which received a daily supplement of cholesterol.

The low amount of fat in the diet could, apparently, also be ruled out as a
cause of the symptom since it was found that linseed oil and triolein could not prevent its appearance. It did not seem likely either that the tendency to hemorrhage was a manifestation of scurvy, even though the artificial diet had not been supplemented with vitamin C. Other authors had already reported that chicks do not require vitamin C, and daily ingestion of lemon juice to a few of the chicks also proved to be ineffective.

In 1931 the hemorrhagic disease in chicks was described by a group of Canadian workers, McFarlane and others at the Ontario Agricultural College. They reared chicks on artificial diets in order to examine their requirements of vitamins A and D, and they observed hemorrhages and delayed clotting of the blood when identification bands were inserted in the wings. The hemorrhages appeared when the diet contained ether-extracted fish or meat meal as the source of protein, but not with ordinary fish or meat meal. They did not follow these observations further.

At this stage of the development I had to interrupt the work with chicks because of absence from my laboratory in Copenhagen until the fall of 1933.

In the meantime Holst and Halbrook at the University of California had also observed the disease and found that it could be prevented by fresh cabbage. They drew the rather sweeping conclusion that the protective factor in the cabbage was vitamin C, and that previous claims to the
effect that chicks do not need this vitamin in their diet, were incorrect.

Shortly thereafter, pure vitamin C became available, and when taking up
the work again, I could easily show that parenteral injections of ascorbic acid
failed to prevent the disease, thus excluding the possibility that the disease
had anything to do with a destruction of vitamin C in or poor absorption of
this vitamin from the intestine under the artificial dietary regime.

The salt mixture could be varied considerably without influence on the
disease, and wheat germ oil was without protective effect, whereas a high
content of cereals and seeds in the diet prevented the symptom. It was there-
fore safe to announce that the new experimental disease was due to the lack
of a hitherto unrecognized factor in the diet. This was done in 1934.

Then a number of animal organs and plant material were examined for
their ability to protect against the disease and it was found that green leaves
and hog liver were among the most potent sources. It was also found that the
factor was fat-soluble, and in 1935 it was characterized as a new fat-soluble
vitamin and given the designation vitamin K. The letter K was the first one
in the alphabet which had not, with more or less justification, been used to
designate other vitamins, and it also happened to be the first letter in the
word "koagulation" according to the Scandinavian and German spelling.

The existence of vitamin K was promptly confirmed by Almquist and
Stokstad at the University of California, Berkeley.

In the following few years an intense study was carried out in Copenhagen
in order to find out how the new vitamin acted on the blood clotting, how it
could be concentrated and whether it played any role in other animals and in
humans. In this work I was aided by several co-workers.

Almquist and co-workers also continued their work at Berkeley, mainly
on the concentration of the factor.

The hemorrhages in vitamin K deficiency develop in this way that minute
vascular lesions caused by minor mechanical trauma are not closed by rapid
clotting, as is the case in normal animals. This causes a continuous oozing of
blood from the impaired region.

According to the accepted theory the process of blood coagulation may be
separated into two stages.

1) Prothrombin + Thromboplastin + Ca $\rightarrow$ Thrombin.

2) Fibrinogen + Thrombin $\rightarrow$ Fibrin.

Fig. 2. Theory of blood coagulation.
(1) The activation of a proenzyme, Prothrombin normally present in blood plasma, into an enzyme, Thrombin, by the action of Thromboplastin or Thrombokinase as it is also called. Thromboplastin occurs in tissue cells and in blood platelets (thrombocytes) and comes in contact with plasma when tissue is injured or when thrombocytes disintegrate through adherence to the surface of a wound. Calcium ions are necessary for this part of the process: the thrombin formation.

(2) The conversion of Fibrinogen into Fibrin by the action of thrombin.

It is easy to show that it is prothrombin and no other component which is lacking when vitamin K has been withdrawn from the diet. It can also be shown that prothrombin precipitated from blood plasma of normal chicks can bring the coagulation power back to normal when added to blood from vitamin K deficient chicks. (This was shown by Dam, Schørnheyder and Tage-Hansen, 1936.)

The use of chicks in the study of vitamin K deficiency has the advantage that these animals develop the disease very easily and it also simplifies the examination of the blood coagulation since in chicks and other birds thrombocytes do not play any important role in furnishing the blood with thromboplastin, as is the case in mammals.

Thus it is easy to collect a sample of blood from an artery and centrifuge and treat it in different ways without risk of spontaneous clotting. The only prerequisite is that admixture of tissue juice is carefully avoided.

In order to produce the disease in chicks it is necessary not only to give them a vitamin K free diet, but also to keep them under very clean conditions so that they do not soil their food and water with feces. Almquist and Stokstad were the first to report that vitamin K can be formed by putrefaction so that even when no vitamin K is present in the diet, the feces of chicks will contain it.

The reason why these animals so easily suffer from the disease when deprived of vitamin K may be due to the fact that in chicks the large intestine is short as compared to that of rats and rabbits. Vitamin K formed by intestinal bacteria is therefore not absorbed to any great extent in the chick.

An exact estimation of the clotting power of the blood reveals the fact that the vitamin K deficiency disease begins to develop a few days after vitamin K has been taken away from the diet, but the full development, i.e. reduction of the prothrombin to about 1 per cent of the normal value, requires a longer time, say 14 to 28 days.
Fig. 3. Relation of prothrombin to the ingestion of a test substance (dried spinach). The substance was given on three days in succession.

The prothrombin level seldom falls to zero and therefore coagulability is not completely lost. It is sometimes found that hemorrhages in vitamin K deficient chicks stop spontaneously and are resorbed without alteration of the diet and without increase of the prothrombin content.

Estimation of vitamin K can best be carried out by determining the prothrombin content of blood before and after the ingestion of the substance to be tested and running a similar experiment with a standard vitamin K preparation.

I shall not bother you with a detailed account of the methods for prothrombin determination but just mention a few principles which are or have been in use.

1. The method of Smith, Warner, and Brinkhous. They first remove the fibrinogen from the plasma by addition of a very small amount of purified thrombin. The excess of added thrombin disappears by itself on standing for about 15 minutes. Then the prothrombin is converted into thrombin by the addition of thromboplastin, and finally the activity of the thrombin is measured against a pure fibrinogen solution. This method is called a two-stage method because the two stages of the coagulation process: thrombin formation and fibrin formation are separated. It is believed to be very accurate but is more cumbersome than the usual clinical method.

2. Quick’s method. This is a one-stage method: you simply add a large quantity of thromboplastin to the plasma or blood and observe the coagulation time. Under these circumstances the coagulation time is largely deter-
mined by the amount of prothrombin and is therefore called the prothrombin time.

3. One can also take advantage of the circumstance that within certain limits low prothrombin can be compensated by using a higher concentration of thromboplastin. This is the basis of the method which was originally used in my laboratory in Copenhagen and was first introduced by Schønheyder.

When these different methods are used for human or mammalian blood it is necessary to prevent spontaneous clotting of the blood by thromboplastin set free from the platelets. This is done by adding oxalate or citrate to the blood thus removing the calcium, and again adding calcium when the conversion of prothrombin into thrombin shall begin. It is also possible to make use of heparin.

The unit for vitamin K activity was originally defined in our laboratory as that quantity which must be given daily per gram body weight of the chick in three days in order to bring the prothrombin value up from a very low level to the normal value. Now when a series of pure substances with high vitamin K activity are available, it is a natural thing to define the unit by means of one of these substances or to express the activity in terms of micrograms of one of the two natural K-vitamins which I shall mention later.

In plants vitamin K is found principally in all kinds of green leaves; leaves which have grown in the dark and therefore have not formed chlorophyll are poor sources. Tomatoes are a good source, but otherwise most fruits contain little vitamin K. Ripe cereals, beans and peas contain little. Carrots, potatoes and beets are practically free from vitamin K. Saprophytes such as mushrooms contain very little if any. Vitamin K is thus largely associated with chlorophyll, but it does not necessarily disappear from a plant organ when the chlorophyll disappears. It remains in tomatoes after they become red and in leaves after they become yellow in the fall. Yeast does not contain vitamin K but certain bacteria are very rich in this vitamin. B. coli is much richer than acidophilus. Its function in these organisms is unknown, but in the green plant it may have something to do with the photosynthetic process. It occurs in the same elements of the plant cell as chlorophyll, xanthophyll, and carotene, namely in the chloroplasts. Vitamin K from green plants is called K1. Chemically it differs slightly from vitamin K formed by putrefaction which is called K2. This difference was first noticed by Doisy and co-workers.

In the animal organism vitamin K does not occur as abundantly as in plants. In chickens small quantities only are deposited in the different organs or in the eggs. The mammalian organ which hitherto has been found to contain
most vitamin K is the liver of pigs. Cow’s milk and human milk are rather poor sources. Feces are rich in vitamin K formed by the putrefaction bacteria in the large intestine.

Before I proceed to a more detailed discussion of the mode of action of vitamin K, it will be convenient to consider briefly the most essential features of its chemistry.

Vitamin K can be extracted by fat solvents from dried leaves, dried alfalfa for instance. It can be concentrated by the removal of chlorophyll by selective adsorption, by chilling of an acetone solution of the remaining material, whereby crystalline non-active substances are removed, by molecular distillation at a pressure of one thousandth of a millimeter mercury and 115-140 degrees centigrade, whereby the vitamin passes up on the condenser, and final purification by repeated chromatographic adsorption. The preparation of pure vitamin K from green leaves was first reported by Dam, Karrer, and co-workers in 1939. The pure vitamin is a yellow oil. It consists of carbon, hydrogen, and oxygen, gives a characteristic color reaction with sodium ethylate and shows an absorption spectrum in the ultraviolet.

The elucidation of its constitution was accomplished by Doisy and co-workers, and by Fieser and co-workers.

Doisy and co-workers also prepared pure vitamin K from putrefied fishmeal and showed that this substance was crystalline at room temperature. It melts at 54 degrees centigrade and gives a color reaction and an ultraviolet spectrum similar to that of K.

Both substances are derivatives of 1,4-naphthoquinone. They are easily destroyed by saponification and by light.

Vitamin K is 2-methyl-3-phytyl-1,4-naphthoquinone (phytyl is the radical of the high-molecular alcohol phytol which also forms a part of the chlorophyll molecule). Vitamin K has a similar structure but the long side chain is different from phytol; it is longer and has more double bonds.

The methyl is essential for activity, but not the phytol group. In accordance herewith 2-methyl-1,4-naphthoquinone has a high activity, as first reported by Ansbacher and Fernholz, 1939. This substance is now official in the U.S. Pharm. under the name of "Menadione". The hydroquinones of the natural K-vitamins as well as of menadione are also active and so are their esters. Some of these (artificially prepared) esters are water soluble and useful for parenteral injection. This applies to the diphosphate "Synkayvite" described by Lee and Foster, for instance.

Almquist and Klose reported, 1939, that the orange pigment Phthiocol,
of the tubercle bacillus has some vitamin-K activity. Phthiocol is 2-methyl-3-hydroxy-1,4-naphthoquinone.

We will now return to the **mode of action** of vitamin K in the animal organism.

When the vitamin is given intravenously, it is possible to study the effect at different intervals from the moment of introduction into the bloodstream. It is thereby revealed that the action does not set in instantaneously but requires a certain time for its development. If the prothrombin content is about 1 per cent of the normal value at the starting-point, it takes about 5 hours to raise it to 50-100%, assuming that a sufficient amount of vitamin K is injected.

The prothrombin level is normal on the day after injection, thereafter it again returns to low values.

When vitamin K is added *in vitro* to the blood from a K-free animal, no improvement of the prothrombin content is observed, even when the vitamin has remained in contact with the blood for many hours at body temperature before the clotting power is tested. This observation suggests that the action of the vitamin takes place within the tissue cells.

Andrus, Lord, and Moore, 1939, excised the liver in normal dogs and studied the prothrombin level with and without ingestion of vitamin K and bile salts. They found that the blood prothrombin decreased in both instances, indicating that the liver is necessary for the action of vitamin K.

Several other observations also show that the liver is the organ concerned with prothrombin formation. Thus Warner found (1938) that removal of 5 of the liver in rats resulted in a decrease of prothrombin. Intoxications in-
Fig. 5. Prothrombin of chicks at different intervals after intravenous injection of vitamin-K, emulsions. (Short duration of experiment.) (From H.Dam & J.Glavind, Z.Vitaminforsch., 10 (1940) 71.)

Ordinate: 100/R. Abscissa: hours.

- 0.05 unit K per g body weight (Chicken No. 6366).
- 0.5 unit K per g body weight (Chicken No. 5511).
- 1 unit K per g body weight (Chicken No. 5509).
- 5 units K per g body weight (Chicken No. 5681).
- 50 units K per g body weight (Chicken No. 6368).

volving severe damage to liver tissue also lead to a fall in prothrombin. This is found, for instance, after the intake of chloroform (Smith, Warner, and Brinkhous, 1937). Vitamin K does neither prevent nor cure hypoprothrombinemia of this origin.

Further it is known that vitamin K does not alleviate the prothrombin deficiency in patients whose liver parenchyma is severely damaged.

On this stage I shall mention briefly the substance dicoumarol which is formed in so-called "spoiled" sweet clover hay, and is now prepared synthetically. Dicoumarol causes low prothrombin probably by reducing enormously the prothrombinogenic action of vitamin K in the liver.

As to the manner in which vitamin K affects the formation of prothrombin, two alternatives may be considered. The first is whether vitamin K is a constituent of prothrombin. Prothrombin is a protein. It accompanies the globulins in many precipitation reactions and does not dialyse. Therefore, and because of the time factor in the development of the action, vitamin K cannot be identical with prothrombin. But one could imagine that vitamin
K might enter the prothrombin molecule as a prosthetic group, just as heme does in hemoglobin. However, this is not very likely. If vitamin K were present in the prothrombin molecule, one would expect prothrombin itself to act as vitamin K, so that the per-oral ingestion of prothrombin would cure the prothrombin deficiency of K-free animals. Experiments in which we precipitated prothrombin from large amounts of normal hen’s plasma (at pH 5.3) and gave it to small chicks living on a vitamin-K-free diet, did not show any definite vitamin K activity. The most likely explanation therefore is that vitamin K merely enables the liver cells to produce prothrombin.

The mechanism of this action is unknown. It is possible that the redox properties of the quinone groups play a role in an enzyme system which has to do with the formation of prothrombin.

The presence of a vitamin-K-like substance in thrombin has been claimed by Lyons (1945) but this is still unconfirmed.
As to vitamin K deficiency in different species of animals the following may be said: While the disease is most easily and regularly developed in chicks, young geese, and ducks, by giving them a vitamin-K-free diet, some rats may become just as ill as chicks, while in a group of rats many individuals may be resistant for a very long period of time. This is probably due to individual differences in the supply of vitamin K from bacteria in the large intestine. Incorporation of a large amount of mineral oil in the diet of rats will minimize the absorption of vitamin K and thus facilitate the development of the deficiency disease.

Rabbits have been observed to develop the disease only to a moderate degree. These animals as well as rats eat feces directly from the anus during the night and thereby partially protect themselves against vitamin K deficiency.

The absorption of vitamin K from the intestine is a point of considerable interest. Several investigators have observed hemorrhages in dogs and rats in which the flow of bile into the intestine had been cut off by ligature of the bile duct or by a complete bile fistula through which the bile is made to flow steadily out of the body (Hawkins and Whipple, 1935; Vadsten, 1936; Greaves and Schmidt, 1937). Hawkins and Brinkhous (1936) showed that the bleeding tendency of bile-fistula dogs is due to a low prothrombin level. Greaves and Schmidt (1937) showed that the deficiency in blood coagulation resulting from bile fistula in rats could be eliminated by giving these rats a diet very rich in vitamin K. Such experiments suggest the importance of bile for the proper absorption of vitamin K. In my laboratory in Copenhagen we have ligated the ductus choledochus in chicks and cured the resulting coagulation deficiency by intravenous injection of vitamin K. It could be shown that the effect of a given dose of vitamin K is quantitatively the same whether the vitamin K deficiency had been developed by means of a K-free diet or by ligature of the choledochus.

The first time that a hemorrhagic disease in man was recognized as a K-avitaminosis was in connection with the cholemic bleeding tendency. This bleeding tendency formerly constituted a great danger in operations on patients suffering from obstructive jaundice, say from gall-stones or a tumor. This was found independently by Warner, Brinkhous, and Smith, by Butt, Snell, and Osterberg, and by Dam and Glavind in the early part of 1938. Since then, the practical utilization of vitamin K in surgery has been tried by a large number of surgeons and its value has been fully established. It is possible, by suitable vitamin K treatment to eliminate completely the risk of bleeding in such
patients, provided, of course, that the case is not complicated by severe damage of the liver so that vitamin K cannot act.

The bile acids are the constituents of bile which aid in the absorption of all fat-soluble substances. If the treatment of such patients is carried out with natural fat-soluble vitamin K given by mouth, it is necessary to give bile acids, say desoxycholic acid, simultaneously with the vitamin in order to secure the absorption of vitamin K. It is easier to use one of the more or less water-soluble vitamin K active substances, which can be absorbed without bile or may be given by parenteral injection (10 mg vitamin K the day before operation, repetition several times during the first two weeks after the operation).

Overdosage with vitamin K does not afford the danger of a too high coagulability of the blood since vitamin K cannot raise the larothrombin content much above the normal value. The fact that vitamin K cannot act when the liver parenchyma is sufficiently damaged, forms the basis of a liver function test.

A bleeding tendency due to reduced absorption of vitamin K from the intestine can also be observed in certain intestinal diseases, where profuse diarrhoea occurs and the intestinal mucosa is damaged. This has been found in cases of sprue, for instance, where the absorption of fat is greatly diminished (Hans Hult, 1939; Mayo Clinic, 1939), or in ulcerative colitis.

The purely alimentary K-avitaminosis in man, that is, a lack of vitamin K due to an insufficient amount of the vitamin in the diet, is a rare disease on account of some vitamin K being supplied by intestinal bacteria. Experiments with a completely K-free diet have not been made with humans, but a moderate prothrombin deficiency which could be treated with vitamin K has been reported in some patients living on a very restricted diet - coffee and doughnuts, for instance (Kark and Lozner, Harvard University and Boston City Hospital, 1939).

A rather interesting occurrence of vitamin K deficiency is that of the newborn infant.

Low coagulation power of the blood of newborn babies was occasionally reported many years ago. Whipple described such cases in 1912 and found low prothrombin in a case of melena neonatorum. The fact that a low prothrombin level which may be raised by treatment with vitamin K regularly occurs in newborn infants in the first week after birth was first recognized by Waddell and co-workers at Virginia University Hospital and independently found by several other workers - also at the University of Copenhagen.
This finding has been further studied by a large number of investigators.

Fig. 7 shows the coagulation time found by means of a particular micro-method for 191 apparently normal and 21 hemorrhagic babies. The abscissa represents days after birth. The points indicated by circles are the cases with actual bleeding. There is a marked prolongation of the coagulation time right at birth, but the prolonged clotting times are seen most frequently on the third day. Thereafter they decline toward normal values.

Fig. 8 shows the same over a longer time; the abscissa represents months. The frequency of cases with bleeding is said to be about 1 per cent of all newborn babies, but this represents only the number of cases with easily detectable bleeding. A closer examination for hemorrhages reveals a much higher figure.

The bleeding may come from the umbilicus, the intestinal tract, the skin, or the cerebral vessels.

Treatment with vitamin K raises the prothrombin to approximately normal values in 24 hours (Fig. 9).

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Fig. 7. Ordinate: Prothrombin time in seconds. Abscissa: Age in days.
1 normal infants; 0 infants with hemorrhages.
(From P.Plum & H.Dam; Ugeskrift Læger, 102 (1940) 1029.)
Fig. 11 shows the effect of giving parturient mothers vitamin K some hours before delivery. Fig. 10 represents a similar experiment without vitamin K treatment.

The treatment does not result in completely normal prothrombin levels.
in all cases, but the values lie always between 20 and 100 per cent of the
normal value for adults, that is, above the danger zone.

How important the treatment with vitamin K is in preventing death

Fig. 10. Ordinate: Prothrombin time of the newborn in seconds. Abscissa: Age in days. (From E. H. Larsen & P. Plum, *Ugeskrift Læger*, 102 (1940) 1038.)

Fig. 11. Ordinate: Prothrombin time of the newborn in seconds. Abscissa: Age in days. (From E.H.Larsen & P.Plum, *Ugeskrift Læger*, 102 (1940) 1038.)
among the newborn, during or shortly after birth, appears from statistics presented, for instance, by Beck in Brooklyn and Hellman at Johns Hopkins Hospital, according to which the treatment of mothers has cut the total death rate among the newborn from 4.6 percent without treatment down to 1.8 percent in the treated groups.

We will now consider the cause of the lack of vitamin K in the infant.

The investigations of Tage-Hansen and of Thordarson in Denmark have shown that the mother’s prothrombin content is increased at the end of pregnancy; the increase may amount to 50 to 100 per cent of the value before pregnancy. This does not suggest that the mothers lack vitamin K. Nevertheless, the newborn child is K-deficient. The simplest explanation of this is that the placenta does not let natural fat-soluble vitamin K pass freely into the circulation of the fetus.

That the prothrombin level decreases further during the first days after birth is not surprising because the supply of vitamin K is low. This is due to the initial sterility of the large intestine and to the low intake of milk in the first few days.

The reason why the prothrombin level normally rises again in the course of some days is to be sought in the increasing bacterial flora together with the increasing volume of the contents of the large intestine, whereby the bacteria have more substrate to act upon.

Milk itself contains only little vitamin K but the daily vitamin K requirement of the baby is very low (about 1 to 10 gamma per day), so that it may be that the low vitamin K content of the milk nevertheless has some importance.

There are some other fields where vitamin K therapy may become necessary. Thus in treatment with sulfa drugs the intestinal flora may become so reduced that the supply of vitamin K from this source is largely cut off. If the diet does not contain enough vitamin K, bleeding tendency may arise.

Excessive and uncontrolled intake of mineral oil may interfere with the absorption of vitamin K.

Salicylate treatment may lead to a hypoprothrombinemia which can be compensated by vitamin K. The mechanism of the action of salicylates on the prothrombin level has not yet been elucidated.

It has been claimed by some authors that hemoptysis in patients with pulmonary tuberculosis is associated with low prothrombin and should be treated with vitamin K. I believe that this is wrong. An investigation of this question was undertaken in Copenhagen by some of my associates (Gyntel-
berg; Plum and Poulsen), and it was not possible to find either hypopro-
thrombinemia or any beneficial effect of vitamin K treatment of such cases. It is also difficult to understand why there should be vitamin K deficiency in this disease.

A. Palladin (1945) has claimed that vitamin K acts in almost any kind of hemorrhagic disease; but this claim seems not to be substantiated by controlled experiments.

Menadione, the official substitute for vitamin K has been reported to interfere with the bacterial formation of lactic acid from carbohydrates, and it has been suggested that it might counteract dental caries when incorporated in chewing gum. Other quinones inhibit lactic acid formation by bacteria, without having vitamin K activity. It therefore seems unlikely that vitamin K as such should play any rôle in the prevention of caries.

As matters stand at present it is safe to say that vitamin K therapy is relevant against diseases which incur bleeding tendency due to low prothrombin whereas its use against other hemorrhagic diseases is lacking a secure foundation.