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Recent Studies on Vitamin K

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The term vitamin K designates a group of methylnaphthoquinone derivatives that prevent a haemorrhagic state due to defective clotting of the blood. Vitamin K_1 from green leaves, phylloquinone, is 2-methyl-3-phytyl-1:4-naphthoquinone. Vitamin K_2 from bacteria has a difarnesyl residue instead of the phytyl side chain.

The artificially produced 2-methyl-1:4-naphthoquinone (menaphthone, menadione) and certain of the water-soluble esters of its hydroquinone are commonly used instead of the more expensive naturally occurring vitamin K_1 and K_2. The list of related compounds with more or less pronounced vitamin K activity is comprehensive.

Mechanism of blood coagulation

It is common knowledge that the coagulation defect that arises when vitamin K is lacking is related to the first stage of the coagulation process, namely the formation of thrombin from its precursor prothrombin. It is safe to say that in vitamin K deficiency the ' prothrombin activity ' is low, but whether this is due to lack of prothrombin itself or to some other factor acting together with prothrombin is more difficult to decide with certainty, because of the intricate development that the theory of blood coagulation has undergone in the past 10 years.

The newer theories are mainly based on the observations of Owren (1949, 1951, *a*, *b*), Owren & Aas (1951), Quick & Collentine (1950, 1951), Quick & Stefanini (1948), Ware, Guest & Seegers (1947), Fantl & Nance (1946) and others, but many other facts about the blood-clotting process are still to be accounted for, and at present no theory can be considered as final. The newer theories maintain the division of the process into two stages: the formation of thrombin and the transformation of fibrinogen into fibrin. The terms thromboplastin and prothrombin are still used, but it is assumed that thromboplastin acts, not directly on prothrombin, but on proconvertin, which it activates to convertin. Aided by accelerin, which in turn is formed from proaccelerin, perhaps by the influence of thrombin, convertin should then transform prothrombin into thrombin. Proaccelerin is particularly unstable on storage. It is likely that it consists of several factors.

Prothrombin is the factor that sets the absolute limit for the amount of thrombin to be obtained from a given plasma under optimal conditions. In order to identify a coagulation factor as prothrombin it is necessary to let the transformation into thrombin occur quantitatively without the presence of fibrinogen and then to test the thrombin obtained against a fibrinogen solution pure enough not to contain substances that may give rise to the formation of thrombin during the transformation of fibrinogen into fibrin. This is not easily done. It has therefore occurred that even an outstanding worker such as Owren (1951*a*) has mistaken prothrombin for proconvertin and vice versa.

Attempts to determine prothrombin merely by the prothrombin time or even by the classical two-stage method of Smith, Warner & Brinkhous (1937) will only result in an estimate of the combined activity of prothrombin and several other factors. Supposedly more accurate methods devised by Owren & Aas (1951) are elaborate.

In spite of this, it is easy to demonstrate that vitamin K deficiency involves the lack of more than one coagulation factor. This has been done by Dam & Søndergaard (1948), who compared plasma from vitamin K-deficient chicks with plasma from chicks treated with dicoumarol (or with coumachlor, Søndergaard & Dam, to be published). Coumachlor is the active principle of a rodenticide. It is 3-(α-phenyl-β-acetylethyl)-4-hydroxycoumarin. It acts in the same way as dicoumarol but is much more potent. The two kinds of plasma were mixed in varying proportions and the prothrombin times of the mixtures determined by the methods of Larsen & Plum (1941).

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It was found that addition of dicoumarol or coumachlor plasma to vitamin K-free plasma shortens the prothrombin time of the latter and vice versa. However, no mixtures of the two plasmas had normal prothrombin times. This is interpreted as follows: The two kinds of plasma have in common the lack of one and the same factor, perhaps prothrombin. But besides that, vitamin K-deficient plasma lacks another factor, which is present in dicoumarolized plasma. Dicoumarolized plasma lacks a third factor, which is present in vitamin K-deficient plasma.*

The factor in dicoumarol plasma that shortens the prothrombin time of vitamin K-deficient plasma has arbitrarily been called the delta-factor (Sørbye, Kruse & Dam, 1950*a*). It is produced independently of the presence or absence of vitamin K in the diet.

It would be of interest to know the position of the three factors in the new coagulation scheme. They are all easily adsorbed on strontium or barium carbonate and can be eluted with sodium citrate; the kappa- and delta-factors have no influence on the prothrombin time of fresh or stored plasma from normal chicks. Because of the latter fact they cannot be identical with the most labile factor found by Owren in human plasma (proaccelerin, factor 5). Further, a preparation of the most labile factor from chicken plasma†, probably corresponding to Owren's proaccelerin, does not shorten the prothrombin times of either vitamin K-deficient or dicoumarolized chicken plasma.

If the factor that is low in vitamin K-deficient as well as in dicoumarolized plasma is prothrombin, there is some reason to believe that the kappa-factor is proconvertin, since Owren has reported that proconvertin (together with prothrombin) is low in dicoumarolized plasma.

However, Koller, Loeliger & Duckert (1951) have announced a factor 7, which seems to be identical with proconvertin, but Koller, Loeliger, Duckert & Hu-Wang (1952) find that proconvertin depends upon vitamin K. This could mean that the factor lacking in both vitamin K-deficient and dicoumarolized plasma is proconvertin.

More experimentation is necessary to settle these questions.

In the further course of this investigation (Sørbye *et al.* 1950*a*, *b*, 1951, 1952; Kruse, Sørbye & Dam, 1952) a series of labile coagulation factors has been shown to exist in chicken plasma. They depend upon the presence in the diet of unknown, fat-soluble and water-soluble factors, different from vitamin K.

The influence of vitamin K on the prolonged prothrombin time caused by dicoumarol (or coumachlor) treatment

It has been known for several years that vitamin K_1, in contrast to its substitutes (menaphthone, Synkavit and the like) is able to counteract the effect of dicoumarol.

* There is a difference between the range of optimal calcium concentrations for the clotting of the two plasmas, but this does not affect the interpretation given.

† This factor (or fraction) is prepared by removing prothrombin, delta- and kappa-factors from normal chicken plasma, precipitating fibrinogen by addition of alcohol and adjusting the pH of the filtrate to 5·5, whereby a precipitate of the most labile factor is formed. This precipitate is dissolved in water and the pH adjusted to 7. The solution is freeze-dried and dissolved in water (half the volume of the original plasma). When added to stored chicken plasma, it shortens the prothrombin time.

The first report on the superiority of vitamin K_1 came from Smith, Fradkin & Lackey (1946) who studied the anticoagulant effect, in rats, of isosteres of phthiocol, substances used as antimalarial drugs. A few years later several authors (James, Bennett, Scheinberg & Butler, 1949; Watkin, Van Itallie, Logan, Geyer, Davidson & Stare, 1951, and others) found similar clinical effects of vitamin K_1 oxide or vitamin K_1 on the prolonged prothrombin time in patients treated with dicoumarol. The prolonged prothrombin time produced by coumachlor also yields to vitamin K_1, and is also largely uninfluenced by menaphthone and Synkavit (Montigel & Pulver, 1952; Søndergaard & Dam, to be published).

In spite of the fact that vitamin K_1 is far superior to menaphthone and Synkavit in counteracting the effect of dicoumarol-like anticoagulants, all three substances are found about equally active on a molar basis when tested by the usual assay methods for vitamin K activity. It has been shown recently, however, that when the prothrombin time is determined during the first hour or two after the intravenous injection of the substances in vitamin K-deficient chicks, vitamin K_1 causes a much more rapid decline of the prothrombin time than the two other substances (Dam & Søndergaard, to be published).

The superiority of vitamin K_1 in counteracting the effect of dicoumarol and its more rapid action in vitamin K-deficient chicks are probably related phenomena.

Some authors have attempted to explain the effect of dicoumarol by assuming that it interferes with the formation of vitamin K_1 from menaphthone; this is, however, hardly likely, for vitamin K does not enter the body as menaphthone except during medication with this and related compounds. Further, dicoumarol also counteracts the effect of vitamin K_1 already present in the body.

The ' displacement hypothesis ', according to which dicoumarol displaces vitamin K from an enzyme system, is more likely. Accepting this hypothesis one must assume that vitamin K_1 is held more firmly together with the protein carrier than menaphthone. Quick & Collentine (1950, 1951) have discussed this possibility, which finds added support in the more rapid action of vitamin K_1 in vitamin K-deficient chicks. However, it has still to be explained why vitamin K-deficient plasma is not identical with dicoumarolized plasma.

Haemorrhagic condition due to hypervitaminosis A

Certain other aspects of vitamin K deficiency have come to the fore in recent years. Thus, the haemorrhagic condition, which is part of the hypervitaminosis A syndrome (Rodahl & Moore, 1943; Moore & Wang, 1945; Rodahl, 1949, 1950) has been found by Light, Alscher & Frey (1944) (in rats) to be due to low prothrombin activity, which could be raised by relatively small amounts of menaphthone. Walker, Eylenburg & Moore (1947) obtained the same result with Synkavit. The way in which vitamin A in large doses produces ' hyperprothrombinaemia ' has not been completely elucidated. It seems, however, that the diets used were low in vitamin K, so that it is possible that vitamin K supply from the intestinal flora was impaired. Rodahl (1950) did not describe haemorrhage as part of the syndrome in chicks, and Quick

& Stefanini (1948) could not produce prolonged prothrombin times in chicks by overdosing with vitamin A. This has been confirmed in the author's laboratory (unpublished).

The route of absorption of natural vitamin K

Mann, Mann, Bollman & Van Hook (1949, 1950) have shown that vitamin K deficiency can be produced rapidly by external drainage of the lymph (in rats). This observation indicates that the natural fat-soluble K-vitamins are transported by the lymph from the intestines to the blood.

Isotope studies by Spinks & Jaques (1950), Lee, Trevoy, Spinks & Jaques (1950) and Solvonuk, Jaques, Leddy, Trevoy & Spinks (1952) have provided information about the fate of dicoumarol and menaphthone in the body. Dicoumarol labelled with ^{14}C in the methylene bridge was administered intravenously to mice and rabbits. After 24 h about 10% of it had been fixed in the liver as structurally unchanged dicoumarol. When Synkavit was given together with radioactive dicoumarol, the radioactivity disappeared from the liver much more rapidly than when dicoumarol was given alone. The period during which dicoumarol remained in the liver was related to the effectiveness of this agent in interfering with the formation of ' prothrombin '.

In later experiments the same group of investigators (Solvonuk *et al.* 1952) injected menaphthone labelled with ^{14}C in the methyl group intramuscularly into mice and dogs with gall bladder and kidneys removed. The radioactivity disappeared rapidly from the blood, but was not stored in any tissue except for traces in liver and lung when large doses had been given.

Vitamin K-deficiency states in man

The cholemic bleeding tendency. This form of vitamin K deficiency in man has been suspected of being complicated by the presence of increased antithrombin over and above lowered prothrombin activity (Marx & Dyckerhoff, 1943).

Owren (1949) found some cases of obstructive jaundice without liver damage to have an increased amount of proaccelerin (factor 5); others had normal amounts. Proaccelerin was not dependent upon the supply of vitamin K. Parenteral administration of 50–100 mg of menaphthone produced a rapid increase of the ' prothrombin ' concentration to normal or supernormal levels. (This was before Owren & Bjerkelund (1949) and Owren (1951*b*) distinguished between prothrombin and proconvertin).

Koller, Loeliger, Duckert & Hu-Wang (1952) find both factor 7 and prothrombin low in obstructive jaundice. Vitamin K increased factor 7 particularly.

The haemorrhagic disease of the newborn. At the university hospital in Copenhagen, Larsen (1952) and Dyggve (1952) have carried out extensive studies on this subject. Larsen studied the alterations in prothrombin activity of the newborn, Dyggve the value of prothrombin treatment. Each investigator has published his work in a monograph.

It was previously known that the prothrombin time of the newborn is somewhat increased at birth, increases further during the following 3 days and then falls, so that about normal values for infants are reached at 7–10 days after birth. Values identical with those of normal adults are not reached until after about 6 months.

Larsen has now shown that the lowered prothrombin activity normally present immediately at birth is not influenced by vitamin K treatment of the mother *ante partum*. Therefore, the relatively low prothrombin activity at birth cannot be due to vitamin K deficiency; other as yet unknown factors of a physiological or a chemical nature must account for the limited production of ' prothrombin ' in uterine life.

At birth the child has no stores of vitamin K to prevent the fall of prothrombin activity in the first days of the 1st week. It is this decline in prothrombin activity after birth that is prevented by treatment with vitamin K either of the mother *ante partum* or of the child immediately after birth. The decline after birth can also be more or less successfully prevented by giving the child cow's milk instead of breast milk in the 1st week. It is now held that it is the small amount of vitamin K in the milk that raises the prothrombin activity rather than vitamin K formed by the intestinal flora.

It is a somewhat puzzling fact that during foetal life surpluses of vitamin K are just enough to allow the production of the amount of ' prothrombin ' possible in the physiological circumstances, but unless the mother has been supplied with a large excess, not enough to furnish the child with the small store of vitamin K that could prevent the fall in the 1st week after delivery. Larsen (1952) has tentatively suggested that in foetal life ' prothrombin ' might be formed in the placenta and not in the liver. This hypothesis would explain the complicated phenomenon, but there is no direct evidence in support of it.

The fact that the prothrombin activity of the infant does not reach the value for normal adults until about 6 months of age, even with sufficient vitamin K supply, must mean that the production of prothrombin or of some of the auxiliary factors is fixed at a lower limit than in later stages of life. The reason for this is as yet unexplained. However, since there is a limit to the amount of prothrombin and auxiliary factors in adult life also, it is not particularly surprising that the limit is not the same at all stages of life. In the later stages of pregnancy, for instance, the limit is higher than at other times.

Koller & Held (1952) have made separate determinations of prothrombin and their factor 7 (probably identical with proconvertin) in the newborn and in mothers during the later part of pregnancy. They found that in the newborn both are about equally depressed. In the later part of pregnancy the amount of prothrombin of the mothers is almost unchanged, while that of proconvertin is increased. This may account for the apparent hyperprothrombinaemia found by methods that do not distinguish between prothrombin and proconvertin. Some authors have reported a seasonal variation in the prothrombin activity of the newborn (Waddell & Lawson, 1940; Snelling & Nelson, 1943, and others). Plum (1949) has examined a large number of cases in Copenhagen throughout the year without being able to find any variation significantly related to season. In this kind of investigation

it is necessary always to compare prothrombin activities at the same time after birth, the 3rd or 4th day, when the minimum occurs being the most important.

There is, however, a seasonal variation in the frequency of haemorrhages (especially melaena) in the newborn of untreated mothers. This has been found by several investigators in various parts of the world. The incidence is minimal in late summer and early spring. Taken together with the apparent absence in seasonal variation in prothrombin times, this must mean that other factors besides prothrombin activity decide whether hæmorrhages will occur or not.

Value of vitamin K treatment of the mothers. Dyggve (1952) studied the occurrence of various forms of haemorrhages in 22,371 newborn from untreated mothers and 10,876 newborn from mothers treated with Synkavit (the dissuccinate), 10 mg daily for some time before and until the day of delivery. There were 371 cases of various haemorrhages in 10,000 newborn in the untreated group and 276 in the group from treated mothers. Kephalhaematomas (111/10,000 in the untreated group and 105 in the treated group) did not respond significantly to vitamin K treatment. The best results were obtained against umbilical haemorrhages, haemoperitoneum and melaena. Dyggve's results were largely in agreement with those reported by Hay, Hudson & Rodgers (1951) on a smaller number of cases.

Dyggve estimates that possibly about 1 out of 1000 newborn die from haemorrhage that can be prevented by vitamin K treatment of the mothers. In Denmark, with about 80,000 births per year, this means a total number of eighty. The number of non-lethal haemorrhages preventable by the treatment is much greater.

It is interesting to compare Dyggve's figures with the more optimistic estimates in the early era of vitamin K, when it was expected that vitamin K treatment would reduce the death rate of newborn infants much more (Hellman & Shettles, 1942, and others), and the entirely pessimistic, but insufficiently founded, statement of Sanford, Kostalik & Blackmore (1949), who claimed that vitamin K treatment of the newborn had no value at all.

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The Fat-soluble Vitamins in Metabolic Processes

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Even with Professor Dam (1953) undertaking the discussion of vitamin K it will be impossible for me to present a comprehensive and fully documented account of the role of the fat-soluble vitamins in metabolism in the short space at my disposal. The ground to be covered includes several popular and highly specialized fields of research, such as the role of vitamin A in dark adaptation, the influence of vitamin D on calcification, and the action of vitamin E as a biological antioxidant and as a protective agent against muscular dystrophy and liver injuries. Any of these topics could be made the subject of a substantial monograph, and a short review which must make reference to them all can be little more than a brief summary of some of the main facts and theories.

Contrasts between vitamins A, D and E

Before our attention is turned to the individual vitamins, however, we may pause to recall the interesting differences in their modes of formation, transport and destruction in the body. Thus the animal is not able to synthesize provitamins A,