

we are told that water and wind remove not less than 3 billion tons of soil from our croplands and associated pastures alone every year.

But I am not to tire you with the quotation of statistics or the recital of experimental data and conclusions. I would merely insist that White Man should cease to boast of having *conquered* nature. That is an important lesson that we should sense from the severe and recurring demonstrations that continue to prostrate

mankind. Certainly the advantage in the contest of White Man versus the prairie in North America in the past several years has been with those superhuman forces that made and that tend to preserve the prairies inviolate. One of the major problems that now faces man throughout the world is to preserve what is left of his heritage in the soil, and to restore the broken lands that have dogged his footsteps through the forests and across the prairies for centuries.

VITAMIN K

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DURING the course of some experiments on the sterol metabolism of the chicken, Dam¹ (1929) observed that chicks raised on certain artificial diets became anemic, had large subcutaneous and intramuscular hemorrhages and that in one chick the clotting time of the blood was markedly increased. This striking hemorrhagic condition and prolonged clotting time were also observed by McFarlane,² *et al.* Although Holst and Halbrook³ did not mention the impairment of coagulation, they observed the hemorrhages and reported their disappearance after the addition of fresh cabbage to the diet.

Continuing his work Dam⁴ reported that the hemorrhagic condition was not relieved by the addition to the diet of vitamin C or any other of the known vitamins or essential dietary factors. He suggested that the hemorrhages and prolonged coagulation time were due to the lack of a new fat-soluble factor, which he named "vitamin K," from the Scandinavian and German term "Koagulations-Vitamin." This terminology has been accepted by other investigators in the field, but with the isolation of two compounds possessing vitamin K activity subscripts were added to K for purposes of designation.

Beginning in 1935, many important reports on the distribution, extraction, assay and chemistry of vitamin K have been published by Dam and his collaborators and by Almquist and his group of investigators. It is unfortunate that space limitations prevent us from referring to several of these publications.⁵

¹ Dam, *Biochem. Zt.*, 215: 475, 1929; 220: 158, 1930.

² McFarlane, Graham and Richardson, *Biochem. Jour.*, 25: 358, 1931.

³ Holst and Halbrook, *SCIENCE*, 77: 354, 1933.

⁴ Dam and Schönheyder, *Biochem. Jour.*, 28: 1355, 1934.

⁵ Since the main purpose of this report is to set forth the present status of the vitamin K problem, an extensive review of the subject has not been attempted. The experimental work has been reviewed by Dam (*Ztschr. f. Vitaminforschung*, 8: 248, 1938-39) and clinical work by Smith, *et al.* (*Jour. Am. Med. Assn.*, 113: 380, 1939) and Butt, Snell and Osterberg (*Jour. Am. Med. Assn.*, 113: 383, 1939).

SOURCES OF VITAMIN K

Dam⁶ and coworkers showed that the antihemorrhagic factor is widely distributed in green leaves and vegetables with an abundance in dried chestnut, spinach, cabbage and alfalfa leaves. Almquist and Stokstad⁷ reported in 1935 that the addition of 0.5 per cent. of dry alfalfa to the deficient diet prevented the appearance of symptoms, and from that time alfalfa has been one of the main sources of the vitamin. Recognition of a different antihemorrhagic factor resulted from the observation of Almquist and Stokstad that rice bran, fish meal and other foods which had been stored in a moist condition developed vitamin K activity. That this production was due to the action of micro-organisms was definitely concluded from Osterberg's⁸ work, which showed that large amounts of an antihemorrhagic substance were produced by bacterial putrefaction of fish meal, and from the report (Almquist, Pentler and Meechi⁹) that a large number of different bacteria, including *B. coli*, were able to synthesize a substance having vitamin K activity.

BIOASSAY

Since progress in the vitamin or hormone field is dependent upon the detection and quantitative measurement of the active principle, several groups of investigators, Dam, Schönheyder, Almquist, Ansbacher and Thayer,¹⁰ have devised bioassay procedures for

⁶ Dam, *Biochem. J.*, 29: 1273, 1935; Dam and Schönheyder, *Biochem. Jour.*, 30: 897, 1936; Dam and Glavind, *Biochem. Jour.*, 32: 485, 1938.

⁷ Almquist and Stokstad, *Nature*, 136: 31, 1935; *Jour. Biol. Chem.*, 111: 105, 1935.

⁸ Osterberg, *Proc. Staff Meetings Mayo Clinic*, 13: 72, 1938.

⁹ Almquist, Pentler and Meechi, *Proc. Soc. Exp. Biol. and Med.*, 38: 336, 1938.

¹⁰ Dam and Glavind, *Biochem. Jour.*, 32: 1018, 1938; Schönheyder, *Biochem. Jour.*, 30: 890, 1936; Almquist and Stokstad, *Jour. Nutrition*, 14: 235, 1937; Almquist and Klose, *Biochem. Jour.*, 33: 1055, 1939; Ansbacher, *Jour. Nutrition*, 17: 303, 1939; Thayer, McKee, Binkley,

vitamin K. In general, the procedures are either curative or preventive; in the former the deficiency is produced by maintaining young chicks on a diet devoid of vitamin K. After the deficiency has been produced in a severe form, the substance to be tested is administered and after a definite time interval a sample of blood taken for the determination of clotting time. In normal chicks the clotting time is less than three or four minutes, in chicks with a severe degree of deficiency over two or three hours. In these deficient chicks treated with the proper quantity of vitamin K, the clotting time is restored to a normal value within a period of six hours.

The development of quantitative biological methods of assay has enabled investigators to ascertain the most concentrated sources of vitamin K, and to study procedures designed to separate the vitamin in pure form from the natural sources.

ISOLATION OF VITAMIN K

The earlier work on the purification of vitamin K was conducted by Dam and by Almquist;¹¹ a number of interesting points were contributed by each. It was found that the vitamin is insoluble in water and methyl alcohol but soluble in many of the common organic solvents. Both acetone and petroleum ether proved to be satisfactory for the extraction of the vitamin from natural sources. One property, namely, thermostability, has proved to be quite important, since it led Almquist¹² to introduce molecular distillation for the purpose of purification.

The extraction of dried alfalfa leaf meal with petroleum ether gave a green solution which upon concentration resembled green axle grease. Fractionation with solvents proved ineffective in the separation of the pure vitamin. Likewise, chemical reactions on the crude product accomplished little, except to show that certain common procedures could not be employed, *e.g.*, saponification proved useless because of the lability of the vitamin toward alkali.

Two important discoveries had a direct bearing on the isolation of vitamin K. Almquist¹³ reported on the lability in alkaline solutions. In our laboratory this report was corroborated and in fact the vitamin proved so sensitive toward alkali that great care was observed always to keep solutions acidic; this was usually accomplished by the addition of glacial acetic acid.

Another important point, also contributed by Alm-

quist,¹³ was the discovery of the destruction of the vitamin by ultra-violet light. This caused us¹⁴ to study the effect of sunlight and illumination from ordinary Mazda light bulbs. Since it was found that the latter destroyed the potency of the vitamin, precautions were taken to limit as much as possible the exposure to light. It seems probable that the isolation could not have been accomplished had not the lability toward light and alkali been recognized.

Since the purification of vitamin K was beset with so many difficulties, investigators turned to the possibility of chromatographic adsorption. Both Dam and Almquist used adsorbents, but the only complete detailed descriptions of chromatographic adsorption are found in reports by McKee and Binkley.¹⁵ Since the procedures devised by Binkley, Thayer, MacCorquodale and Doisy led to the isolation¹⁶ of vitamin K they will be discussed in some detail. Although many adsorbents were studied the most satisfactory in our experience are Permutit and Decalso—two artificial zeolites used in certain procedures of water-softening—and a decolorizing carbon Darco.

Vertical glass columns fitted with perforated porcelain bottoms, which were covered with cotton, were used as suitable containers for the adsorbents. The antihemorrhagic factor obtained by the extraction of alfalfa or putrefied fish meal with petroleum ether was adsorbed by passing the petroleum ether extract through the adsorbent. It was eluted by washing successively with 1:10, 1:7 and 1:5 mixtures of benzene and petroleum ether. By using proper solvents for the selective elution of the vitamin, by constantly observing the movement of the colored layers in the column and by careful fractionation of the solvents which percolate through, a high degree of purification can be obtained. Three or four repetitions of this adsorption process, using only the most potent fractions, gave a product of high potency. Putrefied fish meal extracts yielded a reddish yellow oil which crystallized on standing at -5°C. ; after recrystallizing several times from an acetone-ethyl alcohol mixture or from a 1:1 mixture of methyl alcohol and chloroform, a pure yellow crystalline compound melting at $53.5\text{--}54.5^{\circ}$ was obtained. This compound had a potency of approximately 660 units per mg.

¹³ Almquist, *Jour. Biol. Chem.*, 117: 517, 1937.

¹⁴ MacCorquodale, Binkley, McKee, Thayer and Doisy, *Proc. Soc. Exp. Biol. and Med.*, 40: 482, 1939.

¹⁵ McKee, Binkley, Thayer, MacCorquodale and Doisy, *Jour. Biol. Chem.*, 131: 327, 1939; Binkley, MacCorquodale, Thayer and Doisy, *Jour. Biol. Chem.*, 130: 219, 1939.

¹⁶ Dam, Karrer *et al.* (*Helv. Chim. Acta*, 22: 310, 1939, 1939) have reported the isolation of vitamin K from alfalfa by a procedure which has not yet been described, but on the basis of the extinction coefficient given by them and the value obtained by Professor Ewing (*Jour. Biol. Chem.*, November, 1939) for our product, it seems likely that the product originally described by them was not pure.

MacCorquodale and Doisy, *Proc. Soc. Exp. Biol. and Med.*, 40: 478, 1939; 41: 194, 1939.

¹¹ Dam and Schönheyder, *Biochem. Jour.*, 30: 897, 1936; Dam and Lewis, *Biochem. Jour.*, 31: 17, 1937; Almquist, *Jour. Biol. Chem.*, 114: 241, 1936; 115: 589, 1936.

¹² Almquist, *Jour. Biol. Chem.*, 120: 635, 1937.

The petroleum ether extracts of dehydrated alfalfa leaves, after a similar series of adsorptions, gave a reddish oil which would not crystallize at -5°C . Further purification by molecular distillation or adsorption on "darcos" followed by fractional elution and several recrystallizations from acetone and alcohol at a low temperature (-60°C .) were necessary to obtain a pure product consisting of rosettes of yellow crystals. This compound melted at approximately -20°C . and had a potency of about 1,000 units per mg.

Since it was obvious that the compounds isolated from alfalfa and putrefied fish meal were different, they were named "vitamin K_1 " and "vitamin K_2 ,"¹⁷ respectively.

In order to establish definite proof of the isolation of these two compounds, a derivative¹⁸ of each, the diacetate of the reduced quinone, was prepared by reductive acetylation and the products purified by repeated crystallizations from methyl and ethyl alcohol and analyzed. One of these diacetates, the diacetate of dihydrovitamin K_1 , was subsequently hydrolyzed by the Grignard reaction, giving a product identical in every way with the original vitamin K_1 .

CONSTITUTION

Although it was not possible from the analyses and molecular weight determinations to decide between several alternative formulas it seemed likely that the empirical formula of vitamin K_1 ¹⁹ was $\text{C}_{31}\text{H}_{46}\text{O}_2$ and vitamin K_2 was $\text{C}_{40}\text{H}_{54}\text{O}_2$.

On catalytic hydrogenation vitamin K_1 absorbed eight atoms of hydrogen giving a colorless compound which on exposure to air was oxidized to a compound possessing the same yellow color as the original vitamin. This oxidation product in turn absorbed 2 atoms of hydrogen, thereby losing its yellow color. Reductive acetylation gave a colorless crystalline compound, m.p. $62-63^{\circ}$ having an empirical formula of $\text{C}_{35}\text{H}_{52}\text{O}_4$. Hydrolysis of this compound could not be carried out by common procedures but was effected by means of a Grignard reaction. Oxidation by air then converted the hydroquinone to vitamin K_1 . These reactions as well as ultra-violet absorption indicated that the vitamin was quinonoid in nature. Since all 1,2-quinones are red and 1,4-quinones are yellow, it seemed that the vitamin was probably a 1,4-quinone. Comparison of the ultra-violet absorption of the vitamin with the absorption of synthetic 1,4-naphthoquinones, particularly those substituted in the 2 and 3 positions, indicated clearly that the vitamin was a 2,3-disubstituted 1,4-naphthoquinone. This conclusion was consistent with

the result of the hydrogenation experiment, since six atoms are required by the quinone ring structure and bromination showed the presence of a double bond in the side chain which accounts for the absorption of the other two atoms of hydrogen.

Oxidation²⁰ of the vitamin with an excess of chromic acid gave phthalic acid. This observation, taken with our other data, could lead only to the conclusion that the vitamin is a 1,4-naphthoquinone and that the aromatic non-quinonoid ring has no side chains. Since the vitamin gave a negative Craven's reaction, it must be a 2,3-disubstituted 1,4-naphthoquinone.

Mild chromic acid oxidation of the vitamin gave 2-methyl-1,4-naphthoquinone-3-acetic acid. This was confirmed by synthesis of the acid and its methyl ester. Mild chromic acid oxidation of the diacetate of dihydrovitamin K_1 gave 2-methyl-1,4-diacetoxy-naphthalene-3-acetic acid. This acid was converted to 2-methyl-1,4-naphthoquinone-3-acetic acid, which proved to be identical with the acid obtained by direct oxidation of vitamin K_1 and also the synthetic compound.

The expectation that ozonolysis would break the side chain was realized and a ketone $\text{C}_{18}\text{H}_{36}\text{O}$, the semicarbazone of which was identical with the semicarbazone of the ketone obtained from the chromic acid oxidation of phytol,²¹ was obtained. A mixed melting point and analyses proved their identity.

From these degradation data it seemed likely that vitamin K_1 is 2-methyl-3-phytyl-1,4-naphthoquinone. That our interpretation was correct was shown by synthesis by the direct condensation of phytol with 1,4-dihydroxy-2-methylnaphthalene in benzene solution using anhydrous zinc chloride as a condensing agent and also by the reaction of the sodium salt of 1,4-dihydroxy-2-methylnaphthalene with phytyl bromide in benzene. The synthetic vitamin was purified in the form of the diacetate, which proved to be identical in melting point, potency and crystalline form with the same compound prepared from the natural vitamin. Moreover, oxidation with chromic acid gave the same products, thereby conclusively proving their identity.

Additional evidence that the structure just given is correct is found in the independent synthesis by different procedures by Almquist²⁰ and by Fieser.²⁰ The former reported that he has condensed phytol with 2-methyl-1,4-naphthoquinone and the latter that phytol was condensed with 1,4-dihydroxy-2-methylnaphthalene in dioxane using oxalic acid as a condensing agent.

¹⁷ McKee, Binkley, MacCorquodale, Thayer and Doisy, *Jour. Am. Chem. Soc.*, 61: 1295, 1939.

¹⁸ Binkley, MacCorquodale, Cheney, Thayer, McKee and Doisy, *Jour. Am. Chem. Soc.*, 61: 1612, 1939.

¹⁹ Binkley, Cheney, Holcomb, McKee, Thayer, MacCorquodale, and Doisy, *J. Am. Chem. Soc.*, 61: 2558, 1939.

²⁰ MacCorquodale, Cheney, Binkley, Holcomb, McKee, Thayer and Doisy, *Jour. Biol. Chem.*, Nov., 1939; Almquist and Klose, *Jour. Am. Chem. Soc.*, 61: 2557, 1939; *Jour. Biol. Chem.*, 130: 791, 1939; Fieser, *Jour. Am. Chem. Soc.*, 61: 2559, 2561, 1939.

²¹ It is interesting to note that phytol is present in green leaves in the chlorophyll molecule and also that the phytyl group occurs in vitamin E.

On catalytic hydrogenation²² vitamin K₂ absorbs 18 atoms of hydrogen to give a colorless product which on exposure to air oxidizes to a yellow compound. This yellow compound on catalytic reduction absorbs two atoms of hydrogen and becomes colorless. Reductive acetylation of vitamin K₂ also gives a diacetate of the reduced quinone. This diacetyldihydrovitamin K₂ adds 12 atoms of bromine indicating six double bonds in the side chain. The failure of vitamin K₂ to react with maleic anhydride leads to the belief that these bonds are not conjugated. These data, together with the response to Craven's test and the ultra-violet absorption data, indicate that vitamin K₂ is a 2,3 disubstituted 1,4-naphthoquinone having six double bonds in the side chains.

POTENCIES OF SIMPLE 1,4-NAPHTHOQUINONES AND RELATED PRODUCTS

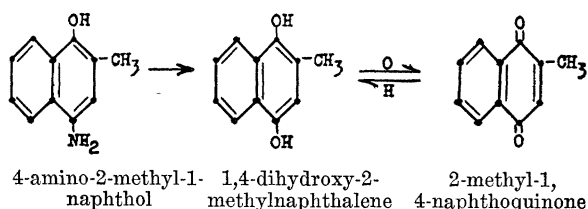
As soon as chemical reactions and degradation results showed vitamin K to be a quinone, the investigation of the simple 1,4-naphthoquinones was begun, and it was promptly found that several possessed vitamin K activity. Since a number of different laboratories became interested in the potencies of the naphthoquinones, the combined results represent a fairly extensive survey. The first report was by Almquist,²³ who apparently correlated the production of vitamin K potency by bacteria with Anderson's phthiocol (3-hydroxy-2-methyl-1,4-naphthoquinone) from tubercle bacilli. This compound possesses potency, but the activity is not comparable with that of the vitamin from alfalfa. Later, it was shown (Ansbacher and Fernholz) that 2-methyl-1,4-naphthoquinone possesses activity of the same order as vitamin K₁. All other members of this group which have been tested are less than 1/20 as active as vitamin K₁.

Since the 1,4-naphthoquinones are oil-soluble and water-insoluble they are used in conjunction with bile salts in oral therapy. Due to the large number of patients who because of nausea, intestinal obstruction, or other complications can not be treated orally, it was highly desirable to find a compound of high activity which could be dissolved in an aqueous medium for intravenous use.

Search for an active water-soluble compound led to the examination of 1,4-dihydroxy-2-methylnaphthalene.²⁴ Although the potency is approximately equal

to that of 2-methyl-1,4-naphthoquinone, the solubility in saline is too low for its use in a convenient volume. In spite of the large volume of solvent required, patients were successfully treated by the intravenous injection of aqueous solutions of 2–10 mgs.

The search was continued and a more satisfactory compound from the standpoint of solubility was discovered. 4-amino-2-methyl-1-naphthol hydrochloride²⁵ is sufficiently soluble in water for convenient intravenous injection and in addition is almost as potent as 2-methyl-1,4-naphthoquinone. This compound was tested because it seemed very probable that deamination would occur producing 1,4-dihydroxy-2-methylnaphthalene, the high potency of which had already been ascertained.



At the present time the mechanism of the action of vitamin K is not known. In fact, in the case of the simple compounds just discussed we do not know whether the active form is the phenol or the quinone. On the basis of work in the benzene series of compounds, it seems likely that the organism can oxidize the phenol to the quinone or reduce the quinone to the phenol.

THE VITAMIN K DEFICIENCY

In 1936 Schönheyder²⁶ examined the blood of chicks suffering from vitamin K deficiency and found that the prolonged clotting time of the blood was due to a diminution in thrombin. Previously, Quick, Stanley-Brown and Bancroft²⁷ (1935) had devised a method for the determination of prothrombin and through the use of this procedure had found subnormal values for prothrombin in jaundiced patients. Shortly after the publication of this report, Warner, Brinkhous and Smith²⁸ published another method for the determination of prothrombin, and Hawkins and Brinkhous showed that the blood of the dog having a bile fistula was deficient in prothrombin.

Although Dam²⁹ had little success in producing the

²² McKee, Binkley, MacCorquodale, Thayer and Doisy, *Jour. Am. Chem. Soc.*, 61: 1295, 1939.

²³ Almquist and Klose, *Jour. Am. Chem. Soc.*, 61: 1611, 1923, 1939; Thayer, Cheney, Binkley, MacCorquodale and Doisy, *Jour. Am. Chem. Soc.*, 61: 1932, 1939; Fieser, Bowen, Campbell, Fieser, Fry, Jones, Riegel, Schweitzer and Smith, *Jour. Am. Chem. Soc.*, 61: 1925, 1939; Fieser, Bowen, Campbell, Fry and Gates, *Jour. Am. Chem. Soc.*, 61: 1926, 1939; Ansbacher and Fernholz, *Jour. Am. Chem. Soc.*, 61: 1924, 1939.

²⁴ Thayer, Binkley, MacCorquodale, Doisy, Emmett, Brown and Bird, *Jour. Am. Chem. Soc.*, 61: 2563, 1939.

²⁵ Doisy, MacCorquodale, Thayer, Binkley and McKee, *Science*, 90: 407, 1939.

²⁶ Schönheyder, *Biochem. Jour.*, 30: 890, 1939.

²⁷ Quick, Stanley-Brown and Bancroft, *Am. Jour. Med. Sci.*, 190: 501, 1935.

²⁸ Warner, Brinkhous and Smith, *Am. Jour. Physiol.*, 114: 667, 1936; Hawkins and Brinkhous, *Jour. Exp. Med.*, 63: 795, 1936.

²⁹ Dam, Schönheyder and Lewis, *Biochem. Jour.*, 31: 22, 1937; Greaves and Schmidt, *Proc. Soc. Exp. Biol. and Med.*, 37: 43, 1937.

hemorrhagic syndrome in the common laboratory mammals, Greaves and Schmidt showed that the blood of rats with bile fistulas had a decreased content of prothrombin and a prolonged coagulation time. They attributed this condition to the failure of absorption of vitamin K in the absence of bile. Quick³⁰ summarized the available data and suggested that vitamin K should be effective in the treatment of the hemorrhagic diathesis of obstructive jaundice.

With the stage thus set by the investigations referred to in the two preceding paragraphs, it was only logical to make the next move—namely, the study of the effect of vitamin K in obstructive jaundice. The first report on the therapeutic use of vitamin K in the treatment of bleeding in cases of obstructive jaundice was published by Warner, Brinkhous and Smith (1938),³¹ but within a very short time Butt, Snell and Osterberg and Dam and Glavind published their observations on the same subject. Several additional publications, chiefly from the Mayo and Iowa groups, have now appeared. In addition to the treatment of obstruc-

tive jaundice and other conditions in which absorption from the intestine is impaired due to a lack of bile in the intestine Waddell and Guerry³² have successfully utilized vitamin K for the treatment of spontaneous and traumatic hemorrhage of the newborn. Brinkhous, Smith and Warner had previously shown that the prothrombin of the blood of babies is subnormal in amount.

SUMMARY

During the decade following Dam's first observations on the hemorrhagic syndrome the combined efforts of several groups of investigators have solved many of the important problems connected with the new vitamin. Sources of vitamin K were discovered, methods of extraction and purification devised, the isolation effected, the structure of K₁ worked out and then verified by synthesis, and a promising start made on the therapeutic applications. In addition, simple water soluble compounds with antihemorrhagic properties have been supplied for clinical work. Preliminary results with these compounds are encouraging.

OBITUARY

FERDINAND AUGUSTUS SILCOX 1882-1939

FERDINAND AUGUSTUS SILCOX, chief forester of the U. S. Forest Service, died at his home in Alexandria, Virginia, on December 20, 1939. The country has lost one of its most distinguished foresters and one of its ablest public servants.

Mr. Silcox was one of the first southerners to enter the profession of forestry. He was born in Columbus, Georgia, and received his undergraduate training in the College of Charleston in South Carolina. He completed graduate work at the Yale School of Forestry in 1905, and was immediately given an appointment in the Forest Service. That was the year in which the administration of the National Forests was placed in the Department of Agriculture under Gifford Pinchot. The progressive withdrawal of forest lands from the public domain as permanent reservations was still under way. Mr. Pinchot had only begun the organization of the National Forest units and development of an effective system of protection and management. Silcox was thus one of the pioneers in National Forest work. He rose rapidly from the positions of field assistant and forest ranger to that of assistant district forester in the northern Rocky Mountain region. In 1911 he was appointed district forester, succeeding William B. Greeley, who later became chief forester of the Forest Service.

The constructive activities and influence of Silcox

were of great importance in the evolution of policies and management of the public forests under his charge. He rendered valuable service in administrative organization, skilful management of forest labor, systematic fire control, development of forestry practice in timber sales, regulation of grazing, fighting fraud in application of mining laws and in previously established homestead claims, and meeting many other problems that in those days were in the early stage of solution.

At the time Silcox was district forester there was trouble in the lumber camps through the activities of the I.W.W. At one time during a very dry season when hundreds of men were needed in the suppression of fires in the forests, the workers refused to fight fire. Through skilful negotiation with labor leaders Silcox secured the cooperation of the I.W.W. to aid in protecting the public forests. This incident is important because it called attention to his ability in labor matters and was doubtless a factor in his assignments during the war. He was commissioned captain in the 20th Engineers and later promoted to the rank of major. Under joint action of the Department of Labor and the Shipping Board he was delegated to handle labor relations in the Seattle shipyards and in spruce production for airplanes. After 1919 he served as director of industrial relations for the Ty-

Staff Meetings Mayo Clinic, 13: 74, 1938; Dam and Glavind, *Acta Med. Scand.*, 96: 108, 1938.

³² Waddell and Guerry, *Jour. Am. Med. Assn.*, 112: 2259, 1939; Brinkhous, Smith and Warner, *Am. Jour. Med. Sci.*, 193: 475, 1937.

³⁰ Quick, *Jour. Am. Med. Assn.*, 109: 66, 1937.

³¹ Warner, Brinkhous and Smith, *Proc. Soc. Exp. Biol. and Med.*, 37: 628, 1938; Butt, Snell and Osterberg, *Proc.*