between age of child and size of the constant, C (in terms of R F = C), together with an analysis of its possible bearing upon the problem of intelligence and of the general meaning of bends from the straight line.

GEORGE KINGSLEY ZIPF
HARVARD UNIVERSITY

SCIENTIFIC APPARATUS AND LABORATORY METHODS

HYPO-PROTHROMBINEMIA PRODUCED BY 3,3'-METHYLENEBIS (4-HYDROXYCOUMARIN) AND ITS USE IN THE TREATMENT OF THROMBOSIS

PROTHROMBIN is formed in the liver, and it can be assumed that one or more enzymes are responsible for its formation. The activity of the enzymes is dependent on the presence of vitamin K, which may possibly be a prosthetic group attached to an active protein. On this assumption, the administration of a compound that could displace vitamin K and thus inactivate the enzymes would produce a hypo-prothrombinemia and thus could be used to reduce the incidence of post-operative thrombosis and thrombosis from other causes. Several naphthoquinone derivatives were tried first but without success.

The work of Quick,[1] Schoefield[2] and Campbell *et al.*[3] showed that the ingestion of spoiled sweet clover (*melilotus albus*) by cattle and rabbits caused a hypoprothrombinemia. The active agent was isolated by Stahmann *et al.*[4] and shown to be 3,3,[1]-methylenebis (4-hydroxycoumarin). This compound, called AP (antiprothrombin), was supplied by the Ferrosan Company of Malmö, Sweden, and used in the following experiments.

When AP is given per os to rabbits in a dose of 3–4 mg/kg the prothrombin index (Quick) was lowered for 1–2 days to between 10–20. (Similar effects have recently been reported by Overman *et al.*[5]). This effect was reproducible and reversible. Fig. 1 shows that the prothrombin index rapidly returns to normal even after almost daily administration of the drug for a month. No toxic effects were seen on the circulation, respiration, intestines, liver, kidney, heart and the composition of the blood. The lethal dose is 250 mg/kg for rabbits, almost ten times the effective dose. The cause of death was not determined but is probably the result of kidney damage. Fig. 2 shows that the simultaneous administration of 5 mg of vitamin K has no effect on the action of AP. Blood transfusion can raise the prothrombin level for 3–5 hours in the animal receiving the drug.

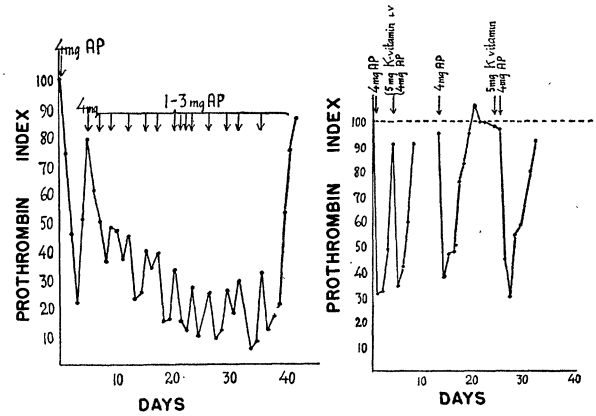

FIG. 1. The restoration of the normal prothrombin index in the rabbit after administration of AP for one month. FIG. 2. The inability of 5.0 mg of vitamin K to antagonize the effect of AP on the prothrombin index of the rabbit.

When 0.25–1.0 gm of AP is given by mouth to normal human subjects a similar fall of the prothrombin index occurs. Seventeen cases of thrombosis of the extremities were treated. When the initial fall in prothrombin index occurred there was a concomitant improvement as indicated by the fall in temperature, and diminished turgor of the leg. Cases of thrombosis cruris (*phlegmasia alba dolens*) were more resistant to the drug and required larger doses. In all cases the course of the disease was shortened and no further thrombosis occurred after the fall in the prothrombin index. Administration of AP is contraindicated in kidney, heart and liver diseases. In actual or suspected vitamin C deficiency, ascorbic acid should be given along with the drug to prevent hemorrhages. The use of AP in the prevention of post-operative thrombosis is under investigation.

In man mild toxic symptoms, such as vomiting and diarrhea, were observed in a few cases after the first administration of the drug, but seldom after subsequent ones. Liver and kidney function tests after treatment with the drug were normal. In two cases minor hemorrhages occurred. These were controlled by the administration of 100–200 mg of 2-methyl-1,4-naphthaquinone disulfate which increased the pro-

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[4] M. A. Stahmann, C. F. Huebner and K. P. Link, *Jour. Biol. Chem.*, 138: 513, 1941.
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thrombin index within 3–12 hours. In 4 cases menstruation occurred while AP was being administered and the prothrombin index was 20, but no excessive bleeding was noted. Two pregnant women in the 5th and 9th months, respectively, were successfully treated for thrombophlebitis. Lactating women excrete AP in their milk, as indicated by the lowering of the prothrombin level in the children. The drug can be administered with sulfathiazole, barbiturates and morphine and can be given to patients with tuberculosis and pneumonia.

JÖRGEN LEHMANN
SAHLGRENSKA SJUKHUSET CENTRAL-LABORATORIUM,
GÖTEBORG, SWEDEN

THE MINERAL PATTERN OF STEMS FROM VEGETATIVE AND FLOWERING PLANTS AS DETERMINED BY MICRO-INCINERATION[1]

THE ashing of thin sections of plant material was described more than a hundred years ago.[2] Since then investigations of this type have been conducted with both plant and animal tissues. However, considerable difficulty has been encountered when dealing with plant sections, since there is a marked tendency for the thick cell walls to shrink and become displaced during incineration.

Previous investigations have shown that the anatomical structure of a flowering stem is different from that of a vegetative stem.[3, 4] Sections of the fourth internode of stems of vegetative and flowering plants were incinerated to observe the mineral pattern in these two types of stems. When observing minerals on a microscopical scale it is necessary to retain as much of the mineral substance after incineration as was present in the living plant. Therefore attention was given to the selection of a fixative which would not dissolve the mineral substance and which would not add mineral substances to the ash. Little or no difference in the amount or distribution of the ash could be detected in the samples fixed in four liquids: absolute alcohol, nine parts of absolute alcohol and one part of formalin, cellosolve and dioxan. Dioxan, however, seemed to have a shrinking effect upon the stem material. The alcohol-formalin mixture was used for further sampling. The material for sectioning was dehydrated in absolute alcohol and cleared in cedarwood oil. After embedding in paraffin, transverse and longitudinal sections 15 μ in thickness were cut on a rotary microtome.

Several substances were tested for their adhesive qualities in an attempt to prevent shrinkage and displacement of the heavy walled cells of the secondary tissue during the incineration process. These adhesives were applied after the paraffin was removed from the sections with xylol. Of the several tried, "Nevillite 123,"[5] which is practically ash free, proved to be the most satisfactory when dissolved one part to two to four parts of xylol depending upon the hardness of the tissue. Photographing of the sections before and after ashing disclosed no change in the position of the crystalline inclusions and wall-impregnating substances during incineration. With this adhesive a more accurate mineral pattern of the thick-walled plant tissue may now be secured.

The amount and pattern of the ash in the vegetative and flowering stems was found to be different. In the plants examined, such as *Cosmos,* poinsettia, *Xanthium* and Wealthy apple, the greater ash residue was present in the flowering stem, particularly in the thick-walled tissues of the vascular cylinder and the outer layers of the cortex.

Samples were also taken of the internodes beginning at the second from the stem-tip through the twelfth inclusive to observe the mineral pattern at different levels of the stem. The greatest difference in the amount of ash in vegetative and flowering stems was in the internodes closer to the stem-tip. Beyond the seventh internode the quantity of ash, although still less in the vegetative stem, was not as different from that of the flowering stem as it was in the higher internodes.

Plants of *Salvia, Cosmos* and *Xanthium* were placed in short days, an environment in which flower primordia are initiated. There was more ash in the stems of plants in the short-day treatment than in those remaining vegetative in long days after 8, 7 and 6 days, respectively.

B. ESTHER STRUCKMEYER
DEPARTMENT OF HORTICULTURE,
UNIVERSITY OF WISCONSIN

[1] Published with the permission of the director of the Agricultural Experiment Station.

[2] F. V. Raspial, Paris. Bailliére, 1833.

[3] O. Christine Wilton and R. H. Roberts, *Bot. Gaz.,* 98: 45–64, 1936.

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