

## **THE SAGA OF BORON IN FOOD: FROM A BANISHED FOOD PRESERVATIVE TO A BENEFICIAL NUTRIENT FOR HUMANS**

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### **I. Introduction**

Boron is an element with a very checkered history in terms of its presumed effect on human health and well-being. Early in the history of the knowledge of boron in food, this element was considered an extremely beneficial element to humankind because of its ability to preserve food without any apparent harm to health. However, this period of history was followed by a time when boron was considered a dangerous poison for humans. Also at this time, students of biology were being taught that boron was essential for plants, but not for animals and humans. In the 1980s, this concept began to change when reports appeared, first from animal studies, then from human studies, indicating that boron was of nutritional importance to higher animals including humans. Today, there is good evidence that consuming boron in amounts commonly found in diets high in fruits and vegetables is beneficial, if not essential, for maintaining optimal calcium metabolism and utilization in humans. Thus, boron might be a factor in some human disorders of unknown etiology with disturbed macromineral metabolism, e.g., osteoporosis.

### **II. Boron as a Food Preservative**

Boron always has been present in foods. However, recognition that there are benefits and

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detriments from having boron present in defined quantities in food seems to have begun in the 1870s. At that time it was discovered that borax and boric acid could be used to preserve foods. For about the next 50 years, borates were considered one of the best methods of preserving or extending the palatability of foods such as fish, shellfish, meat, sausages, bacon, ham, cream, butter and margarine. According to a recent historical review (13) of boron as a food preservative, an English Royal Commission appointed in 1899 to investigate preservatives and colorings in foods recognized in 1901 that borates were used as such for all foodstuffs except milk. Also in England, an act of 1907 named borax and boric acid as the only permitted preservatives in butter and margarine. In other words, for the last 30 years of the past century and the first part of this century, boron was considered a beneficial element only, and medical opinion was that boron was rather innocuous--after all, no corpses resulted from the use of boron as a preservative. Actually, boron probably was more beneficial to humankind at this point in history than most people currently recognize; it had a vital role as a preservative in preventing food crises during World War I.

Nonetheless, as early as 1902, German and American scientists began to question the orthodox view that large amounts of borates in foods were innocuous. Foremost among the works that changed perceptions about boron was a study performed by H.W. Wiley for the United States Department of Agriculture. In a report of 477 pages (50), Wiley described a study involving feeding daily to human volunteers borax and boric acid in small doses for extended periods of time, or large doses for short periods of time. When doses equivalent to over 0.5 g B/day for 50 days were consumed, disturbances in appetite, digestion and health occurred. Wiley concluded that 0.5 g B/day was too much for a normal man to receive regularly, and that "4.0 g B/day was the limit beyond which a normal man cannot go without harm." Subsequent to his report, the opinion that boron posed a risk to health gained momentum; by the mid 1920s many countries of the world began legislating against the addition of borates to food. Only during World War II were the restrictions involving boron in foods eased; food shortages were making food preservation a major concern in many countries (13). After the war, restrictions were gradually reimposed; by the middle 1950s, boron as a food preservative was essentially forbidden throughout the world. At this time, in terms of human health, borates and boric acid were considered dangerous substances because they had caused adverse effects when used in high amounts for purposes for which they were not well-suited, e.g., as a bactericide. Examples of the writings about boron after World War II are the following: "The medical profession as a whole probably puts unwarranted confidence in boric acid preparations and is likely to forget that boric acid is a poison" (48). "However, a most simple and effective method of treatment (of boron toxicity) is the one that has apparently met with the greatest resistance for over 100 years--the removal of this poison from our therapeutic armamentarium" (2). The saga of the change in attitude from boron being a beneficial substance that helped save the lives of people

because of its food preservative properties to being a poison that required legislation to prevent it from being added to food is fascinating. In other words, it is quite amazing what one published study at the turn of the century by a respected scientist brought to pass. The study by Wiley (50) apparently is the only one in which humans were subjected to regular controlled, relatively high dosages of boron. However, that study combined with a few cases of misuse of boric acid in hospitals, such as applying boric acid on massive burns and open wounds which do not have skin to prevent entry into the body and mistakenly feeding babies a boric acid solution instead of a sugar solution (2,7,42,48), created the general belief that boron was nothing more than a poison for humans. Today, the direct addition of borates in foods either produced or imported by the United States is not permitted. Joint Food and Agricultural Organization/World Health Organization Expert Committees on Food Additives stated in 1962 and 1967 that boric acid and borates should not be used as a food preservative (20,21). This has occurred in spite of the fact that apparently no case of boron intoxication has ever been reported from the proper use of boron preservatives in food.

### **III. Boron as a Nutrient for Plants and Animals**

While the pendulum of opinion about relatively high amounts of boron in food was swinging, opinions about the importance of relatively low amounts in biological systems was also vacillating. The history in this regard probably begins in 1857 when the presence of boron was detected in some plant seeds (see ref. 43). It was not until 1910, however, that boron was recognized as an element of possible physiological importance; that is when Agulhon (1) reported findings indicating that boron is essential for higher plants. However, conclusive evidence and acceptance of the essentiality of boron for plants is usually indicated as emanating from 1923 when the work of Warrington (47) appeared. Interestingly, 68 years have elapsed since that report, yet today a biochemical role for boron in plants has not been conclusively identified.

About 15 years after the plant work by Warrington, some eminent scientists in nutrition, including E.B. Hart and C.A. Elvehjem, attempted to show that boron is essential for higher animals. However, these attempts were apparently unsuccessful (14,38,46). In 1945, a report appeared showing that high dietary boron, 100 to 1000  $\mu\text{g/g}$  diet, enhanced survival and maintenance of body fat, and elevated liver glycogen in potassium-deficient rats (45). These findings were not confirmed in a subsequent study in which rats were fed a different diet with an unknown boron content and with different amounts of boron supplementation (11). These reports apparently were the ones that led to students of biochemistry and nutrition being taught that boron was a unique element because it was essential for plants but not for higher animals including humans. Nonetheless, in the 1960s and 1970s evidence appeared that indicated some scientists questioned this dogma.

For example, in 1967 Weser (49) reported that young rats fed a diet containing less than

0.001  $\mu\text{g B/g}$  incorporated a pulse of  $^{14}\text{C}$ -orotic acid into liver RNA in increased amounts when they were given an intraperitoneal dose of borate. This increased incorporation was diminished if the rats were fed a diet containing 1  $\mu\text{g B/g}$  diet as boric acid. Unfortunately, shortly after this work, the scientist involved turned his attention to other research areas.

In the 1970s I developed some diets low in several mineral elements to study the possible essentiality of arsenic, nickel and vanadium. Because I was not convinced that it had been proven that boron was unimportant in animal nutrition, these diet formulations always were supplemented with 1  $\mu\text{g B/g}$ . This routine supplementation allowed the serendipitous findings which initiated the serious study of the nutritional importance of boron in my laboratory about 1980. At that time, a graduate student, E.O. Uthus, reformulated one of my diet formulations in an attempt to decrease its arsenic content. The formulation was similar to one used by a post-doctorate, C.D. Hunt, in my laboratory for vanadium studies. Thus, it was mystifying when chicks in the arsenic studies, when compared to chicks in the vanadium studies, grew about 50% slower and showed leg abnormalities. Examination of the diets revealed that, in the reformulation of the arsenic diet, the routine additions of boron, fluoride and nickel had been omitted, and the cholecalciferol source was different in the two studies.

As a result of the comparison, a preliminary study lasting three weeks with chicks was performed to ascertain whether supplemental boron, fluoride or nickel would improve the performance of the chicks fed the basal arsenic diet. It was somewhat surprising and exhilarating when we found that boron stimulated growth and partially prevented the leg abnormalities present in the chicks. Further study revealed that the diet contained inadequate cholecalciferol because the indicated potency of the supplement used in the arsenic diets apparently was not correct. As the result of these findings, experiments were performed which led to the first report involving boron by Hunt and Nielsen in 1981 (18). The experiments showed that boron deprivation depressed the growth of chicks with the effect seemingly more marked when dietary cholecalciferol was deficient. An interaction between boron and cholecalciferol affected plasma alkaline phosphatase activity; cholecalciferol deficiency increased the activity with the increase more marked in boron-deprived chicks. Morphological examination of the tibias of the chicks also indicated that an interaction between boron and cholecalciferol affected bone formation. Rachitic long bones were found in 17 of 21 boron-deprived chicks, but only in 9 of 22 boron-supplemented chicks, fed a cholecalciferol-deficient diet; moreover, the lack of calcification generally was more severe in the boron-deprived chicks. The collaboration between Hunt and myself also yielded findings which showed that magnesium status affected the response of chicks to boron deprivation (19). Subsequent to this finding, Hunt has independently studied the importance of boron in bone formation and carbohydrate metabolism in studies using chicks and rats (16,17). My attention became focused upon the possible

importance of boron in calcium metabolism and utilization with studies initially involving rats and, later, humans.

In the rat studies, my approach was to use factorially arranged experiments in which the response to dietary boron was examined in animals fed diets manipulated to possibly cause changes in cell membrane structure or function, or in hormone responsiveness, that would alter calcium metabolism and utilization. These dietary manipulations included magnesium, potassium or calcium deficiencies, and aluminum toxicity (4,33-35). Because this presentation is focused on the human aspects of boron, only a few brief summary statements of the findings from those studies, in addition to those of Hunt et al. (16-19) and Penland (40) will be given here. These studies have shown that the response of experimental animals to low dietary boron is not very marked if they are fed diets apparently optimal in all other aspects. Responses to low dietary boron have been most marked when an experimental animal has had to respond to a stressor that adversely alters hormonal or cellular membrane status, such as calcium, cholecalciferol or magnesium deprivation. Under these conditions, boron deprivation apparently affects the function or composition of several body systems including the skeleton, kidney and brain. The variables affected by boron deprivation are associated with the metabolism of several other nutrients including calcium, copper and nitrogen.

#### **IV. Boron as a Nutrient for Humans: Early Studies**

In 1986, I seized upon an opportunity to extend to humans the study of the nutritional importance of boron. At that time I had concluded, based on studies with animals, that the need for boron by humans most likely was quite low when systems involving calcium metabolism were not stressed in any manner. However, if humans were exposed to a stressor that markedly altered hormonal action or cellular membrane function related to calcium metabolism or utilization, a response to low dietary boron might occur. Thus, in my first human experiment, variables included a suboptimal intake of magnesium and a high intake of aluminum (30,31). The subjects were postmenopausal women because it is known that in this stage of life women undergo hormonal changes that are associated with an increased loss of calcium from bone or the body. The 13 Caucasian women between the ages of 48 and 82 years who participated in the first study lived in a metabolic ward under close supervision for 167 days. They were fed a diet which, at an intake of 2000 kcal, provided 0.25 mg boron. After being fed this diet for 119 days, the women were fed the same diet with a boron supplement of 3 mg/day for 48 days. Seven of the women were fed a low magnesium diet (116 mg/2000 kcal); the other five women had their diet supplemented with 200 mg Mg/day. The boron supplementation reduced the total plasma concentration of calcium and the urinary excretions of calcium and magnesium, and elevated the serum concentrations of  $17\beta$ -estradiol and testosterone. The effect of dietary boron seemed more marked in the magnesium-low women.

Subsequently, a study was performed in which five men over the age of 45, four postmenopausal women, five postmenopausal women on estrogen therapy and one premenopausal woman were fed a boron-low diet (0.23 mg/2000 kcal) for 63 days (25,32). Then they were fed the same diet supplemented with 3 mg B/day for 49 days. The diet was low in magnesium (115 mg/2000 kcal) and copper (1.6 mg/2000 kcal) throughout the study. Serum calcitonin, 25-hydroxycholecalciferol and ceruloplasmin, plasma copper and erythrocyte superoxide dismutase activity were lower, whereas serum creatinine and glucose and blood urea nitrogen were higher during the boron depletion period than the boron repletion period. Comparing electroencephalograms obtained during the boron depletion with those from the boron repletion period indicated that low dietary boron depressed mental alertness (41). During the boron depletion period, the subjects displayed impaired performance in tapping, pursuit, search, counting and encoding tasks with a computer.

#### **V. Boron as a Nutrient for Humans: Recent Findings**

As indicated by the preceding, the two human experiments described yielded a bewildering and surprising array of significant findings when it is considered that boron apparently has a biochemical role so subtle that it was considered unimportant in nutrition until the 1980s. However, if one closely analyzes the findings, the results from the first two human experiments indicate that boron affected many variables affected by calcium, and suggest that the similarity between the effects of boron and calcium occurred because they affected a similar system, or systems, which indirectly affected many variables. Based upon plant studies and chemical properties of boron, and upon the known biochemical functions of calcium, one can be easily led to the hypothesis that boron and calcium are both involved in maintaining cell membrane structure and function which, when modified by a change in the presence of one or both of the elements, would alter hormone action and transmembrane signalling (29). This, of course, would affect a large array of variables including those associated with hematopoiesis, erythropoiesis, macromineral and electrolyte metabolism, and even the response to estrogen therapy. Unfortunately, the first boron nutritional studies with human subjects were not conducive to examining the specific effect of boron on many of these processes because the studies were complicated by diets low in magnesium, marginal in copper and high in aluminum, dietary substances that also affect these processes (26,37). Thus, a third experiment was recently completed with human subjects consuming a diet apparently adequate in all nutrients, including copper and magnesium, but low in boron (28). This most recent study will be described in the most detail here.

The subjects were four men over the age of 45, four postmenopausal women, five postmenopausal women on estrogen therapy, and one woman who was thought to be postmenopausal,



but estrogen analysis during study revealed that she was not. The subjects were fed a three-day menu rotation diet containing conventional foods including beef, pork, rice, bread and milk, but was low in fruits and vegetables. The diet energy was 11% as protein, 54% as carbohydrate and 35% as fat. During the first 32 days of the experiment, the diet provided only 1.7 mg Cu/2000 kcal; this was lower than intended. Thus, from day 33 onward, the diet was supplemented to contain 2.4 mg Cu/2000 kcal. Iron was supplemented in the diet to provide 29 mg/2000 kcal; this high amount was fed to limit the effect of phlebotomy on the blood variables examined. At an intake of 2000 kcal, the diet provided about 680 mg of calcium, 300 mg of magnesium, 0.25 mg of boron and 450 IU of cholecalciferol. During the study, energy intake was adjusted to maintain body weight within  $\pm 2\%$  of admission weight; there were no major adjustments. The range of energy intakes among the subjects was 1800-3400 kcal. The subjects consumed one meal each weekday at the Grand Forks Human Nutrition Research Center. The other two meals and evening snack each weekday, and all weekend meals, were prepared at the Research Center but consumed by the subjects elsewhere. After a 14-day equilibration period during which the basal low boron diet supplemented with 3 mg B/day as sodium borate was fed, there was a 63-day depletion period during which the basal low boron diet only was fed; this was followed by a 49-day repletion period during which the basal diet was once again supplemented with 3 mg B/day.

Blood was drawn from the subjects by standard phlebotomy techniques between 7:00 and 9:00 a.m. after nine hours of fasting. On a weekly basis, mean corpuscular hemoglobin (MCH) and red blood cell counts (RBC) were determined by a Coulter S+4 Electronic Counter<sup>2</sup> (Coulter Electronics, Hialeah, FL); 17 $\beta$ -estradiol was determined by a radioimmunoassay method (Radioassay System Laboratories, Carson, CA). Every two weeks, radioimmunoassay techniques were used to determine serum immunoreactive ceruloplasmin (M-Partigen<sup>™</sup> Ceruloplasmin, Calbiochem-Behring, LaJolla, CA), and plasma copper was determined by atomic absorption spectrophotometry (8).

Although the volunteers were allowed an equilibration period of 14 days, all variables being examined did not stabilize into a steady change or plateau at that time. Moreover, some variables responded to the extra copper supplementation started on day 32. Thus, to limit the influence of dietary factors other than boron depletion in the statistical comparisons, only the values from the last 35 days of depletion were used; they were compared with the values from the last 35 days of repletion. For each variable, a mean was computed for each dietary period for each volunteer. Paired *t*-tests were then used to test for dietary effects (10). In this test, each individual was his or

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<sup>2</sup>Mention of a trademark or proprietary product does not constitute a guarantee or warranty of the product by the U.S. Department of Agriculture and does not imply its approval to the exclusion of other products that may also be suitable.

her own control.

Numerous significant findings were obtained from this experiment; selected ones are shown in Table I. These were chosen because they exemplify the type of findings which suggest that boron affects cell membrane function in humans.

Table I shows that, when the comparison included all 14 subjects, or each group separately, MCH was lower during boron depletion than boron repletion. On the other hand, the number of red blood cells was higher during boron depletion than repletion. The serum  $17\beta$ -estradiol concentration was elevated by estrogen therapy; the elevation was significantly higher during boron repletion than the boron depletion period. Dietary boron apparently did not affect serum  $17\beta$ -estradiol concentrations in the men or women not ingesting estrogen. Estrogen therapy also elevated plasma copper; here too, the elevation was higher during boron repletion than boron depletion. Dietary boron did not affect plasma copper in men or postmenopausal women not ingesting estrogen. The selective changes in plasma copper were not mirrored by the serum immunoreactive ceruloplasmin values. With this variable, all three groups alone or combined exhibited higher concentrations during boron repletion than boron depletion; however, the effect with men and women not ingesting estrogen was marginal ( $P < 0.06$ ).

## **VI. Possible Biochemical Role of Boron**

The hypothesis that boron influences cell membrane structure, stability and/or function makes it possible for one to suggest reasons for the preceding diverse findings. For example, the binding of transferrin to high affinity surface receptors of the plasma membrane is an essential step in the cellular accumulation of iron (22). One of the most important functions of iron is in the synthesis of heme (12). Heme and globin synthesis and their attachment to each other occur in erythroid cells of bone marrow. It has been stated that the most critical determinants of hemoglobin concentration are the availability of iron and the presence of heme (12). Thus, perhaps through an effect on membrane structure or function, which resulted in changes in the cellular internalization of iron, boron affected the concentration of hemoglobin in the red blood cell.

Immunocytochemical studies have demonstrated that erythropoietin localizes on the cell membranes of nucleated erythroid cells in human bone marrow (9); erythropoietin is the primary humoral agent which regulates erythropoiesis. Thus, it is possible that boron affected RBC numbers by altering erythroid cell membrane characteristics which influenced its ability to bind erythropoietin.

The finding that physiological amounts of dietary boron caused higher peak  $17\beta$ -estradiol concentrations in women ingesting estrogen suggests that boron can enhance  $17\beta$ -estradiol absorption or decrease its breakdown or excretion in postmenopausal women. The higher concentration of  $17\beta$ -estradiol in serum of postmenopausal women on estrogen therapy during boron repletion versus boron



**Table I.** Effect of boron on mean corpuscular hemoglobin (MCH), red blood cell (RBC) numbers, serum  $17\beta$ -estradiol and immunoreactive ceruloplasmin, and plasma copper concentrations.

Dietary <sup>a</sup> Boron	$17\beta$ -estradiol pg/mL	Copper $\mu$ g/dL	Ceruloplasmin mg/dL	MCH pg	RBC $10^{12}/L$
Men over age 45 (n=4)					
0	$20 \pm 1^b$	$83 \pm 5$	$25 \pm 2$	$30.4 \pm 0.5$	$4.83 \pm 0.10$
3	$17 \pm 2$	$86 \pm 5$	$28 \pm 2$	$31.9 \pm 0.5$	$4.64 \pm 0.08$
P value	0.12	0.14	0.06	0.003	0.007
Postmenopausal women (n=4)					
0	$11 \pm 2$	$107 \pm 6$	$30 \pm 2$	$29.6 \pm 0.3$	$4.35 \pm 0.06$
3	$11 \pm 3$	$108 \pm 6$	$33 \pm 2$	$30.6 \pm 0.4$	$4.28 \pm 0.07$
P value	0.86	0.71	0.06	0.008	0.30
Postmenopausal women on estrogen therapy (n=5)					
0	$99 \pm 15$	$146 \pm 9$	$42 \pm 2$	$30.3 \pm 0.3$	$4.30 \pm 0.11$
3	$157 \pm 27$	$159 \pm 11$	$50 \pm 5$	$31.8 \pm 0.6$	$4.19 \pm 0.12$
P value	0.02	0.04	0.05	0.01	0.03
Above combined plus one premenopausal woman (n=14) <sup>c</sup>					
0	$48 \pm 13$	$115 \pm 9$	$33 \pm 2$	$30.1 \pm 0.2$	$4.46 \pm 0.08$
3	$69 \pm 22$	$121 \pm 10$	$38 \pm 3$	$31.3 \pm 0.3$	$4.34 \pm 0.07$
P-value	0.06	0.02	0.002	0.0001	0.0002

<sup>a</sup>Amount of boron as sodium borate supplemented per day to a diet containing 0.25 mg B/2000 kcal; there was a depletion period of 63 d when no supplement was given followed by a repletion period of 49 d when the supplement was given. Values obtained during the last 35 d of each dietary period were compared.

<sup>b</sup>SEM.

<sup>c</sup>The  $17\beta$ -estradiol and copper values do not include those from the one premenopausal woman.

depletion probably was the basis for the significant plasma copper findings; estrogen ingestion increases plasma copper (5). However, the serum immunoreactive ceruloplasmin findings suggest that the boron supplementation not only enhanced the effects of estrogen therapy but also mimicked some of its effects; boron caused changes in this variable similar to that caused by estrogen ingestion. The purpose of estrogen therapy is to inhibit bone loss in postmenopausal women; it has been postulated that estrogen has this effect through a calcium-sparing action rather than by a direct effect on bone itself (36,44). The mechanism through which estrogen affects calcium metabolism is also

unclear (36,44), but it apparently can modify the action of hormones that affect calcium metabolism. It seems possible that both boron and estrogen can interact with plasma membranes to modify their properties or receptors which results in an influence on hormone action that affects calcium metabolism.

The preceding findings have led me to believe that boron has a biochemical role in humans similar to that in plants. Marmé (23) presented evidence that the low  $\text{Ca}^{2+}$  concentration in the cytoplasm of a plant cell is maintained by a calmodulin-dependent  $\text{Ca}^{2+}$  transport ATPase located most likely in the plasma membrane. He suggested that, by changing  $\text{Ca}^{2+}$  fluxes through the membranes surrounding the cytoplasm, primary signals like light and hormones (e.g., auxin, gibberellic acid) alter cytoplasmic  $\text{Ca}^{2+}$  and consequently change  $\text{Ca}^{2+}$ -dependent or -responsive biochemical and physiological reactions. A number of studies have indicated that, in plants, boron has a regulatory role involving hormones such as auxin, gibberellic acid and cytokinin, and the control of a second messenger such as calcium at the cell membrane level (6,39). Blaser-Grill et al. (3) found that boron influences membrane potential and proton movement through membranes of plant cells. Moreover, the effect of boron on net proton release as well as proton uptake was strictly dependent on the presence of auxins, and the addition of vanadate to inhibit plasmalemma ATPase in part mimicked the effects of boron deficiency.

## **VII. Dietary Considerations of Boron**

Regardless of the role of boron, the findings from the human studies indicate that boron is of nutritional importance. In these studies, most subjects consuming 0.25 mg B/day responded to boron supplementation. Thus, the basal requirement for boron most likely is higher than 0.25 mg B/day. There is evidence that chicks need about 1  $\mu\text{g}$  B/g diet to meet their needs (15). If it is assumed that adult humans consume 500 g of a mixed diet daily (dry basis), a boron concentration of 1  $\mu\text{g}/\text{g}$  would result in an intake of 0.5 mg/day. Based on this chick study, humans may have a daily requirement of at least 0.5 mg/day. However, further studies are needed to clarify the issue.

The daily intake of boron by humans can vary widely depending upon the proportions of various food groups in the diet (27). Foods of plant origin, especially fruits, leafy vegetables, nuts and legumes, are rich sources of boron. Wine, cider and beer are also high in boron. Meat, fish and dairy products are poor sources. A limited number of surveys indicate average daily intakes of boron of 0.5-3.1 mg/d (24,27).

## **VIII. Concluding Statements**

Boron most likely is an essential element for higher animals, including humans. However, a biochemical function for boron has not been elucidated, even for plants for which boron has been

known to be essential for almost 70 years and where its deficiency also has a multiplicity of effects. Many findings to date suggest that boron and calcium action is interrelated, or that these two elements affect similar systems that indirectly affect many variables; these include the modification of hormone action and the alteration of cell membrane characteristics or transmembrane signalling. Because of its apparent nutritional importance in calcium metabolism and utilization, humans should consume diets that supply at least 0.5 mg B/day.

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