(as 1 RU certainly is) several subthreshold doses are produced which cannot induce the gonadotropic response in the ovary.

Summary. Comparing the gonadotropic response of the organism to subcutaneous or intraperitoneal administration of pregnancy urine prolan the following results were secured: (1) If the minimum dose is split up into 6 portions intraperitoneal and subcutaneous administration are equally effective. (2) If the minimum dose is split up into 3 portions the intraperitoneal route is approximately half as effective as the subcutaneous one. (3) If the minimum dose is given in one injection the intraperitoneal administration is about 1/10 as effective as subcutaneous. (4) Using the subcutaneous standardization method with minute doses as *e.g.*, 1 RU (estrous effect) the gonadotropic effect of 6 subthreshold doses is less marked than that of one single threshold dose.

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Cheilosis Successfully Treated with Synthetic Vitamin B_6.

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Aykroyd and Krishnam[1] observed that the incidence of angular stomatitis (sores in the corners of the mouth, perleche, cheilosis) coincided with a deficiency of some factor or factors of the vitamin B_2 complex.

More recently Sebrell and Butler[2] produced these lesions in 10 out of 18 women subsisting on a riboflavin-deficient diet. The lesions developed in a period of 94 to 130 days. They failed to respond to nicotinic acid but responded to riboflavin, the complete healing requiring from 5 to 58 days. Sebrell and Butler[3] added more evidence to their previous findings and these have been confirmed by others.[4, 5, 6]

1 Aykroyd, W. R., and Krishnam, B. G., *Ind. J. Med. Res.*, 1937, **24**, 707.

2 Sebrell, W. H., and Butler, R. E., *U. S. Pub. Health Rep.*, 1938, **53**, 2882.

3 Sebrell, W. H., and Butler, R. E., *U. S. Pub. Health Rep.*, 1939, **54**, 2121.

4 Sydenstricker, V. P., Geeslin, L. E., Templeton, C. M., and Weaver, J. W., *J. A. M. A.*, 1939, **113**, 1697.

5 Spies, T. D., Vilter, R. W., and Ashe, W. F., *J. A. M. A.*, 1939, **113**, 931.

6 Jolliffe, N., Fein, H. D., and Rosenblum, L. D., *New Eng. J. Med.*, 1939, **221**, 921.

In view of these facts, it seems important to report our observations on 4 consecutive cases of cheilosis occurring spontaneously in association with other deficiency syndromes in patients admitted to this hospital and treated with synthetic vitamin B_6 [2 methyl, 3 hydroxy, 4.5 di(hydroxymethyl) pyridine].*

The first patient treated was a 7-year-old colored girl admitted to the hospital with a diagnosis of pellagra. Pellagrous lesions were present on the hands and feet. A dietary history revealed a marked deficiency of the vitamin B-complex. There were typical cheilosis lesions of the lips, characterized by maceration and fissuring at the angles. (Fig. 1a.) There was an associated severe anemia. The patient was placed on the basic diet of Smith and Ruffin which is known to be low in the B-complex and especially so in riboflavin.[7] Treatment with synthetic vitamin B_6 hydrochloride† was started with 20 mg intravenously 24 hours after admission. Within 5 hours slight but definite objective improvement could be observed in the mouth lesion. In 24 hours the improvement was demonstrable by

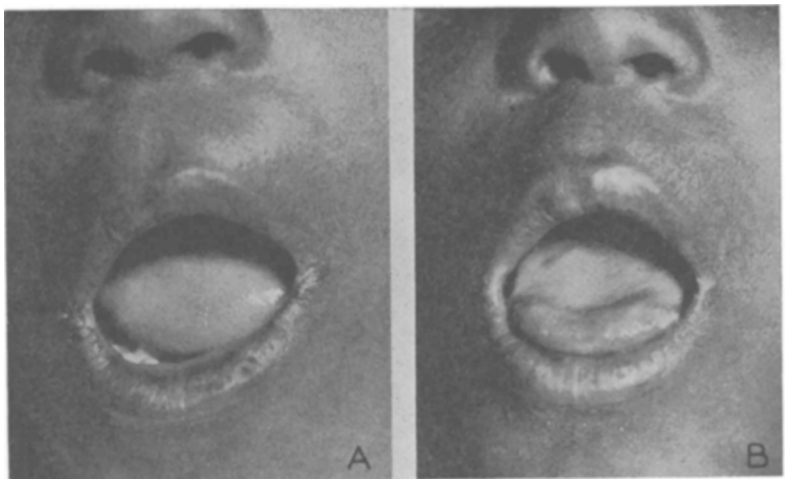

FIG. 1.
A. Before treatment was initiated.
B. Five days after starting treatment with B_6.
(20, 20, and 40 mg given 1st, 2nd, and 4th day respectively).

* The synthetic vitamin B_6 used in this work was obtained through the courtesy of Merck and Co., Rahway, N. J.

7 Smith, D. T., and Ruffin, J. M., *Arch. Int. Med.*, 1937, **59**, 631.

† The vitamin B_6 was prepared for intravenous use by dissolving it in freshly distilled water at a concentration of 50 mg per cc. The vitamin is readily soluble in water and no difficulty is encountered in getting this concentration. The solution was placed in a vaccine bottle and sterilized by autoclaving.

photograph. A 20 mg dose was given intravenously the next day with continued improvement. The next 2 days B_6 therapy was omitted and there was a slight regression. At this time a 40 mg dose was given intravenously and the improvement obtained within 24 hours was marked. (Fig. 1b.) The lesion healed completely from the effects of this dose. This is the only anemia patient studied in which the anemia responded after B_6 treatment, while the patient was subsisting on a diet very low in iron.

The second case of cheilosis occurred in a white woman, aged 62 years, suffering from severe gastric distress, pain, nausea, distension. There was an accompanying anorexia, anemia and extreme weakness of arms and legs. The cheilosis was not quite so typical as in the first case, because the fissures were not as prominent. They were smaller, and tended to bleed and later form encrustations. An inclination on the part of the patient to pick at these lesions resulted in some infection. The first dose of 100 mg B_6 hydrochloride was given intravenously. No treatment was given the next day. On the third day 50 mg B_6 hydrochloride was given by mouth and a second 50 mg on the fourth day. On the fifth day the lesions were entirely healed and did not return during the course of the illness, though the patient died two months later with a blood dyscrasia. The anorexia, anemia and severe weakness were unaffected.

The third case of cheilosis occurred in an 18-months-old white girl with a diagnosis of celiac disease. Her lesions were characterized by small fissures in the corners of the mouth with red areas surrounding them. They developed while she was subsisting on a diet composed primarily of milk and bananas. At this time the only change of regime was the intravenous administration of 50 mg of B_6 hydrochloride daily for 4 days. This resulted in the healing of the mouth lesions which remained healed during the rest of her stay in the hospital.

A fourth case of cheilosis, mild, but characteristic, occurred in a 27-year-old sprue patient. This patient was extremely deficient in many of the vitamin factors. There was slight improvement of the mouth lesion with B_6, but complete healing did not occur either with vitamin B_6 (1000 mg) or with a combination of B_6 (300 mg), riboflavin (140 mg) and nicotinic acid (1000 mg). The lesion finally healed completely, however, when 445 units of a concentrated liver extract‡ was given intramuscularly over a period of one week.

It is interesting in these 4 cases that the first was cured while receiving a basic diet deficient in riboflavin and the third developed

‡ Lederle solution liver extract parenteral refined and concentrated (N.N.R.).

the lesion while receiving what should have been an adequate supply of riboflavin from approximately one quart of milk a day and a fair amount of vitamin B_6 in the banana which was assayed in this laboratory and found curative of the typical B_6 deficient dermatitis of rats when fed in daily doses of 0.75 g.[8]

We have found it true in controlled laboratory experiments that often a primary vitamin deficiency results in symptoms not altogether characteristic of that deficiency. This is brought about by the precipitation in the later stages of the primary deficiency of a secondary deficiency which is responsible for the symptoms observed.[9] It is probable that some such phenomenon may explain the curative powers of both riboflavin and B_6 in clinically similar lesions.

The nearest thing we have to an animal analogue of the cheilosis is the mouth lesion observed in the B_6-deficient rat. This occurs when as much as 100 μg of synthetic riboflavin are fed individually but yields to treatment with synthetic B_6. Similar lesions also occur in riboflavin-deficient rats but less frequently.

There are then 3 possible explanations of the observations that both riboflavin and B_6 cure cheilosis, (1) that riboflavin is the primary and specific deficiency responsible for the cheilosis and the B_6 operates only indirectly, (2) that vitamin B_6 is the primary and specific deficiency responsible for the cheilosis and the riboflavin acts only indirectly, and (3) that both riboflavin and vitamin B_6 are necessary to maintain the integrity of the lips at the mucocutaneous junction and that a deficiency of either will precipitate the lesion.¶

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8 Smith, S. G., unpublished data.

9 Margolis, L. H., Margolis, G., and Smith, S. G., *J. Nut.*, 1939, **17**, 63.

¶ Since this paper went to press two more patients with cheilosis have been treated, one with vitamin B_6 (350 mg) and one with riboflavin (50 mg) and both responded promptly. It should be noted here that Aykroyd and Krishnam[10] have reported the cure of cheilosis with a yeast preparation freed from flavin.

10 Aykroyd, W. R., and Krishnam, B. G., *Ind. J. Med. Res.*, 1938, **25**, 643.