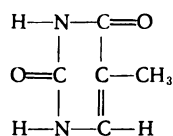


## ANTI-ANEMIC PROPERTIES OF THYMINE

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**T**HYMINE (2,4-dioxo-5-methyl pyrimidine), one of the nucleotides found in thymo-nucleic acid, was isolated by Kossel and Neumann in 1893,<sup>1</sup> and a few years later was synthesized by a number of other investigators. Since it is an integral portion of the biologic cell we have had special interest in the possibility of its having a role in hemopoiesis for some time. Our recent studies<sup>2</sup> showed that no hemopoietic response in macrocytic anemias occurred following the administration of one gram or less of thymine daily and that even 4.5 grams given daily produced only a submaximal response. The present communication is concerned with the effect of administering larger doses of thymine to patients with Addisonian pernicious anemia in relapse.

Thymine (2,4-Dioxo-5-methyl pyrimidine)



Three patients with macrocytic anemia and a histamine refractory achlorhydria and achylia were admitted to the hospital for study. The diet, which excluded all meat, meat products, fish, poultry, and uncooked fresh leafy vegetables and which allowed only one pint of milk and one very well cooked egg a day, was rigidly controlled. Daily hematological studies were performed as previously described.<sup>3</sup>

Physical examination on admission in all three subjects revealed the characteristic signs of pernicious anemia and, in addition, arteriosclerosis of moderate degree. One of the patients had a chronic pelvic infection which was active during the first eleven days of her treatment period. The other two subjects had no evidence of acute or chronic infection.

Prior to treatment a complete blood count, blood indices, sternal bone marrow studies, icterus index, urinalysis, stool analysis, gastric analysis, oral glucose tolerance tests and gastro-intestinal X-rays were made on each patient. In each of the three cases the color index was above 1.0, and the mean corpuscular volume was greater than 110.0 cubic microns; the mean corpuscular hemoglobin and mean corpuscular hemoglobin concentration were greater than 32 micro-micrograms and 34 per cent, respectively. Sternal bone marrow was obtained by means of the Turkel trephine, the puncture being made through the sternum opposite the second

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intercostal space. The bone marrow preparation from each patient showed arrest of the cells at the megaloblastic level. In each case the icterus index was above normal and the urine and stools were essentially negative. Gastric analysis after histamine stimulation showed achlorhydria and achylia in all the patients. In each case, upper gastro-intestinal series and oral glucose tolerance tests were essentially normal.

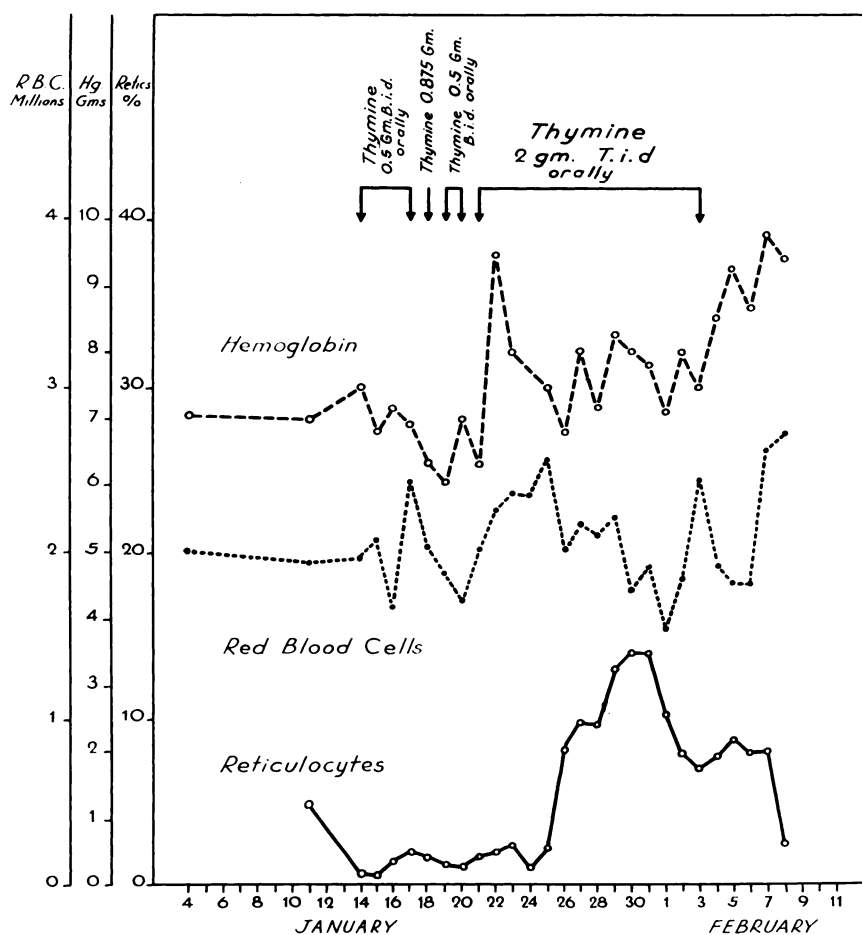


FIG. 1. THE HEMATOLOGIC RESPONSE IN A PATIENT WITH PERNICIOUS ANEMIA IN RELAPSE TO VARYING DOSES OF THYMINE

The thymine was weighed on an analytical balance and suspended in one-half glass of cold tap water. The glass was rinsed twice with water which the patient drank in order to insure his obtaining any undissolved thymine which might cling to the sides of the glass.

Case I was given 0.5 grams of thymine twice daily for six days without any hematological or clinical response. The dose was then increased to 2.0 grams three

times a day for fourteen days. The effectiveness of these dosages is shown in Fig. 1.

Case II received 3.4 grams three times a day for eleven days.

Case III was given 1.5 grams three times a day for fourteen days. The dose was then increased to 3.4 grams three times a day. The response of these three patients to this therapy is shown in the accompanying tables.

In Case I the initial reticulocyte response and the peak reticulocytosis were delayed. This might have been due to an acute exacerbation of a chronic pelvic

TABLE 1.—Effect of Oral Administration of Thymine on Peripheral Blood in Pernicious Anemia

Case	R.B.C. (millions per cu. mm.)			Hg. (Gm. per 100 cc.)			Reticulocytes (%)			Dosages thymine			Remarks
	Initial	14 days	Final day	Initial	14 days	Final day	First day of rise	Day of peak	Per cent at peak	Daily dose (Gm.)	No. of days	Total Gm.	
I (B. B.)	2.01	2.43	2.88 (22)	6.3	7.5	10.4 (22)	6	11	14.2	6.0	14	84	59 year old Negro female Chr. pelvic inflammatory disease. Moderate arteriosclerosis Received 1.0 Gm. q.d. × 6 without response
II (H. R.)	1.58	2.29	2.51 (17)	6.2	10.1	9.8 (17)	4	6	19.0	10.2	11	112.2	57 year old white female Moderate arteriosclerosis
III (D. L.)	1.67	1.93	2.34 (18)	7.5	9.4	9.8 (18)	6	11	9.0	4.5 10.2	13 4	58.5 40.8	75 year old white male Moderate arteriosclerosis

TABLE 2.—Effect of Oral Administration of Thymine on Leucocytes in Patients with Pernicious Anemia

Case	Initial	7th day	14th day
I (B. B.)	2950	4950	9200
II (H. R.)	4200	5200	6100
III (D. L.)	6950	7750	8950

infection during the first eleven days of therapy. Case II showed the type of reticulocyte response which could be expected following adequate therapy with a potent liver extract.<sup>4, 5</sup> In Case III an effort was made to determine the optimal dose by means of the double reticulocyte response described by Castle and Minot.<sup>6</sup> After what appeared to be a submaximal reticulocyte response to 1.5 grams of thymine three times a day and after the reticulocytes were consistently decreasing in number, the dose was increased to 3.4 grams three times a day. The second reticulocyte peak of 8.8 per cent occurred on the 6th day after the increase of dosage. Coinci-

dent with the reticulocyte response in each case, there was a great increase in appetite, strength, and vigor.

Sternal bone marrow studies were repeated on the 17th, 7th, and 12th days after treatment was instituted in Cases I, II, and III respectively. In Cases I and II the bone marrow smears showed a reversion from bone marrow characteristic of megaloblastic arrest to bone marrow which was normoblastic. Such a change was indicative of adequate therapy with a potent anti-anemic substance and a reversion toward a normal bone marrow. The bone marrow in Case III did not show as marked a normoblastic reversion as in Cases I and II. Although some megaloblastic arrest was evident, there was a definite increase in the number and percentage of normoblasts with a concomitant decrease in the number and percentage of megaloblasts as compared with the control bone marrow smear. Thus, the marrow in this case was characteristic of an inadequately treated case of erythrocyte maturation factor deficiency anemia.

#### SUMMARY

Three patients with Addisonian pernicious anemia were selected, hospitalized and given a diet devoid of meat and meat products. After baseline hematological studies were made and checked repeatedly, daily large doses of thymine were given orally.

The clinical and hematological improvement in these three patients was in every way similar to that which follows the administration of folic acid to patients with pernicious anemia in relapse. The exact mode of action of thymine is obscure, but it is possible that folic acid may act as an enzyme or co-enzyme in the synthesis of thymine or a thymine-like compound. Such synthesis may take place in the gastro-intestinal tract. The present findings indicate that thymine has anti-anemic properties and a profound effect on the general metabolism of patients with Addisonian pernicious anemia in relapse.

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