

Unlike other methods used in physiology,⁹ the present method determines the instantaneous rate of absorption. It can be used repeatedly in the same animal and is probably the only method that can be used in man. It throws a different light on the interpretation of the cumulative average absorption as calculated by Cori's method.¹⁰ Thus, in the experiment on Subject G.N.B., the amount absorbed in 1 hr is 3.06 g, in 2 hr, 5.89 g, and in 3 hr, 6.13 g. Cori's coefficients are $3.06/1 = 3.06$, $5.89/2 = 2.95$, and $6.13/3 = 2.04$ g per hr. According to the usual interpretation, the rate

of absorption of creatinine would have been considered constant in the first 2 hours. A glance at Fig. 2 shows that this conclusion would have been erroneous. In other words, the cumulative average amount absorbed per hour (Cori's coefficient) should not be considered the same as the rate of absorption.

Summary and Conclusions. For an inert substance in diffusion equilibrium, the rate of absorption at any time is shown to be equal to the rate of excretion plus the product of the volume of distribution and the rate of change in the concentration of the substance in the plasma. Two solutions of this equation are described and are applied to the absorption of creatinine in 3 human beings.

⁹ McGee, H. E., *Physiol. Rev.*, 1930, **10**, 473.

¹⁰ Cori, C. F., *J. Biol. Chem.*, 1925, **66**, 691.

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Effect of Pyridoxine on Granulopenia Caused by Thiouracil.*

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In the course of an investigation of the effect of thiouracil on the basal metabolic rate of 96 hyperthyroid subjects¹ we encountered a marked fall in the granulocytic cells of 20% of these patients among which were 4 cases of true agranulocytosis. It has been noted by Bilter, Schiro and Spies² that intravenous injection of pyridoxine into 3 pellagrins with pernicious anemia resulted in an increase in the white cell count and that this increase took place principally in the granulocytic series. Cantor and Scott³ have administered pyridoxine hydrochloride intravenously in daily doses of 125-200 mg to 3 cases of agranulocytosis of varied origin and have noted a marked and rapid return to a normal granulocyte count in each instance.

Although thiouracil reduced the B.M.R. in our hyperthyroid subjects at an average rate of 1 unit % per day, with parallel amelioration of all accompanying signs and symptoms of thyrotoxicosis, it had to be withdrawn forthwith after a rapid or precipitate fall in the white count. We therefore used pyridoxine in the hope of lowering the incidence of these hematological accidents.

To 8 hyperthyroid subjects receiving the usual dose of thiouracil 200 mg of pyridoxine were given daily by mouth. Fig. 1 shows the total leucocyte count for 8-week periods prior (open symbols), and during (solid symbols) pyridoxine administration. The average white counts were increased between 1500-2000 cells per cu mm.

Fig. 2 shows the leucocyte count of a subject receiving a 0.2 g maintenance dosage of thiouracil, in whom owing to the destructive action of thiouracil on the bone marrow, the granulocyte count dropped from 3700 to 400 cells per cu mm within 2 days. Four cc of a 5% solution of pyridoxine hydrochloride (200 mg) were injected and resulted in an increase

* Thiouracil and pyridoxine supplied by Dr. Staunton Hardy of Lederle Lab.

¹ Fishberg, E. H., and Vorzimer, J., *J. Am. Med. Assn.*, 1945, **128**, 915.

² Vilter, R. W., Schiro, H. S., and Spies, T. D., *Nature*, 1940, **145**, 388.

³ Cantor, M. M., and Scott, J. W., *Science*, 1944, **100**, 545.

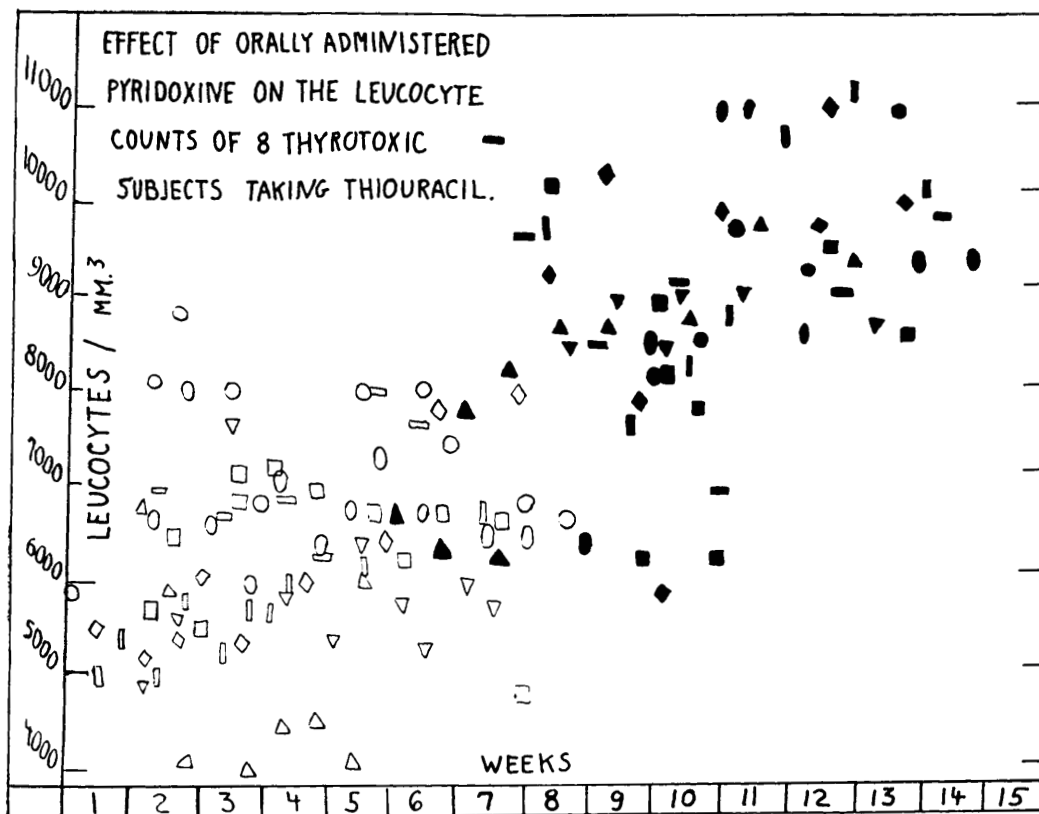


FIG. 1.

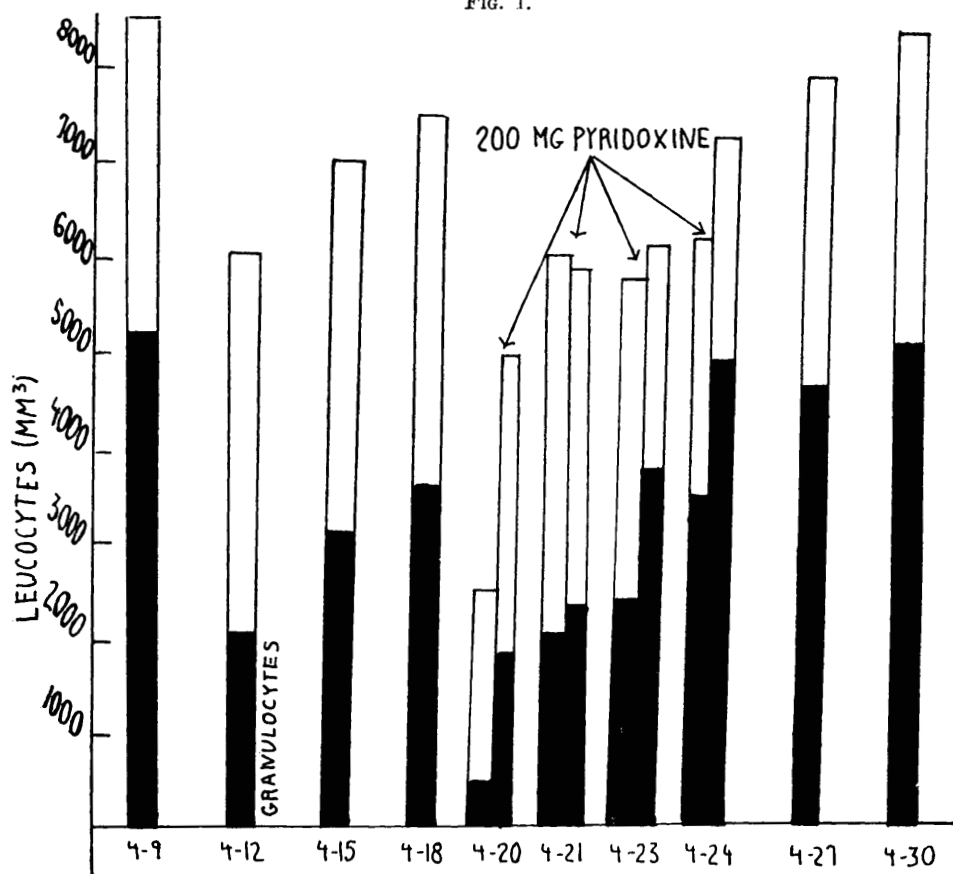


FIG. 2.

CHART I.
Differential Leucocyte Count in a Thiouracil-sensitive Subject.

Date.	Thio- uracil g	Pyri- doxine mg intrav.	Leuco- cytes per mm ³	Polys per mm ³	% Polys	% Lympho- cytes	% Mono- cytes	% Eosin.	% Staff
3/28	.6	0	13,500						
4/ 2	.6	0	13,500						
5	.6	0	11,200						
9	.6	0	6,550	3,210	49	46	3	2	
12	.3	0							
19	.3	0	7,800						
23	.3	0	6,600	2,508	38	54	6	1	2
26	.2	0	2,000	500	25	63	8	3	1
26	0	200	4,000	1,520	28	58	7	2	
27	0	200	5,750	1,610	28	60	6	4	
27	0	200	5,150	1,751	34	55	6	4	
28	0	200	6,000	2,400	40	57	5	2	2
29	0	100	7,500	3,300	44	47	1	5	1
5/ 4	0	0	7,900	4,101	52	43	1	1	2
5	0	0	12,250						
28	0	0	9,500						
31	.2	0	9,650						
6/ 4	.2	0	7,600						
7	.2	0	3,600	648	18	73	5	2	2
7	0	200	5,900	2,301	39				
8	0	200	7,000	3,010	43	50	3	1	3
9	0	200	8,950	4,674	52	43	3	1	1

to 1800 granulocytes per cu mm within 2 hours. This was repeated on 4 successive days (thiouracil being withdrawn) with an increase of the granulocyte count to 4900 cells per cu mm.

In Fig. 3 the curves of the granulocyte counts in 2 cases of agranulocytosis due to thiouracil are drawn on the same coordinates. In curve II no pyridoxine was used and there ensued the usual picture of agranulocytic angina with high fever and a necrosing lesion of the tonsillar area. In curve I 4 cc of a 5% solution of pyridoxine were injected at the points shown by arrows. Within 48 hours the granulocytes had increased to the same level reached in 13 days in the subject treated with transfusions and penicillin.

Chart I shows the blood picture in a 28-year-old man, obviously sensitive to thiouracil, in whom the white blood count had been 10,000 cells for the previous 2 weeks while taking 0.6 g of thiouracil daily. The count fell suddenly to 6,500 leucocytes per cu mm and the thiouracil was reduced to 0.3 g daily. The leucocyte count rose a little but on April 26 suddenly fell to 2000 with only 25% polymorphonuclear cells. After withdrawing thiouracil an injection of 200 mg of pyri-

doxine doubled the leucocyte count and tripled the granulocyte count within 4 hours. On May 31 an attempt was made to resume thio-

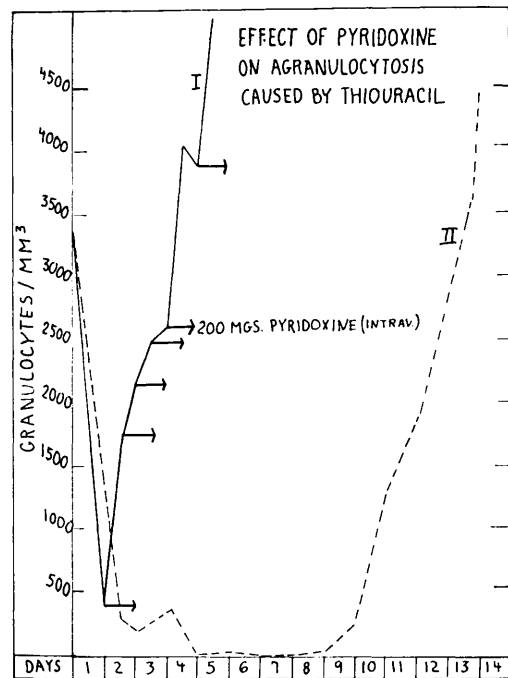


FIG. 3.
Solid line with pyridoxine. Broken line without pyridoxine.

uracil therapy with an initial small dose of 0.2 g daily but the leucocyte count fell within a week to 3,600 with 18% polys.

The appearance of the normal number of granulocytes in the blood stream is dependent on two factors: a hypothetical and as yet undemonstrated substance which regulates the orderly maturation of the myeloblast into the completely segmented granulocyte and the second which governs the entrance of the mature cell into the peripheral blood stream. The rapidity of action of the pyridoxine would seem to indicate that the primary action must be on the release mechanism. However,

the possibility of a direct stimulation of the myelocytic elements of the bone marrow is a question which can only be answered by extensive bone marrow studies.

Summary. Our results would seem to indicate that pyridoxine can bring about a rapid and significant rise in the number of circulating granulocytes in the blood in human subjects after a depression caused by thiouracil. Although there is a large element of self recovery after removal of the toxic agent there seems to be no doubt that the recovery process is much accelerated by pyridoxine.

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Experimental Tumors after Nerve Section in an Insect.*

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In the course of a study of the endocrine functions of the corpora cardiaca and allata in insects the occurrence of tumors was noted. The corpora cardiaca in the species used (*Leucophaea maderae*, Orthoptera) are elongate structures behind the brain which continue postero-laterally into the corpora allata. In a series of experiments both corpora allata together with the posterior part of the corpora cardiaca were removed (Fig. 3, b). Following these operations tumors developed predominantly in 2 locations, namely, in the anterior portion of the alimentary canal and in the salivary reservoir. In rarer instances the salivary glands were involved (Fig. 1).

The appearance of these tumors was first suspected to be due to an endocrine disturbance resulting from the removal of the corpora allata or cardiaca. Such an interpretation would be supported by the fact that in young nymphs of another Orthopteran (*Dixippus*) allatectomy was followed by abnormal tissue growth and degeneration.¹ Furthermore,

endocrine factors play a role in the origin of certain mammalian tumors.^{2,3} Of the two endocrine glands here under consideration the corpora allata seemed by far more likely to be connected with the formation of neoplasms, since tumors developed also in such operations where a major portion or almost all of the corpus cardiacum tissue had been left intact (Fig. 3, c). Furthermore, the known hormonal actions of the corpora allata include the regulation of the rate of tissue growth and maturation, metabolism, and egg development.⁴⁻⁸

If the tumors to be described are caused by the lack of a corpus allatum hormone, it should be possible to prevent their occurrence by reimplantation of corpora allata into allatec-

² Gardner, W. U., *Surgery*, 1944, **16**, 8.

³ Nathanson, I. T., *New Eng. J. Med.*, 1944, **231**, 764, 795.

⁴ Wigglesworth, V. B., *Quart. J. Micr. Sci.*, 1936, **79**, 91.

⁵ Pfeiffer, I. W., *J. Exp. Zool.*, 1939, **82**, 439.

⁶ Pfeiffer, I. W., *Anat. Rec.*, 1941, **81**, suppl., 57.

⁷ Scharrer, B., *Anat. Rec.*, 1943, **87**, 471.

⁸ Scharrer, B., *Anat. Rec.*, 1944, **89**, 539.

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¹ Pflugfelder, O., *Z. wiss. Zool.*, 1938, **151**, 149.