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Valine and Isovaleric Acid Show Positive Influence upon Hemoglobin Production in Anemia Due to Blood Loss.

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The experiments tabulated below give evidence that the anemic dog can use valine to aid in the building of new hemoglobin. Moreover the dog can use the optical isomer (antipode) as well as the naturally occurring amino acid (*d*-form). It has been reported[1] that histidine and phenylalanine react as does valine. It is generally believed that before the optical isomer can be utilized in the body it must be deaminized and perhaps be recast in the natural form. A variety of mechanisms could come into play to explain the observations relating to the optical isomers.[2] When these observations were reviewed with Dr. Rose, he raised the question as to the related fatty acids. The experiments below indicate that isovaleric acid can at times be used by the anemic dog in building new hemoglobin under the conditions of these experiments.

The technical procedures related to these experiments have been fully described[3] and the preparation of the basal ration (salmon bread) has been reviewed. Pure crystalline amino acids were used in these experiments. These anemic dogs are standardized over a period of years and their response in hemoglobin production to various factors well established. The control figures are given in Table I not only for the standard feeding of liver but for iron in 40 mg doses per day. The standard salmon bread used in all but 2 experiments contained 3 mg Fe per 100 g as fed. The 2 experiments under *d*-valine, Table I (Dogs 35-7 and 32-5) were carried out with a salmon bread which contained approximately 9 mg Fe per 100 g and this accounts for the high output on the salmon bread alone. Under these experimental conditions we consider a production of 10 g hemoglobin over and above the control basal bread output to be significant.

Table I shows that the natural *d*-form of valine may influence hemoglobin production. In 3 experiments the output of hemoglobin

1 Whipple, G. H., and Robscheit-Robbins, F. S., Proc. Soc. Exp. Biol. and Med., 1937, **36**, 629.

2 *Ann. Rev. of Biochemistry*, 1936, 253.

3 Whipple, G. H., and Robscheit-Robbins, F. S., *Am. J. Physiol.*, 1936, **115**, 651.

TABLE I.
Valine and Isovaleric Acid Influence Hemoglobin Production in Anemia.

Dog No.	Valine and isovaleric acid fed: Daily dose, g	Valine and isovaleric acid fed: Hemoglobin net output per 2 wk, g	Control net hemoglobin output per 2 wk: Iron 40 mg daily-oral, g	Control net hemoglobin output per 2 wk: Liver 300 g daily-oral, g	Control net hemoglobin output per 2 wk: Basal bread ration alone, g
		Valine, d-form (natural)			
35-7	1	33	61	82	22
35-2	1	35	48	104	4
32-5	1	3	69	86	34
29-326	1	4	56	84	4
35-4	1	26	56	89	4
		Valine, l-form (optical isomer)			
35-7	1	21	51	82	4
36-11	1	12	65	66	4
33-14	1	7	58	72	4
32-5	1	3	58	98	4
		Isovaleric Acid			
34-148	1	11	52	85	4
35-2	1	10	48	104	4
35-7	1	32	51	82	4
35-4	1	53	56	89	12

ranges from 26 to 35 g above the control levels. Two other experiments are negative (3 to 4 g hemoglobin).

Valine (optical isomer or *l*-form) is a little less potent. Two experiments may be listed as positive (12 and 21 g hemoglobin net output) and 2 as negative (3 and 7 g hemoglobin net output).

Isovaleric acid (Table I) if anything is a little more potent than *l*-valine but we would not stress these differences—at least the general trend is similar. Two experiments are on the border line (10 and 11 g hemoglobin net output) but 2 others show significant outputs of hemoglobin (32 and 53 g).

In a considerable number of experiments with a variety of amino acids we have observed that in the majority of experiments there is a positive response—that is more than 10 g hemoglobin produced during the test period over and above the bread base line. There are also frankly negative experiments as recorded in Table I.

It is difficult to give a satisfactory explanation for the observed facts but we prefer the following argument. The standard dog ingests with his food one gram a day of the given amino acid which is absorbed together with a great mixture of amino acids coming from the digested protein in the standard salmon bread (wheat protein and canned salmon muscle). To make extra hemoglobin the dog must supply the other amino acids to supplement the specific amino acid given and these accessory amino acids must be derived from the food intake (standard bread), from body stores, or from protein catabolism. We assume that in this long continued anemia there is a stimulus for the dog to utilize all available material to make new and badly needed hemoglobin. The added amino acid may accelerate the flow of other amino acids in the direction of globin production which globin we assume is the limiting factor in certain experiments. When the amino acid feeding experiments are frankly negative we may assume that one or more of the many supplements which the body must add are not available during that particular period and hemoglobin synthesis fails.

If the animal can break up certain amino acids and recombine the mangled remains[4] to form other amino acids and body protein, there is no reason why this same reaction can not take place in the rapid production of the protein hemoglobin in experimental anemia. Therefore it is reasonable to test various simple substances closely related to amino acids to ascertain whether the dog can utilize these substances in hemoglobin construction. Isovaleric acid appears to qualify in this respect and we plan to continue a study of related compounds.

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Some Effects of Feeding Thyroid to Immature Fishes (*Platypoecilus*).

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Striking effects have been obtained by feeding desiccated mammalian thyroid (Parke Davis & Co.) to sexually immature poeciliid fishes of the genus *Platypoecilus*. The details of the response are now under investigation but its general nature may be briefly described.

Control and experimental animals were secured by dividing single progenies and placing them in adjacent tanks. Both groups received routine laboratory feeding—ground liver and young brine shrimp on alternate days. In addition, the experimental groups each morning throughout the experiment received a pinch of thyroid powder scat-

[4] Schoenheimer, R., Ratner, S., and Rittenberg, D., *J. Biol. Chem.*, 1939, **127**, 333.