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dl-Methionine in Developmental Growth.*

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(Introduced by A. J. Goldforb.)
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It is known that methionine can replace cystine as a growth essential in the diet of rodents.[1, 2, 3] This report extends to the invertebrate marine hydroid *Obelia geniculata* the premise that this sulfur-containing amino acid is a growth stimulant. The purpose is to see whether lower as well as higher organisms can utilize —S— sulfur for growth purposes, and whether any particular phase of growth activity is responsive thereto, since this point is unsettled in work with rodents.

Through the courtesy of Professor du Vigneaud we obtained enough dl-methionine for 32 experiments. In these the developmental growth of some 6000 animals in methionine cultures was compared with that of a like number in plain sea water. Description of the organism and its growth together with that of the experimental and other procedures is given in detail elsewhere.[4, 5] Tests and controls were run simultaneously under like conditions of temperature, illumination, and pH. Results are tabulated as condensed consistency data from which is seen the trend of test deviation from control in expression of new growth initiation, proliferation, differentiation, and organization, as well as that for maintenance, regression, and catabolism.[6] The table also gives the concentrations used and the number of experiments, colonies, hydranths, and gonophores. Since general reaction was essentially the same in the stated concentrations the data were combined into one set of figures to save space. Those for the 6 experiments at

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1 Jackson, R. W., and Bloch, R. J., *J. Biol. Chem.*, 1932, **98**, 465.

2 Weichselbaum, T. E., *et al.*, *Nature*, 1932, **129**, 795.

3 du Vigneaud, V., Dyer, H. M., and Harmon, J., *J. Biol. Chem.*, 1933, **101**, 719.

4 Hammett, F. S., *Protoplasma*, 1933, **7**, 297.

5 Hammett, F. S., *Protoplasma*, 1935, **23**, 326.

6 Lavine, T. F., *Am. J. Cancer*, 1935, **25**, 809.

TABLE I.
Trend of Test Deviation from Control with Respect to Developmental and Metabolic Activity in dl-Methionine Cultures.

"S" M/1000x	8x10-8 400(7) +	—	0	1.6x10-7 200(10)	3.2x10-7 100(9) Control	Test
New Growths	10	5	6	No. Experiments	26	
Proliferation	9	6	9	" Colonies	326	321
Differentiation	9	10	10	" Hydranths	5247	5240
Organization	7	8	9	" Gonophores	368	330
Maintenance	5	20	1	% Regression	27	30
Catabolism	8	16	2	% Catabolism	93	86

M/50,000 and M/25,000 were omitted because they show nothing but toxicity.

The table shows methionine acts to stimulate growth in obelia as in rodents but that the early stages, not the later, are influenced. Thus both new growth production and proliferation were enhanced while the succeeding phases of differentiation and organization were essentially unaffected. The evidence is the fact that test progression was greater than control in 19 and less in but 11 of the combined expressions of the early activities, while it was greater than control in but 16 and less in 18 of the later. The fact that catabolic disintegration was less in tests than controls is consistent.

The demonstration that it is growth in which cell increase in number plays a major part that was differentially enhanced is significant. For since it is the —SH group which appears to be specifically effective in this direction[7] these findings support the possibility that methionine is converted first to cystine[1] and then to cysteine.[8, 9]

Probably consistent with the foregoing is the fact that somewhat higher concentrations were effective and toxic with sulfur as —S— than with sulfur as —SH. This would be expected if conversion preceded activity.

Finally it is recorded that cystine increases respiratory metabolic activity[10] and our results show that such occurred with methionine. Maintenance was less and regression increased.[5] Whether this be expression of specific dynamic effect or not, a matter which should be studied with higher organisms, the correlation supports the assumption of conversion.

[7] Hammett, F. S., *Protoplasma*, 1930, **11**, 382.

[8] Loring, H. S., Dortmann, R., and du Vigneaud, V., *J. Biol. Chem.*, 1933, **103**, 399.

[9] Lewis, H. B., *Physiol. Rev.*, 1924, **4**, 394.

[10] Miyao, S., *Gann*, 1935, **29**, 10.

Summary and Conclusion: Thirty-two experiments with nearly 12,000 obelia, half of which were exposed to dl-methionine in varied concentration showed this sulfur containing amino acid acts as a growth stimulant to this lowly animal as it does to higher. The effect was differentially produced on growth in which cell increase in number was dominant. The results taken with correlated data are consistent with the assumption that methionine may be converted to cystine in the living organism.

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The Action of Ergometrinine.

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Ergometrinine is one of the newer alkaloids of ergot isolated by Smith and Timmis.[1] It decomposes at about 195° and has an optical rotation of $[\alpha]^{20}_{5461}$ + 598°. Its empirical formula is the same as that for ergometrine, that is, $C_{19}H_{23}O_2N_3$. Raymond-Hamet[2] reported that in the dog ergometrinine caused a rise of blood pressure and vasoconstriction, and that with a dose of 24.5 mg. per kg., it abolished the vasoconstricting action of adrenalin. He concluded that ergometrinine was weaker than ergometrine.

With the aid of Mr. Howard B. Fonda, Experimental Research Laboratories, Burroughs Wellcome and Company, Tuckahoe, we were able to secure 50 mg. of ergometrinine nitrate. The material is easily soluble in water and exhibits a blue fluorescence in aqueous solution. Unlike ergotoxine or ergotamine, ergometrinine does not inhibit the adrenalin response on the isolated rabbit's uterus in a concentration as strong as 1:27,777 (the Broom-Clark test[3]), but on the contrary, it exerts a weak stimulating action itself. When assayed by the method described previously,[4] ergometrinine HNO_3 was shown to be 1/100 as active as ergotocin maleate in 6 observations (Fig. 1A). Since the results obtained in our laboratory indi-

[1] Smith, S., and Timmis, G. M., *Nature*, 1935, **136**, 259.

[2] Raymond-Hamet, *Compt. rend. Soc. de biol.*, 1935, **120**, 1208.

[3] Broom, W. A., and Clark, A. J., *J. Pharm. and Exp. Therap.*, 1923, **22**, 59.

[4] Swanson, E. E., Hargreaves, C. C., and Chen, K. K., *J. Am. Pharm. A.*, 1935, **24**, 835.