INTERACTIONS OF GROWTH STIMULANTS AND PROTEINS*

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Tissue proliferation stimulants are of interest in the field of malignant growth and in normal physiological repair. Proliferation is stimulated in the development of cancer, Loeb et al (1), Hammett (2), Owen (3) and others.

Among the reported growth stimulants are the sulphydryl containing complexes, Hammett (4), larva, Baer (5), larval preparations, Livingston (6) allantoin, Greenbaum (7), urea Hetherington et al (8), calcium salts Stewart (9) and dextrose, Lafresniere (10). In addition embryo extracts have been long used in tissue culture media. In the above substances free sulphydryl groups may readily be demonstrated in the sulphydryl complexes, in appropriate larval preparations and in freshly prepared embryo extracts. Non-antigenic extracts of embryonic tissues may be made which are effective in stimulating growth, Owen and Cutler (11) and a discussion of the probable chemical mechanisms or growth stimulation has been presented by Owen (12).

The effect of growth stimulants and carcinogenic chemicals on protein in vitro as regards release of free sulphydryl was tested for as follows: saturated solutions of the chemical growth stimulants in phosphate buffer at either pH 5.8 or 7.4 were added to equal volumes of solution of edestin or crystalline egg albumin or to human serum. The mixtures were tested immediately and after incubation for free sulphydryl by the phosphotungstate procedure. Cystine but not cysteine was demonstrable in the control proteins and in serum. The influence of the carcinogenics were similarly tested. Testable sulphydryl appeared in the albumin-urea and in the edestin-urea mixtures. Other growth stimulants and the carcinogenics failed to cause the appearance of free —SH.

It appears that substances which indirectly or directly release sulphydryl groups from proteins should act as growth stimulants. Substances which release urea by mild hydrolysis e. g. allantoin, arginase and guanidine derivatives should also stimulate tissue growth. Materials which tend to produce a reducing situation in wounds might also be expected to cause tissue proliferation as a reduction of the sulfur-sulfur linkages in tissue proteins would be favored thus producing the essential –SH groups. The concentration of free sulphydryl (2×10^{-7}) to cause growth stimulation is extremely small and would not be picked up by the usual chemical tests. It may be noted that solution potential is lowered by nearly all reputed growth stimulants, indicating a possible increase in reduction value, Owen (13).

* Published under R. & P. 6727 Veterans' Administration.

The importance of free sulphydryl in the probable mechanism of some growth stimulants may be summarized as follows:

A. Free sulphydryl groups stimulate tissue growth.

B. Urea plus appropriate proteins releases free sulphydryl.

C. Allantoin hydrolyses to urea which then acts as in B.

D. Other guanidine derivatives may act as does allantoin.

E. Arginase releases urea from proteins, the urea then acts as in B.

F. Alkaline salts plus appropriate proteins release free sulphydryl.

G. Urease releases ammonia from tissue urea, the ammonia acts as in F.

H. Reducing conditions favor sulphydryl generation from disulfide groups.

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