CELL PROLIFERATION RESPONSE TO SULFHYDRYL IN MAMMALS

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Studies made at this Institute during the past two years have brought out the fact that the sulfhydryl group is an essential stimulus to cell proliferation in simple types of plants and animals (root-tips and *Paramecium*) (1:2). The practical and theoretical bearings of this finding are clear. They have been briefly outlined in the papers cited and elsewhere (3:4). It remained to test whether the principle developed from the work with the simple forms would be demonstrable in more complex and highly developed species. Not that there was any doubt as to the essential validity of the principle, but it was felt that its exhibition in mammals would strengthen the theoretical position by extending the boundaries of support, and at the same time provide a basis for one phase of its practical application, namely, to the healing of wounds.

It was decided to combine these two aspects of the problem within a single bracket. Consequently thio-glucose was chosen as the compound to be tested. The choice was based on the fact that this substance contains the cell proliferation stimulating -SH group attached to the natural sugar glucose which presumably would provide an easily utilizable source of energy for the multiplying cells. Thio-glucose possesses other advantageous properties. Its sodium salt is fairly easily prepared in high degree of purity (5) in crystalline form. This is quite soluble in water and on neutralization with HCl yields the free -SH compound which is reasonably stable at a phosphate buffered pH of 6.8 if kept cool and in a dark place. The compound as made by Dr. Gerrit Toennies, chemist to the Institute, was used in a concentration of 1:10,000 *S*, in the experiments to be described.

Male albino rats of about 100 grams weight served as the test objects. The procedure was as follows.

The rat was anesthetized with ether or urethane and the hair removed from the back or abdomen by clipping and shaving. Two approximately circular pieces of skin, $\frac{3}{8}$ inch in diameter, were then cut out on opposite sides of the depilated area, taking care that no muscle or fascia was removed therewith.

Each wound was then covered with a small piece of gauze on which was placed a small wad of absorbent cotton. This dressing was covered with a square of thin rubber dam sealed with collodion to the body surface so that communication between the two wounds was prevented. A small hole cut in the dam over the cotton wad allowed the application of the test and control solutions to the two wounds respectively. The whole was held in place by an appropriate strip of adhesive tape encircling the body and suitably perforated over the dressings.

The test solution contained sulfur in 1:10,000 concentration as thio-glucose liberated by HCl from sodium-thio-glucose. This was buffered to a pH of 6.8 by 1.0 cc. Sorensen's phosphate mixture to 100 cc. solution. The control solution contained glucose, NaCl, and phosphate mixture in concentrations equivalent to those of the test.

Each of the two wounds was kept moist with one of the solutions by simultaneously saturating the dressing therewith every two or three hours for a period of 48 to 72 hours. At the end of this time the dressings were removed and the results recorded. Which solution contained the thio-glucose was unknown to us until this had been done, the information being solely in the hands of the chemists.

Three series of experiments were run with ten, eight, and seven rats respectively.

In the first series, eight out of the ten rats showed a distinct acceleration of wound healing on the side to which thio-glucose had been applied. In the second lot six out of the eight were similarly affected, and in the third six out of the seven. In the last two series the failures could be attributed to the fact that the rubber dam barrier between the wounds was not complete and intermingling of the solutions occurred.

The evidences of more rapid healing were as follows: More rapid contraction of the edges of the wound; lack of bleeding on removal of the gauze; obviously greater cellular growth over the surface of the wound; and in some cases inability to remove the gauze because of its interpenetration by the new growth.

The accompanying photograph demonstrates some of these points. The lower wound which had been treated with the control glucose

solution was raw and showed but little evidence of healing. The gauze though in close contact with the raw surface lifted off easily. The upper wound, to which the thio-glucose had been applied, was dry, the area was diminished, and the cells had so grown on to and within the meshes of the gauze that its removal without tissue destruction was impossible.

The advantage possessed by the sulfhydryl-treated wound was in general maintained, this coming to complete healing some days before that of the control side.

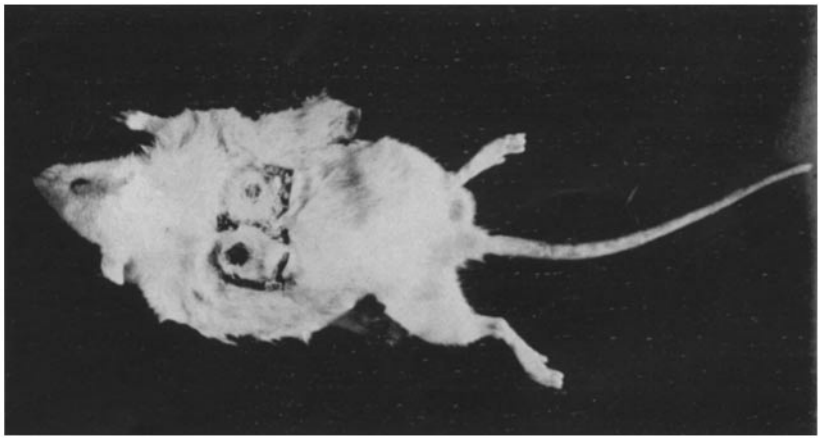

FIG. 1. Photograph showing accelerating influence of sulfhydryl on cell proliferation in the rat.

Like stimulation of cell proliferation in man has been obtained. A report of the clinical application of these findings to wound healing is being prepared by Reimann.

SUMMARY AND CONCLUSIONS

These experiments establish the fact that the sulfhydryl group is stimulative of cell proliferation in mammals as in lower organisms. The fact that the stimulation is exhibited in such a wide diversity of species including both plants and animals is justification for the belief that it is the expression of a fundamental biological phenomenon.

The literature and discussion of the subject are to be found in the papers cited.

LITERATURE CITED

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