Serine Derivative with Antitumor Activity

Abstract. The sodium salt of N-dichloroacetyl-DL-serine depresses the growth of sarcoma-37 in mice, causing complete regressions of the tumor. The compound is nontoxic to mice in doses up to 4 gm/kg of body weight. The animals do not lose body weight and show no alteration in the formed elements of the blood or in hemoglobin content.

Amino acid derivatives which might serve as antagonists in the metabolism of tumor cells have been investigated for many years (*1*). Since some antibiotics have the ability to destroy neoplastic cells in experimental animals (*2*), it was reasoned that a natural amino acid modified to contain a portion of a natural antibiotic may have antimetabolite properties. As a starting point we chose the N-dichloracetyl group of chloramphenicol, since the natural amino acids are easily acylated. We have synthesized a number of N-dichloroacetyl derivatives of α-amino acids and are investigating them for antitumor activity in experimental animals.

We wish to give at this time a brief account of preliminary experiments concerning the effect of one of these derivatives—namely, the sodium salt of N-dichloroacetyl serine—on tumor growth.

Commercial DL-serine was treated with dichloroacetyl chloride in an aqueous alkaline medium at 0°C, according to the usual procedure employed for N-acylating amino acids. The purified, colorless, crystalline N-dichloroacetyl-DL-serine melted at 119° to 121°C. The sodium salt of N-dichloroacetyl-DL-serine [Frosst-T-9045 (FT-9045)] was also a white crystalline compound and melted at 178° to 179°C (with slight decomposition). Both compounds were readily soluble in water at room temperature. The sodium salt was used in the experiments described below.

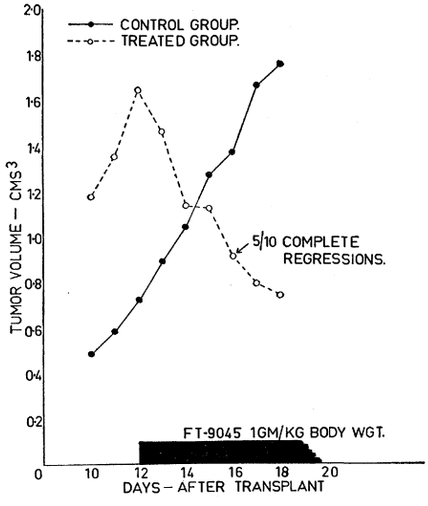

Fig. 1. Effect of 1 gm of the sodium salt of N-dichloroacetyl-DL-serine per kilogram of body weight per day on the growth of sarcoma-37 in mice. Each point represents the average tumor volume for ten animals.

Sprague-Dawley rats and Connaught mice tolerated doses up to 4 gm of the salt per kilogram of body weight, injected intraperitoneally, with no visible abnormal effects. None of the animals died. Connaught mice receiving a daily dose of 1 gm of the salt per kilogram of body weight, injected intraperitoneally for 7 days, showed no alteration in white blood cells, red blood cells, or hemoglobin content.

An anesthetized cat was given a continuous intravenous infusion of 1 ml of a 10-percent solution of the compound per minute. Blood pressure, respiration, and heart rate were recorded. At the end of 4 hours, 21 gm (7 gm per kilogram of body weight) had been infused. During this time there was no change in blood pressure, respiration, or heart rate. The cat responded physiologically to acetylcholine and to adrenaline at the end of the infusion. Autopsy revealed no gross abnormality.

Twenty Connaught mice with actively growing transplanted sarcoma-37 were divided into two groups of ten each. One group was kept as an untreated control. On the 12th day after subcutaneous transplant, the other group was injected intraperitoneally daily with 1 gm of the compound per kilogram of body weight. The volume of the tumors was determined daily by measuring three dimensions with calipers. The results are shown in Fig. 1. On the 6th day of treatment, five out of ten of the treated animals showed complete regressions of their tumors, and on the 25th day, seven out of the ten tumors had completely regressed. In the remaining three animals the tumors continue to regress. The tumors in the untreated control animals progressed in size, as was expected. The tumors in the treated animals became very small and hard during their regression and eventually sloughed off, leaving an ulcer which finally healed. Histological study of tumors on the 6th day of treatment in a parallel experiment showed extensive necrosis with a few isolated islands of tumor cells. Sections from untreated animals studied at the same time showed actively growing tumor cells with numerous mitoses. The lack of toxicity of this compound which has been shown in normal animals was again evident in the tumor-bearing animals. There was no weight loss such as one usually finds with toxic drugs (mustards and so on), and there were no deaths.

In view of the low toxicity of the sodium salt of N-dichloroacetyl-DL-serine and its apparent specific effect on neoplastic growth, this compound is now being investigated clinically on patients with advanced malignant disease.

IRVING LEVI
HAROLD BLONDAL
EZRA LOZINSKI
Research Laboratories, Charles E. Frosst and Company, Montreal, Canada

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Selective Uptake of Serum Globulins and Glycoproteins by Cells Growing in vitro

Abstract. It has been demonstrated in preliminary experiments that two strains of rat tumor cells (WRC-256 and TSAT-72) utilize alpha-2-globulin more selectively than other protein components of human serum. Cells of strain TSAT-72 show some utilization of beta-globulins also. Separate experiments demonstrated the utilization of glycoproteins by both strains.

Pathological manifestations in man and other mammals are very often reflected in the biochemistry of the circulating blood. Especially during the last decade, valuable information has been obtained by applying new electrophoretic methods to the study of the blood and serum components of normal and diseased subjects. Among the major constituents of the serum, large molecules as well as their conjugated forms such as lipo- and glycoproteins have been shown to fluctuate considerably in various physiological and pathological conditions.

The role of serum proteins in growth processes and particularly in neoplastic growth represents still another problem which needs to be investigated further. Tissue culture has provided a good tool for the study of the biological activity and the nutritional value of these complex macromolecules during the growth of mammalian cells in vitro. Jaquez and Barry (*1*) observed that the growth-promoting activity of serum is associated with such nondialyzable protein fractions as the globulins. We have already reported (*2*) the utilization of serum alpha- and beta-globulins by several malignant cell strains and a normal strain growing in tissue culture. Madden and Whipple's experiments (*3*) on the participation of serum proteins in the metabolism of cells show another example of the