9. Effect of Tropolone and Related Compounds on Yoshida Sarcoma (2nd Report).

Azo-, Amino- and Sulfonic Acid Derivatives of Tropolone and Hinokitiol.

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The effect of tropolone, hinokitiol and their halogen derivatives on Yoshida sarcoma was reported in the 1st report. The substances tested in the 1st report were hardly to dissolve in water except tropolone and its methylether and so there were examined the amino- and sulfonic acid derivatives of tropolone and hinokitiol as soluble substances in water in the 2nd report.

The substances examined in this report are as follows:

(name, molecular formula, m.p. and structure).

- (1) p-Tolyl-azo-hinokitiol,¹⁾ C₁₇H₁₈O₂N₂, m.p. 138°, (A)
- (2) p-Tolyl-azo-hinokitiol sulfonic acid di-kalium salt,²⁾
C₁₇H₁₆O₅N₂SK₂, (B)
- (3) o-Bromotropolone-p-sulfonic acid ammonium salt,³⁾
C₇H₈O₅NSBr, (C)
- (4) Hinokitiol sulfonic acid ammonium salt,²⁾
C₁₀H₁₅O₅NS, m.p. 233°–235°, (D)
- (5) Hinokitiol sulfonic acid ammonium copper complex salt,²⁾
(C₁₀H₁₄O₅SN)₂Cu
- (6) Hinokitiol sulfonic acid copper complex salt,²⁾
C₁₀H₁₀O₅SCu

(7) Hinokitiol sulfonic acid ammonium ferric complex salt,²⁾

(8) p-Aminotropolone,³⁾ $\text{C}_7\text{H}_7\text{O}_2\text{N}$, m.p. 177°, (E)

Technic and assays of the effect on tumor cells: were the same as in the 1st report.

Results.

(1) p-Tolyl-azo-hinokitiol: 20 mg. of it was used per 100 g. body weight as a suspension.

(2) p-Tolyl-azo-hinokitiol sulfonic acid di-kalium salt: 20 mg. of it was used.

(3) o-Bromotropolone-p-sulfonic acid ammonium salt: 40 mg. of it was used.

(4) Hinokitiol sulfonic acid ammonium salt: 20 mg. of it was used.

These four substances were examined as soluble ones except p-Tolyl-azo-hinokitiol. There appeared some changes in the resting cells, but the mitotic cells were almost normal. The prolongation of life was not obtained and the tissue invasion of tumor cells was remarkable.

(5) Hinokitiol sulfonic acid ammonium copper complex salt: By administration of 4 mg. of it, there appeared hypochromasies, achromasies and caryorrhexes in many resting cells 3 hours after injection. 6 to 12 hours after injection the resting cells were almost destroyed and disappeared gradually. The mitotic cells decreased markedly but the chromosomes in the remaining mitotic cells were almost intact. The cellular reactions were highly observed. The mitotic cells began to appear again 24 hours after injection. The prolongation of life was not obtained but the tissue invasion of tumor cells was not so remarkable.

(6) Hinokitiol sulfonic acid copper complex salt: The damages in the resting cells were much stronger but the chromosomes in the mitotic cells showed no remarkable changes.

(7) Hinokitiol sulfonic acid ammonium ferric complex salt: There appeared no remarkable changes.

(8) p-Aminotropolone: All rats died 3 hours after injection of 20 mg. of it intraperitoneally. There appeared aggregations of the chromosomes in half the number of the mitotic cells in metaphase 1 hour after injection. 3 hours after injection the proportion of mitoses was quite low and moreover the chromosomes of mitotic cells in metaphase showed fragmentations, scatterings, coagulations and abnormal masses. The changes were observed also in some

resting cells, that is, caryorrhexes, achromasies and hypochromasies. In order to observe these changes in a much longer time, 10 mg. of it was injected. Then the proportion of the mitoses began to decrease 1 hour after injection and it dropped from 3-3.5% to less than 0.5% 3-9 hours after injection but 24 hours after injection it recovered that proportion before injection. There appeared no remarkable changes in the proportion of each phase in mitoses and in the appearances of the chromosomes. The prolongation of life was not achieved but the tissue invasion of tumor cells was not remarkable.

Summary and conclusion.

Eight substances were examined in the 2nd report and there showed no colchicine-like effect except p-amino-tropolone. There appeared the damages in the mitotic cells similar in cases of colchicine by administration of the lethal dosis of p-amino-tropolone, the proportion of the mitoses decreased markedly by injection of M.T.D. of it, and though the prolongation of life was not achieved, the tissue invasion of tumor cells was slight relatively as shown by autopsy. It was impossible to find the interruption of the mitotic process in metaphase as in colchicine.

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References.

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