upon the capacity of women to perform maximal anaerobic work, nor any apparent effect upon the improvement in power due to training. Gelatin does not prevent the development of "staleness" when brief work of extreme severity is repeated daily over a long period of time. A comparison of the published data of Ray, *et al.*,[7] with that of our series of experiments suggests that the increase in work output attributed by these investigators to gelatin may also have been a training effect.

*Acknowledgments.* Our best thanks are due to Betty McLaughlin, Mary Stowell, Helene Sanger and Beatrice Hellebrandt for the faithfulness with which they "played themselves out" each time they rode the bicycle ergometer, and to Prof. Kelso of the School of Engineering for his analyses of the discrepancies in work evident in the comparison of our observations with those of Ray, Johnson and Taylor.

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## Further Approach Toward Control of Spontaneous Cancer of Mammary Gland in Mice by Heptyl Aldehyde-Sodium Bisulphite.

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Evidence has been presented that demonstrates quite convincingly that the growth rate and fate of spontaneous carcinoma of the mammary gland in mice may be significantly influenced by heptyl aldehyde.[1] The effect of liquefaction (both partial and in some cases complete) together with a slower growth rate and complete disappearance of the tumor mass could be brought about by the introduction into the organism of the drug either by the diet or by subcutaneous injection (at areas remote to the spontaneous tumor). One of the limiting factors in the introduction of the material

* This experiment has been made possible by grants from the Anna Fuller Fund and the Jane Coffin Childs Memorial Fund for Medical Research. Acknowledgments are also due to Dr. R. Auchincloss of Columbia University and to Dr. F. R. Greenbaum, Director Pharmaceutical Research, National Drug Company, for their kindness in supplying the material, heptyl aldehyde-sodium bisulphite addition compound, used in this investigation.

1 Strong, L. C. PROC. SOC. EXP. BIOL. AND MED., 1932, **30**, 386.

through the diet is the fact that the resulting mixed food becomes so bitter with the larger effective doses that the normal food habits of the mouse may be interfered with. The greatest limiting factor of the injection technic is that local ulceration is sometimes quite pronounced.

In a recent paper, it was pointed out that in order to influence malignancy the heptyl aldehyde must be used fresh. It was found that as soon as the heptyl aldehyde-normal diet mix had "aged" even for a few days the efficacy of the drug was greatly diminished. One way of "protecting" the precocious deterioration of the heptyl aldehyde was the addition to it of a small amount of methyl salicylate —that is, to approach more or less the chemical situation in the original true or natural oil of Gaultheria.[2] Since, however, the heptyl aldehyde undergoes oxidation readily, one may prohibit or delay, to a certain extent, this change by either of two methods: (1) the addition of a known anti-oxidant, such as salicylic aldehyde to it, or (2) the combining of it with such a chemical as sodium bisulphite. Both of these suggestions have been tried, but the results obtained on spontaneous cancer with the second method alone will be discussed in the present communication.

Heptyl aldehyde-sodium bisulphite addition product† is water soluble. It is fairly stable in the dry state, but when in solution, it comes into contact with the tissues of the body, it slowly gives up its heptyl aldehyde.

Seventy-five female mice of the Strong A strain with spontaneous tumors of the mammary gland have so far been injected with freshly

2 Strong, L. C., *Yale J. Biol. and Med.*, 1939, **11**, 207.

† The material from National Drug Company was prepared by mixing heptyl aldehyde C.P. and sodium bisulphite C.P. together in equimolecular proportions. Upon stirring, the mixture became solid in from 5 to 10 minutes. It was then filtered and dried. The compound, thus formed, is of a brilliant mother-of-pearl lustre and appears to be crystalline. It contains 52.3% of heptylaldehyde. The sample from R. Auchincloss was prepared according to Cumming, Hopper and Wheeler (Systematic Organic Chemistry. Modern Methods of Preparation and Estimation, p. 518) from a reactive solution of $NaHSO_3$. Fifteen grams of $Na_2CO_3$ were put into 100 cc $H_2O$. $SO_2$ was bubbled through. This gave a white precipitate. The $SO_2$ was passed 50 minutes when solution was cleared of white precipitate. At this time the solution did not yet smell of $SO_2$. After another 25 minutes the evolution of $CO_2$ stopped and the solution smelled of $SO_2$. 18.8 cc heptaldehyde (Eastman) was then added and shortly later another 18.8 cc (100% excess). White precipitate was formed quickly. It was left in the ice box overnight. The material was then filtered and the crystals were washed with a small amount of 95% alcohol. A micro sulfur determination was 13.9%; theoretical 14.6%. The resulting compound is water soluble and is stable in solution at neutral pH.

prepared distilled water solutions of heptyl aldehyde-sodium bisulphite addition compound. The mice were divided into 5 groups depending upon the amount of the addition product they received daily. The first group of 5 mice received 2 mg of the material dissolved in 0.20 cc of distilled water; the second group of 5 mice, 3 mg in the same amount of water; the third group of 15 mice, 4 mg; the fourth group of 25 mice, 5 mg; and the fifth group of 25 mice 6 mg. The growth rates of the tumors in the various experimental groups are compared with that for the tumors of 120 control mice of the same strain in Chart 1.

All injections were done at sites remote to the spontaneous tumors. The variable factors involved in the tolerance to, and the physiological effect of the drug are (1) age of the mouse, (2) body weight, (3) physical condition of the mouse, (4) size of the tumor, and (5) individual peculiarities of both the mouse and certain tumors. The dosage administered to each mouse was carefully determined each day and was altered according to the above variable criteria. The idea used throughout was to inject the maximum effective dose

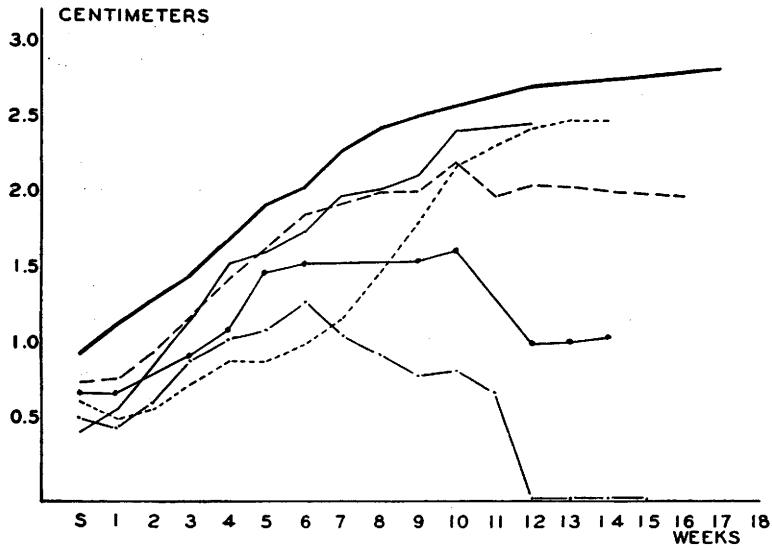


CHART 1.

Chart 1 presents data obtained on the growth rate of spontaneous tumors of the mammary gland in mice on: (a) 120 control mice (heavy solid line); (b) 5 mice receiving 2 mg per day heptyl aldehyde-sodium bisulphite addition product (light solid line); (c) 5 mice receiving 3 mg daily of the same drug (short dash line); (d) 15 mice receiving 4 mg per day of the same drug (long dash line); (e) 25 mice getting 5 mg per day (solid ball and solid line); and (f) 25 mice getting 6 mg per day (dot and broken line).

without interfering with the body weight or physical condition of the mouse.

By an inspection of the chart it may be seen that there is an indirect correlation between the growth rate of spontaneous tumors and the amount of heptyl aldehyde-sodium bisulphite addition compound injected. The same large areas of liquefaction were found here as were obtained by the use of heptyl aldehyde alone. Complete disappearance of some of the spontaneous tumors (6 out of 25 in the fifth series) did occur when the level of 6 mg per day was reached. There have been no recurrences in these cases and the mice are living in normal health at the present time.

A mouse, in which a large tumor is breaking down and being eliminated, is in a critical stage. Some of them die during this process primarily by hemorrhage from the surface of the tumor. This untoward result may be prevented by (1) clipping the hair over the tumor, (2) a periodic bathing of the tumor in 70% alcohol, (3) a drainage by sterile puncture and (4) packing a delicate or thin layer of sterile cotton over a potential "break" in the surface of the tumor. So far the largest tumor that has completely regressed in this series on the chemotherapy of cancer was one that measured 1.5 cm in longest linear diameter.

Heptyl aldehyde-sodium bisulphite addition compound has the further advantage over heptyl aldehyde alone by the fact that local ulceration is considerably reduced.

Experiments with other series of mice receiving larger daily doses of heptyl aldehyde-sodium bisulphite addition compound are being done.