these two responses. With decrease of either intensity or duration, the latencies of all responses increase. (Fig. 2.)

We infer from such records that the retinal activity arises in elements distal to the ganglion cell layer, and probably in the sense cells; and that the total *b* wave represents the summation of impulses which are individually briefer. Records obtained with and without a diffusing screen are so closely similar as to indicate that the responses observed following projection of a small bright image on the retina are chiefly due to stray light, illuminating the retina as a whole by internal dispersion from the image.

11349

Influence of Aldehydes on Transplanted Tumors.

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Strong obtained retrogressive changes and liquefaction of spontaneous tumors in mice[1, 2] and in dogs[3] by heptaldehyde. He also observed that the low boiling fraction of the oil of gaultheria was more effective than heptaldehyde alone,[4] an effect probably due to the presence of naturally occurring antioxidants which prevent the autooxidation of heptaldehyde. Boyland and Mawson[5] were able to induce some inhibition of both grafted and spontaneous tumors with citral, but heptaldehyde only inhibited the latter.

On the other hand, Baumann, Kline, and Rusch[6] were unable to influence a spontaneous mammary adenocarcinoma, or tumors induced by ultraviolet light, or by benzpyrene by adding heptaldehyde to the diet of mice. Clarke[7] found that heptaldehyde had no significant effect upon a transplanted spindle cell sarcoma in 14 rats. Orr and Strichland[8] were likewise unable to affect spontaneous and trans-

1 Strong, L. C., *Am. J. Cancer*, 1939, **35**, 401.

2 Strong, L. C., *Science*, 1938, **87**, 144.

3 Strong, L. C., and Whitney, L. F., *Science*, 1938, **88**, 111.

4 Strong, L. C., *Yale J. Biol. and Med.*, 1938-39, **11**, 207.

5 Boyland, E., and Mawson, E. H., *Biochem. J.*, 1938, **32**, 1982.

6 Baumann, C. A., Kline, B. E., and Rusch, H. P., PROC. SOC. EXP. BIOL. AND MED., 1938, **39**, 354.

7 Clark, W. G., PROC. SOC. EXP. BIOL. AND MED., 1939, **40**, 562.

8 Orr, J. W., and Strichland, L. H., *Yorkshire Council of the British Empire Cancer Campaign*, 1938-39, 8.

planted tumors in mice, guinea pigs and in a dog by oral administration or injection of heptaldehyde.

Experiments were therefore undertaken to study the effect of aldehydes, especially heptaldehyde and some of its compounds, on transplanted carcinomas.

*Oral administration of pelargonic aldehyde and of heptaldehyde.** Emulsion from one tumor was injected at the same time into enough mice to serve for the experimental groups and for controls. The food was Purina Chow. As soon as tumors became palpable, the mice were divided into groups of comparable tumor diameters. One group received pelargonic aldehyde, one received heptaldehyde, while the other served as controls. Forty to fifty mg of the aldehyde were administered orally every day until the experiment was terminated. The product of the maximum length and width ($L \times W$), was used as a criterion for the growth rate of the tumors. The results of this experiment are indicated in Table I. The products of the tumor dimensions are recorded every 5 days and the increase in size can be observed as one reads the table from left to right. The first column shows the number of mice for the different groups with letters to indicate the type of treatment. The product of the tumor dimensions for any 5-day period for any of the 3 particular groups can be found by reading under the letter in question. Since Strong's outstanding results were with small tumors, in this and in the following experiments, treatment was begun when tumors were either not palpable, or were very small, in order to study the effect of aldehydes upon tumors before they became so large that any inhibitory effect might not be indicated. Hence, there are as many horizontal columns as there are tumors grouped according to initial tumor dimensions. There is no significant inhibition on the growth rate of the transplanted Marsch Buffalo Adenocarcinoma even when the aldehydes were administered to mice bearing small tumors.

To check the possibility that oral administration of heptaldehyde might have an effect on a transplantable tumor not manifested by changes in the growth rate, portions of a tumor were removed from a mouse which had received heptaldehyde (40-50 mg) daily for 27 days, and the tumor suspension was inoculated into 8 females. Since tumors developed in all the mice and grew rapidly, it is evident that the ability of the tumor to "take" was not lost.

To determine whether heptaldehyde given before transplantation would have any effect upon the subsequent growth of the Marsch Buffalo Adenocarcinoma, 20 mice were fed 40-50 mg of the alde-

* From Eastman, redistilled weekly and stored at 0-5°C.

TABLE I.

Effect of Oral Administration of Heptaldehyde and of Pelargonic Aldehyde on the Marsch Buffalo Adenocarcinoma. Product of average tumor dimensions (L × W) in cm at days after treatment was started.

			Days															
No. of mice			0			5			10			15			20			25		
C	H	P	C	H	P	C	H	P	C	H	P	C	H	P	C	H	P	C	H	P
1	5	4	.5	.4	.4	1.3	1.3	1.2	1.9	1.3	2.0	3.0	2.4	3.2	3.6	2.9	3.9	4.4	5.2	4.0
4	5	1	.9	.8	.7	1.4	1.6	1.8	2.7	2.7	3.4	3.6	3.8	4.9	4.9	5.8	6.0	6.2	6.4	6.4
3	5	4	1.5	1.3	1.4	2.3	2.2	2.4	3.7	3.5	3.4	4.4	4.4	4.5	5.7	5.5	5.6	6.2	6.2	7.2

TABLE II.

Effect of the Intraperitoneal Injection of Heptaldehyde on the A Carcinoma.

Sum of average tumor dimensions (L + W) in cm at days after treatment was started.

			Days															
No. of mice			0	5			10			15			20			25		
C	H	E	Initial tumor (L + W) cm	C	H	E	C	H	E	C	H	E	C	H	E	C	H	E
0	4	0	T.N.P.		.5			1.1			1.6			2.3			2.9	
6	10	4	T.P.	1.7	1.1	1.7	2.8	1.8	2.9	3.3	2.7	3.8	4.7	3.9	4.8	4.8	4.8	5.8
2	1	0	.0-1.0	2.2	1.8		3.4	2.8		3.9	3.8		5.3	4.4		5.8	5.0	
0	0	1	1-2.0			2.2			3.1			3.9			4.7			6.6
0	1	0	2-3.0		3.7			4.3			5.3			6.1			6.1	

C—Control; H—Heptaldehyde; P—Pelargonic Aldehyde; E—Ethyl Esters of Lard; T.N.P.—Tumors not Palpable; T.P.—Tumors Palpable.

hyde orally every other day for 19 days prior to inoculation of the tumor, and up to the time the experiment was terminated (25 days). Seven mice served as controls. Nineteen tumors occurred in the experimental group and in all of the controls, and the subsequent growth rate of the tumors in both groups was not significantly different.

Intraperitoneal injection of heptaldehyde. It has been observed that heptaldehyde is capable of causing resorption of mouse embryos, and is especially effective when dissolved in the ethyl esters of lard and injected intraperitoneally.[9] On the assumption that the amount of aldehyde reaching the tumor after oral administration is less than after intraperitoneal injection, an attempt was made to inhibit the growth of transplanted tumors by intraperitoneal injection. Twenty-eight strain A mice were inoculated with an emulsion obtained from a spontaneous mammary carcinoma of the same strain, and as soon as tumors became palpable in some of the mice, heptaldehyde was injected intraperitoneally in graded doses because of its toxicity every day into 16 mice: For 3 days .03 cc of aldehyde in .06 cc ethyl esters of lard, for 2 days .045 cc of the aldehyde in .075 cc ethyl esters of lard, for 8 days .06 cc of the aldehyde in .06 cc ethyl esters of lard, for 13 days .09 cc of the aldehyde in .075 cc ethyl esters of lard.

Five mice were likewise treated with the ethyl esters of lard without aldehyde, while 8 served as untreated controls.

The sum of the maximum length and width (L + W) in cm was used as a criterion for the growth rate. Since the treatment was started as soon as a few tumors became palpable (in order to study the effect of heptaldehyde on the growth of tumors not palpable when the treatment was started), the initial tumor size for 3 groups varied. The results given in Table II show that heptaldehyde did not inhibit the growth rate of this carcinoma when the initial tumors were small (T.P.), and, also, that it was ineffective even when the tumors were not palpable (T.N.P.) when the injections were started. Similar results were obtained for the transplanted Marsch Buffalo Adenocarcinoma in 9 mice in which the tumors were either not palpable or were very small when the treatment was started.

Intraperitoneal injection of n-heptaldoxime. N-heptaldoxime (Eastman) was dissolved in the ethyl esters of lard (.05 cc contained 2 or 4 mg of the oxime) and its effect upon the 2 transplanted tumors was studied. As soon as tumors became palpable after transplantation, each mouse received 2 mg of the oxime per day for 2 days, then

[9] Carruthers, C., PROC. SOC. EXP. BIOL. AND MED., 1939, **41**, 336.

TABLE III.

Effect of Intraperitoneal Injection of N-heptaldoxime on A Carcinoma and on Marsch Buffalo Adenocarcinoma.
Sum of average tumor dimensions (L + W) in cm at days after treatment was started.

No. of mice			Days															
			0	5			10			15			20			25		
				A Carcinoma.														
C	R	E	Initial tumor (L + W) cm	C	R	E	C	R	E	C	R	E	C	R	E	C	R	E
1	1	0	T.P.	1.7	1.3		1.5	2.0		2.1	2.8		2.5	3.1				
6	10	3	1-2.0	2.9	2.2	2.4	3.3	2.9	2.9	3.5	3.5	3.4	4.3	3.9	3.8			
0	1	1	2.1-3		3.7	3.4		4.6	4.1		5.2	4.6		—	4.9			
				Marsch Buffalo Adenocarcinoma.														
	1		T.P.		.6			1.3			2.6							
5	6	4	0-1.0	1.9	2.0	2.0	2.9	3.2	3.0	3.7	4.1	3.8	3.7	4.1	4.0	4.3	4.4	4.4

TABLE IV.

Effect of the Bisulfite Addition Compound of Heptaldehyde on A Carcinoma.

No. of mice		Days									
		0	5		10		15		20		25	
C	R^1	Initial tumor (L + W) cm	C	R^1	C	R^1	C	R^1	C	R^1	C	R^1
	3	T.N.P.		1.0		1.8		2.7		4.1		4.9
6	3	T.P.	1.7	1.8	2.8	2.8	3.3	3.5	4.7	4.9	4.5	5.2
2	1	0-1.0	2.2	2.0	3.4	3.2	3.9	4.0	5.3	5.1	5.8	5.8
	1	1.1-2.0		3.7		4.3		6.0		6.8		7.0

C—Control; R—N-Heptaldoxime; E—Ethyl Esters of Lard; R^1—$NaHSO_3$—Addition Compound; T.N.P.—Tumors Not Palpable; T.P.—Tumors Palpable.

4 mg per day until the experiment was terminated. One group of mice served as controls, while another received injections of the ethyl esters of lard. Evidently (Table III), n-heptaldoxime had no significant effect upon these 2 transplanted tumors even when treatment was started when they were small (T.P. and [L + W] of 0–2.0).

Subcutaneous injection of the bisulfite addition compound of heptaldehyde. Heptaldehyde was added to a saturated solution of $NaHSO_3$, the addition compound was thoroughly washed with distilled water, and dried over $CaCl_2$. The addition compound was made weekly and dissolved in distilled water prior to subcutaneous injection. In a preliminary experiment 5 mg of the addition compound were injected daily into 6 strain A mice bearing the A carcinoma, but no inhibitory effect was noticed, although the tumors were small when the treatment was started. Later 20 mg of the compound were injected daily into the same strain bearing the same carcinoma, but the results (Table IV) give little indication of any inhibition even when the initial tumor (L + W) is small (T.P.), or even when tumors could not be palpated when treatment was started (T.N.P.). Nine mice bearing the transplanted Marsch Buffalo Adenocarcinoma were also treated with 20 mg of the addition compound daily, with the same results. Mice bearing both of these tumors were also treated with an equivalent amount of $NaHSO_3$, but without effect.

None of the above compounds induced noticeable liquefaction of the tumors. Subcutaneous injection of heptaldehyde resulted in necrosis which prevented this type of administration. Heptaldehyde ammonia had a similar effect and it was highly toxic via the intraperitoneal route.

Strong's success with heptaldehyde was with spontaneous tumors. Practically no effect has been demonstrated on transplanted tumors. The reason for this difference is unknown. However, Cramer and Horning[10] have shown that "brown degeneration" occurs in the adrenals, at least in several strains of mice which have a high incidence of spontaneous mammary carcinoma. Since spontaneous tumors arise in older females, the question arises as to the relative efficacy of heptaldehyde in young and in old mice bearing tumors, especially in the latter, because "brown degeneration" of the adrenals may be indicative of other endocrine changes, thus possibly allowing greater aldehyde activity. "Brown degeneration" has been observed in the adrenals of strain A mice in this laboratory, but was not a

[10] Cramer, W., and Horning, E. S., *Lancet*, 1939, 192.

complicating factor as young mice were used as hosts for transplanted tumors. Bischoff and Long[11] have shown that sarcoma 180 grew to a greater size in young Marsch Buffalo mice than in older mice. This strain of mice also develops spontaneous mammary carcinoma.

On the other hand, Strong's results are obtained over a long period of time and in most of his experiments the aldehyde was mixed with the diet. This procedure might allow the proöxidant, heptaldehyde, by initiating autoöxidation or by the formation of peroxides, to induce dietary changes and thus influence tumors indirectly. The odor of heptaldehyde disappears quite rapidly when mixed with diets at room temperature.

Experiments are in progress to determine whether or not heptaldehyde will inhibit the growth of transplanted tumors in mice whose vitamin E stores have been depleted, since the tocopherols are known antioxidants[12] which may inhibit, at least partially, the action of the proöxidant, heptaldehyde.

Summary. Under the conditions of these experiments, the growth rates of the transplanted Marsch Buffalo Adenocarcinoma, of the transplanted A carcinoma were not significantly altered when: (1) heptaldehyde and n-heptaldoxime were dissolved in the ethyl esters of lard and injected intraperitoneally; (2) the bisulfite addition compound of heptaldehyde was injected subcutaneously. The oral administration of heptaldehyde and of pelargonic aldehyde was also without influence on the progress of the transplanted Marsch Buffalo Adenocarcinoma.

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11 Bischoff, F., and Long, M. L., *Am. J. Cancer*, 1936, **27**, 104.

12 Olcott, H. S., and Emerson, O. H., *J. Am. Chem. Soc.*, 1937, **59**, 1008.