same manner as pyridinoanthracene methiodide; m.p. 239-240°C dec. The 3-aminophenanthrene used in this preparation was prepared from phenanthrene by the method of Bachmann and Boatner.[5]

A 2% solution of each of these compounds in benzene was painted twice weekly on the neck of 100 mice over a period of approximately 5 months. In addition to this .02 g of each of the compounds was suspended in 0.5 cc of paraffin and this dose was planted subcutaneously in 20 mice. These animals were observed for approximately 7 months. Neither in the instance of the skin paintings nor in those of the subcutaneous implantations did carcinoma occur.

Though certain polycyclic hydrocarbons of the benzanthracene type are carcinogenic, and despite the fact that certain nitrogen-containing compounds have also been found to be carcinogenic, these compounds, prepared and tested containing nitrogen and chemically analogous to benzanthracene, are probably non-carcinogenic. This observation serves to render our concept of carcinogenic substances more precise.

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Aldehydic Resorption in Mice.

CHRISTOPHER CARRUTHERS. (Introduced by E. V. Cowdry.)

From the Research Department of The Barnard Free Skin and Cancer Hospital, St. Louis, Mo.

Kudrjashov and Agatov[1] reported that they were able to induce temporary sterilization, or failure of implantation, in female rats and rabbits by means of fractions obtained from rancid fat and oleic acid. The rancid fat did not act upon the sexual system of the rat, but caused the death of the embryo at or soon after implantation, the placental sign occurring on the 9-10th day (normal 13th day). The authors believe that the active substance may consist of aldehydes and ketones.

Strong's[2] very interesting observations on the liquefaction and regression of spontaneous mammary tumors by means of heptaldehyde have aroused considerable interest, and any light on the mechanism of heptaldehyde on tumors should be welcome at this time. He[3]

[5] Bachmann, W. E., and Boatner, C. H., *J. Am. Chem. Soc.*, 1936, **58**, 2097.

[1] Kudrjashov, B. A., and Agatov, P. A., *Ginekologia i Akusherstvo*, 1935, **6**, 1.

[2] Strong, L. C., *Am. J. Cancer*, 1939, **35**, 401.

[3] Strong, L. C., *Science*, 1938, **88**, 11.

has also noted that this aldehyde can cause resorption of the embryos in mice, but no details have been given. Kudrjashov and Agatov's observations may be explained by the fact that heptaldehyde is one of the constituents of rancid fat.[4]

Experiments were undertaken to study the resorptive effectiveness of various substances, especially heptaldehyde. Old Buffalo, New Buffalo,* C57 (black) and market mice were used. Purina Dog Chow was fed *ad libitum*. Six to 8 females were penned with one male. Vaginal smears were made daily, and the animals weighed every 5 days.

In the first experiment the substance to be tested was fed orally with a medicine dropper at various days after a positive mating. Of the following substances fed (40-50 mg daily) from the first to the fourth day after insemination to a resorption or successful pregnancy, unsaponifiable fraction of rancid lard, propionaldehyde, n-butraldehyde, n-valeraldehyde, heptaldehyde, pelargonic aldehyde, and benzaldehyde, only heptaldehyde gave marked results (Table I). Benzaldehyde, n-butraldehyde and pelargonic aldehyde induced an occasional resorption. When a resorption did follow the feeding of an aldehyde, no more was fed until the mouse had had a successful gestation.

The administration of heptaldehyde causes an earlier appearance of the placental sign (extremes 5-12 days) when a resorption follows than when a pregnancy ensues. The amount of blood was somewhat variable, from a small amount of light colored blood to a more copious exudate of dark stringy masses. The placental sign usually lasted from one to 4 days, sometimes longer. The aldehyde was fed

TABLE I.
Resorptive Effectiveness of Heptaldehyde Fed Orally.

	Resorptions			Pregnancies		
	Avg			Avg		
Fed at days after insemination	Placental sign, days	No. of days aldehyde fed	No. of mice	Placental sign, days	No. of days aldehyde fed	No. of mice
0	7	8	3	11	16	1
1	8.1	8.3	28	9.3	9.5	9
2	7.5	7	2	10	14	4
3	7	3	1	10	12	2
4	7	3	1	10	16.4	8
5	5	12	1	9.5	14.5	2

[4] Powick, W. C., *J. Agri. Res.*, 1923, **26**, 323.

* Generously supplied by The New York State Institute for the Study of Malignant Diseases, Buffalo, New York, Burton T. Simpson, Director.

until the estrous cycle returned, or until it could be seen that the feeding was going to be ineffective (10-16th day). The placental sign appears in normals on the 9th to the 13th day. It was impossible to induce resorptions when the administration of the aldehyde was started after the 9th to 13th days after insemination. Resorptions did not occur in all the mice presumably due to individual variations in the amount required to destroy fertility. Oral feeding rarely caused a loss in weight, but heptaldehyde caused a loss of hair around the mouth and face of the mice.

Since heptaldehyde was incapable of causing resorptions, either in all the mice or after the 9th to the 13th day after insemination, when fed orally, it was assumed that some of the aldehyde had been destroyed prior to absorption. To test this assumption the ethyl esters of lard were made according to the method of Olcott and Mattill[5] and a solution of the aldehyde in the esters was prepared so that .2 cc esters contained .02 cc heptaldehyde. With this solution injected intraperitoneally the mice could tolerate .02 cc of the aldehyde daily throughout the entire gestation period. Similar injection of the aldehyde alone proved highly toxic and subcutaneous injections resulted in necrosis. Lethal doses of the aldehyde, in the ethyl esters of lard, ranged from .08 to .09 cc. Usually .02 to .06 cc of the aldehyde was injected daily at different days after a positive mating (Table II).

The results are particularly interesting, because resorption could be induced as late as the 13th day after insemination with as little as .10 cc heptaldehyde. Resorptions later than the 13th day have been obtained, but death usually followed. Resorptions were easily induced from the first to the fourth day after insemination by .08 cc of the aldehyde. The entire process was usually completed in 3 to 7 days. If oral feeding did not induce resorptions by the 11-13 days, they could be induced by several injections (.04 to .12 cc of the aldehyde). These results would seem to indicate that little of the aldehyde, administered orally, reaches the blood stream. In agreement with this is the fact that the oral feeding of heptaldehyde had no effect on the growth of the Marsh Carcinoma. This may be due to poor absorption or destruction of the aldehyde before it reaches the tumor.

Resorptions were easily caused by the intraperitoneal injections of heptaldehyde in the ethyl esters of lard if the mice had not received the aldehyde orally or intraperitoneally previously. Of 17 young females (New Buffalo and C 57 [black]), which had received no

[5] Olcott, H. S., and Mattill, H. A., *J. Am. Chem. Soc.*, 1936, **58**, 2204.

TABLE II.
Resorptive Effectiveness of Heptaldehyde Dissolved in the Ethyl Esters of Lard.

Injections begun at days after insemination	Resorptions Placental sign, days		cc aldehyde injected		No. of mice	Pregnancies Placental sign, days		cc aldehyde injected		No. of mice
	Avg	Extremes	Avg	Extremes		Avg	Extremes	Avg	Extremes	
1	8.2	6-13	.19	.08-.42	7					0
2	5.5	5-6	.08	.04-.12	2					0
3	7		.62		1					0
4	5.8	4-7	.12	.08-.20	6					0
8	8		.44		1	10		.20		1
9	9		.12		1					0
10	11.5	10-13	.11	.10-.12	2	10		.14		1
11	11	11	.18	.16-.20	4	11	11	.16	.12-.20	4
12	12	12	.13	.10-.16	2	13		.20		1
13	13	13	.29	.12-.38	5	13		.12		1

aldehyde previously, 15 resorbed their embryos; while of 25 females, which had received the aldehyde orally or intraperitoneally (or both), 11 had resorptions, when the intraperitoneal method was used. Many mice failed to respond to a second oral administration of heptaldehyde, although pregnancy could be terminated in some of these cases by intraperitoneal injections. Apparently the mice are capable of building up a resistance to heptaldehyde. Even the ethyl esters of lard, which had become rancid, could stop pregnancy from the 4th to the 13th day after insemination with a dose of .3 to .6 cc injected intraperitoneally. Intraperitoneal injections of the other substances previously mentioned have not been tried.

Of 464 positive matings throughout these experiments, 86 (18.5%) were not followed by implantation. Heptaldehyde brought about a large number of these failures, and the other aldehydes were also capable of similar action. There were 264 successful gestations (with and without aldehydic administration). The sexual system of the mouse is apparently not impaired, because fertility returns after cessation of the aldehydic treatment. Whether the resorption of embryos and the liquefaction and regression of spontaneous tumors by heptaldehyde (Strong) are expressions of a similar phenomena—destruction of vitamin E—remains to be determined. The work of Kudrjashov[6] indicates that the fractions obtained from rancid fat act directly on the embryo and do not destroy vitamin E.

Conclusions. Heptaldehyde is capable of inducing resorption of mouse embryos when it is administered orally from the first to the fifth day after insemination, but it is most effective on the first and second days after insemination. Dissolved in the ethyl esters of lard, it can cause destruction of fertility as late as the thirteenth day after insemination. The oral feeding of heptaldehyde had no appreciable effect on the growth of the Marsh Carcinoma, but these experiments indicate that further work is necessary to determine the best conditions whereby heptaldehyde (or other aldehydes) can have greater access to tumors before its therapeutic value can be established.

[6] Kudrjashov, B. A., *Arch. f. exper. Path. und Pharmakol.*, 1932, **169**, 275.