CCLVII. EXPERIMENTS ON THE CHEMOTHERAPY OF CANCER

II. THE EFFECT OF ALDEHYDES AND GLUCOSIDES

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IN a series of recent papers Strong [1932; 1934; 1935; 1936, 1, 2] recorded that the feeding of natural oil of gaultheria inhibited the growth of spontaneous tumours in mice. Synthetic methyl salicylate had no such effect. Strong [1938, 1] showed that the effective substance was in the low-boiling fraction of the oil, and later that it was probably heptaldehyde [Strong, 1938, 2]. For this reason a number of aldehydes and ketones have been tested for their inhibitory action on the growth of grafted tumours in mice. The more promising compounds, citral and phloroglucinol aldehyde, have been tested on spontaneous tumours in mice.

The ease with which glucose penetrates into tumour cells made it appear possible that glucosides might be preferentially absorbed by tumour tissue and for this reason some available glucosides have been administered to mice with grafted tumours. None of them appeared to be effective in inhibiting growth and they were not tested on mice with spontaneous tumours.

Experiments with the Crocker Sarcoma 180

Substances were tested on groups of 5 mice with Crocker Sarcoma 180 as previously described [Boyland, 1938]; all compounds were given by oral injection 5 or 6 times weekly. The dosing was commenced immediately after grafting of the tumours, which were grafted into pure strain mice of either the Strong A or Little Dilute Brown (dba) strains. The tumours were measured thrice weekly and their growth compared with that of control tumours, which were growing in the same strain of mice grafted at the same time from the same tumour. Figs. 1, 4 and 7 show typical growth curves for the Crocker Sarcoma 180 in Strong A, Dilute Brown, and in stock mice. In stock mice the rate of growth in different mice is so variable that it is almost impossible to show the effect of inhibitory substances unless large numbers of mice are used. It is for this reason that mice from pure lines have been used for all the experiments with grafted tumours which are described in this paper. The compounds tested were administered in doses which would not injure the mice. The positive effects appeared to be of two kinds indicated in Table I.

Retardation in the rate of growth of the tumour as compared with that of the controls is indicated by *R*.

Increase in the length of life of the animals without effect on the rate of growth is indicated by *L*.

When no indication is made in the table the tumours in the treated animals were not significantly different from the tumours in control mice.

Table I. *The effect of orally administered substances on the Crocker Sarcoma 180 in Dilute Brown or Strong A mice**R* = retardation of tumour growth. *L* = increase in length of life.

Substance	Dose administered daily mg.	Effect
Anisaldehyde	5	—
<i>o</i> -Chlorobenzaldehyde	5	—
<i>m</i> -Chlorobenzaldehyde	5	—
<i>p</i> -Chlorobenzaldehyde	5	—
Cinnamic aldehyde	5	—
Citral	10	<i>R</i>
3:4-Dimethoxybenzaldehyde	5	<i>R</i>
<i>p</i> -Dimethylaminobenzaldehyde	5	—
3:4-Diethoxybenzaldehyde	5	—
Gentisic aldehyde	4	—
Heptaldehyde	5	—
	50	—
<i>o</i> -Hydroxybenzaldehyde (salicylaldehyde)	4	—
<i>m</i> -Hydroxybenzaldehyde	4	—
<i>p</i> -Hydroxybenzaldehyde	4	—
2-Hydroxy-6- <i>tert</i> -butylbenzaldehyde	5	—
<i>o</i> -Methoxybenzaldehyde	5	<i>L</i>
2-Naphthol-1-aldehyde	10	—
6-Nitro-3-hydroxybenzaldehyde	5	—
Octaldehyde	5	—
Phloroglucinaldehyde	5	<i>R</i>
Resorcaldehyde	4	—
3:4:5-Trimethoxybenzaldehyde	5	—
Valeraldehyde	10	—
Oils:		
Oil of Wintergreen (from <i>Betula lenta</i>)	10	—
Crude oil of <i>Betula</i>	20	—
Refined oil of <i>Betula</i>	20	—
Betulol	20	—
Glucosides:		
Aesculin	10	—
Amygdalin	10	—
Arbutin	20	<i>L</i>
Helicin	10	—
Salicin	10	<i>L</i>
Ketones:		
Acetophenone	10	—
Dimedone	5	—
Methylheptanone	10	<i>R</i>
Methylheptenone	10	—

Retardation of growth was obtained with citral, phloroglucinaldehyde and 3:4-dimethoxybenzaldehyde. The effect with phloroglucinaldehyde is shown by comparison of Figs. 1 and 3. Fig. 2 shows the growth of grafted tumours in mice treated with heptaldehyde. Other experiments with heptaldehyde also showed no inhibition of the growth of grafted tumours. The results with phloroglucinaldehyde and citral were of sufficient promise to make it seem worth while to test related compounds.

The prolongation of life observed in mice treated with *o*-methoxybenzaldehyde and salicin is illustrated in Figs. 5 and 6 as compared with the controls in Fig. 4. The effect may be due to antiseptic action of these compounds reducing the toxic effects of any contamination which may be present in the grafted tumour.

Fig. 7.

Fig. 10.

Fig. 11.

Figs. 1-3. Growth of Crocker Sarcoma 180 in Strong A mice.

Figs. 4-7. Growth of Crocker Sarcoma 180 in mice. Figs. 4-6 in Dilute Brown mice. Fig. 7 in Stock mice.

Fig. 8. Growth of spontaneous mammary tumours in mice treated with heptaldehyde (50 mg. per day).

Fig. 9. Growth of spontaneous mammary tumours in treated mice.

Fig. 10. Growth of spontaneous mammary tumours in mice treated with citral.

Fig. 11. Growth of spontaneous mammary tumours in mice treated with phloroglucinolaldehyde.

Fig. 9.

Fig. 8.

Experiments with spontaneous mammary tumours

Some experiments were carried out on spontaneous mouse tumours under the same conditions as previously described [Boyland, 1938]. Unless otherwise stated the dose was that given in Table I. Fig. 8 shows the experiment with heptaldehyde. In the case of one mouse (497) treatment caused partial retrogression and in mice 504 and 518 retardation of growth. Methyl heptanone and methyl heptenone were each tried on one tumour (Fig. 9), and the latter produced a temporary retrogression when first administered. Valeraldehyde (Fig. 9) caused inhibition of tumour growth but the mouse did not survive the treatment very long.

Experiments with citral and phloroglucinaldehyde, which were the two most effective aldehydes tested with the Crocker Sarcoma, are shown in Figs. 10 and 11. Citral produced partial retrogression in two mice and inhibition of growth of the other two tumours used. Phloroglucinaldehyde inhibited one of the two tumours on which it was tried.

An experiment was carried out to determine the effect of heptaldehyde on growth in body wt. of normal young mice. The groups of 4 mice each of the average wt., 11.3 and 13.5 g. respectively, were weighed daily. In one group each mouse was given 50 mg. heptaldehyde daily while the other group was left as controls. At the end of 20 days the average wt. of the first group was 19.5 g., while that of the second group was 20.5 g. The heptaldehyde did not affect body growth.

DISCUSSION

Of the series of aldehydes and ketones which have been tested, citral caused some inhibition of growth of both grafted and spontaneous tumours. Strong (personal communication) found that citral had some inhibitory action on spontaneous tumours in 1931. Heptaldehyde inhibited spontaneous tumours but not grafted tumours. The relative ineffectiveness of heptaldehyde in inhibiting grafted tumours while it inhibits spontaneous tumours to some extent is of interest in that its action is the converse of that of colchicine. Colchicine produces haemorrhage and some inhibition of grafted tumours but not of spontaneous tumours [Boyland & Boyland, 1937].

It is conceivable that the action of aldehydes is due to peroxide formation. Aldehydes are known to form peroxides on exposure to air and it is possible that different samples might contain varying amounts of organic peroxide. Maisin *et al.* [1938] have described the anticarcinogenic action of formaldehyde peroxides and the effect of heptaldehyde may conceivably be due to similar products.

SUMMARY

A number of aldehydes, ketones and glucosides have been tested for inhibitory action on tumour growth. Of these citral and heptaldehyde inhibited the growth of spontaneous tumours in mice.

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REFERENCES

- Boyland (1938). *Biochem. J.* **32**, 1207.
— & Boyland (1937). *Biochem. J.* **31**, 454.
Maisin, Pourbaix & Caeymaex (1938). *C.R. Soc. Biol., Paris*, **127**, 1479.
Strong (1932). *Proc. Soc. Exp. Biol., N.Y.*, **30**, 386.
— (1934). *Amer. J. Cancer*, **20**, 387.
— (1935). *Amer. J. Cancer*, **25**, 797.
— (1936, 1). *Amer. J. med. Sci.* **192**, 546.
— (1936, 2). *Amer. J. Cancer*, **28**, 550.
— (1938, 1). *Amer. J. Cancer*, **32**, 227.
— (1938, 2). *Science*, **87**, 184.