vessels which were relatively few in number and whereas in the untreated tumours blood was in direct contact with malignant cells, in the treated mice it was not.

It is not yet clear whether the apparently better development of the vasculature in the treated animals is due to the slight retardation of tumour growth thus permitting the vessels more time to develop, or whether the influence of the drug is at the more fundamental level of the growth pattern of the tumour.

REFERENCES

CREIGHTON, A. M., HELLMANN, K. & WHITECROSS, S. (1969). Antitumour activity in a series of bisdiketopiperazines. *Nature, Lond.*, **222,** 384–385.

HELLMANN, K. & BURRAGE, K. (1969). Control of malignant metastases by ICRF 159. *Nature, Lond.*, **224,** 273–275.

HELLMANN, K. & FIELD, E. O. (1970). The effect of ICRF 159 on the mammalian cell cycle: significance for its use in cancer chemotherapy. *J. natn. Cancer Inst.*, in the Press.

HELLMANN, K., NEWTON, K. A., WHITMORE, D. N., HANHAM, I. W. F. & BOND, J. V. (1969). Preliminary clinical assessment of ICI 159 in acute leukaemia and lymphosarcoma. *Br. med. J.*, **1,** 822–824.

## Inhibition of alcohol dehydrogenase by aminophenoxyalkanes: a possible mechanism of their retinotoxicity

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Numerous *p*-aminophenoxyalkanes have a powerful chemotherapeutic effect in experimental schistosomiasis (for example, Raison & Standen, 1955; Caldwell & Standen, 1956). To varying degrees they can also induce a retinopathy in monkey, cat and dog but not in rodents (Edge, Mason, Wien & Ashton, 1956; Goodwin, Richards & Udall, 1957) and can prevent regeneration of rhodopsin in the dark-adapting frog (Goodwin, Richards & Udall, 1957).

A third characteristic of these compounds is their ability to inhibit alcohol dehydrogenase (ADH), some of them at concentrations as low as 0·1 $\mu$M. Inhibitory potency of representative compounds has been measured *in vitro* with ADH of horse liver as the main test enzyme; some of the more important results have been confirmed with ADH of ox retina. Results from these experiments have been compared with the relative abilities of the same compounds to inhibit resynthesis of rhodopsin in the intact frog and to cause blindness in the cat, as described by Goodwin, Richards & Udall (1957), Collins, Davis, Edge & Hill (1958) and Goodwin & Richards (personal communication).

The effects of several types of structural alteration to model compounds upon their biological activities will be described. Inhibitory potency against ADH and ability to produce ocular damage were found always to change in the same direction and to a similar extent.

Alcohol dehydrogenase is regarded as playing an essential role in the visual cycle (Wald & Hubbard, 1960), catalysing the equilibrium between retinal and retinol. It is suggested that inhibition of this enzyme by aminophenoxyalkanes may be a primary biochemical lesion associated with their retinotoxicity.

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REFERENCES

CALDWELL, A. G. & STANDEN, O. D. (1956). The activity of *p*-amino-phenoxyalkane derivatives against *Schistosoma mansoni*. *Br. J. Pharmac. Chemother.*, **11**, 367–374.

COLLINS, R. F., DAVIS, M., EDGE, N. D. & HILL, J. (1958). The schistosomicidal and toxic effects of some αω-di(*p*-aminophenoxy) alkanes and related monoamines. *Br. J. Pharmac. Chemother.*, **13**, 238–243.

EDGE, N. D., MASON, D. F. J., WEIN, R. & ASHTON, N. (1956). Pharmacological effects of certain diaminodiphenoxyalkanes. *Nature, Lond.*, **178**, 806–807.

GOODWIN, L. G., RICHARDS, W. H. G. & UDALL, V. (1957). The toxicity of diaminodiphenoxyalkanes. *Br. J. Pharmac. Chemother.*, **12**, 468–474.

RAISON, C. G. & STANDEN, O. D. (1955). The schistosomicidal activity of symmetrical diaminodiphenoxyalkanes. *Br. J. Pharmac. Chemother.*, **10**, 191–199.

WALD, G. & HUBBARD, R. (1960). Enzymic aspects of the visual processes. In *The Enzymes*, ed. Boyer, P. D., Lardy, H. & Myrback, K., vol. 3. pp. 369–386. London: Academic Press.

## Relationship between the pharmacological and biochemical properties of a monoamine oxidase inhibitor preferentially affecting 5-hydroxytryptamine oxidation

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Monoamine oxidase (MAO) present both in brain and peripheral tissues can act on various amines including noradrenaline, 5-hydroxytryptamine (5-HT) and dopamine. The majority of drugs known to inhibit MAO appear to affect equally the oxidation of these substrates. Evidence from a number of sources (Gorkin, 1963; Youdim & Sandler, 1967; Johnston, 1968; Youdim, Collins & Sandler, 1969) indicates that MAO is not a homogeneous enzyme but consists of a series of iso-enzymes with substrate specificity.

Clorgyline (M&B 9302: N-methyl-N-propargyl-3-(2,4-dichlorophenoxy)propylamine) is a compound which preferentially inhibits the oxidation of 5-HT by rat brain monoamine oxidase at concentrations which have a less marked effect on the oxidation of tyramine or of benzylamine (Johnston, 1968; Hall, Logan & Parsons, 1969).

Rats were treated with graded doses of either clorgyline, tranylcypromine, or phenelzine. The pharmacological response was measured using two tests: (i) prevention of the sedative activity of tetrabenazine in rats, and (ii) antagonism of reserpine-induced hypothermia in the rat. *In vitro* determinations were made of the degree of inhibition of the rat brain MAO using 5-HT, tyramine, and benzylamine as substrates. Changes in the brain levels of both noradrenaline and 5-HT were determined.

Clorgyline (4 mg/kg orally) produced 24% inhibition of tetrabenazine induced sedation and 53% antagonism of reserpine induced hypothermia. This dose of clorgyline produced almost complete (94%) inhibition of the oxidation of 5-HT by rat brain homogenates, 64% inhibition of the oxidation of tyramine and little or no effect on the oxidation of benzylamine. Increasing the dose of clorgyline to 8 or 16 mg/kg orally produced a progressive increase in the pharmacological response, but there was only slight further increase in the inhibition of the oxidation of 5-HT or benzylamine. There was, however, a graded increase in the inhibition of the oxidation of tyramine. Doses of clorgyline (4 to 16 mg/kg) produced increases in the brain concentrations of noradrenaline (131 to 160%) and 5-HT (137 to 165%).