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Department of Pharmacology,
University of Mississippi,
University, Miss., U.S.A.

C. L. HUANG
K. HIRANO*

* Warren-Teed Pharmaceutical Co., Columbus, Ohio.

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Metronidazole and atypical human alcohol dehydrogenase

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IT IS well known that human enzymes may exist in a variety of forms. Further, these forms may differ in their response to various inhibiting agents (e.g. the inhibition of various forms of cholinesterase by dibucaine). Two varieties of human liver alcohol dehydrogenase are known, the *typical* and the *atypical* forms.[1]

Recently[2] we reported our finding that metronidazole was a non-competitive inhibitor of a crude preparation of typical human liver alcohol dehydrogenase. We have now had the opportunity of investigating the effect of metronidazole on a crude preparation of atypical human liver alcohol dehydrogenase, using identical methods.

The liver was obtained at laparotomy (which was negative) for a suspected peptic ulcer from a 59 yr old male who had no clinical evidence of liver disease. An homogenate was subjected to the screening test of von Wartburg *et al.*[1] and typed as atypical on the basis of results set out below:

Assay conditions	Relative activity	
	Atypical enzyme	Mean of 24 typical enzyme samples
Sodium pyrophosphate buffer (pH 8·8) = control = 1	1·0	1·0
Glycine-NaOH buffer (pH 11·0)	0·53	1·92 ± S.D:0·30
Sodium pyrophosphate buffer (pH 8·8) + $6{\cdot}6 \times 10^{-1}$ M thiourea	0·39	1·29 ± S.D:0·15

The screening test and part of the metronidazole work was carried out on the fresh homogenate (i.e. within 4 hr of its removal from the body) and the rest of the work was carried out on the homogenate after it had been stored at −20° for 11 days, by which time it had lost 63 per cent of its original activity.

The results obtained with metronidazole are as follows:

pH	Concentration of metronidazole	Percentage inhibition	
		Fresh homogenate	Stored homogenate
8·8	$4{\cdot}8 \times 10^{-3}$ M	20·5	39·1
	$5{\cdot}4 \times 10^{-3}$ M	—	48·8
	$6{\cdot}4 \times 10^{-3}$ M	—	64·3
11·0	$4{\cdot}8 \times 10^{-3}$ M	49·7	—

From this data it is computed that the concentration of metronidazole producing 50 per cent inhibition of the stored, crude preparation of atypical human alcohol dehydrogenase at pH 8·8 is $5{\cdot}5 \times 10^{-3}$ M and the concentration of metronidazole producing 50 per cent inhibition of the fresh crude preparation at pH 11·0 is very nearly $4{\cdot}8 \times 10^{-3}$ M.

The figure we reported[2] for the concentration of metronidazole producing 50 per cent inhibition of a fresh, crude preparation of typical human liver alcohol dehydrogenase at pH 11·0 was $6{\cdot}6 \times 10^{-3}$ M.

We conclude that the inhibitory effect of metronidazole on crude preparations of atypical and typical human liver alcohol dehydrogenase is of the same order.

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Nuffield Unit of Medical Genetics,
Department of Medicine,
University of Liverpool

J. A. EDWARDS
J. PRICE*

* Bates Research Fellow, Mental Health Research Fund. Request for reprints should be addressed to Dr. J. Price.

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The effect of *N*-hydroxyurethane upon the rapidly labelled RNA of the mouse

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COUNTER-current distribution (CCD) analysis has been used to detect possible precancerous changes in the rapidly labelled RNA isolated in association with DNA from the liver of rats given hepatocarcinogens in their diet[1, 2] and it was considered of interest to compare the early responses of two tissues with different susceptibility to a carcinogen. Urethane was considered a suitable carcinogen