half-life would have been expected. The finding of identical values in the chlorpromazine group and in the elderly drug-free patients clearly demonstrates that chlorpromazine has not increased drug-metabolizing capacity. This is further emphasized by the fact that the chlorpromazine group are appreciably younger than the elderly control patients and for this reason would be expected to be faster metabolizers of antipyrine (O'Malley & others, 1971). Possible reasons for the discrepancy between the present findings and those of Curry & others (1971) are, firstly, people in the age group of the chlorpromazine patients studied may not be inducible. A second possibility is that chlorpromazine may produce only weak induction in man. This degree of induction might be sufficient to reduce the steady-state plasma level of the drug when administered over a long period but not sufficiently great to affect measurably the plasma half-life of a concomitantly administered drug. Certainly, from our rat studies (Table 2) chlorpromazine while being an inducer, produced only 33% of the stimulation caused by barbitone and must be considered a weak inducer.

Department of Pharmacology and Therapeutics,
University of Dundee,
Dundee, U.K.

I. H. STEVENSON
K. O'MALLEY
M. J. TURNBULL
B. R. BALLINGER

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Spironolactone—a weak enzyme inducer in man

Animal experiments indicate that spironolactone is an inducer of hepatic microsomal oxidizing enzymes. Thus, in mice it increases hexobarbitone metabolism *in vitro* and *in vivo* (Gerald & Feller, 1970) and increases microsomal protein, cytochrome P-450 and cytochrome c reductase activity (Feller & Gerald, 1971). In female, though not in male, rats it has the same effects as in mice (Stripp, Hamrick & others, 1971) and, also in female rats, it shortens the half-life of its main metabolite (Solymoss, Tóth & others, 1970). In view of its widespread clinical use, particularly in combination with drugs known to undergo oxidation in the liver, a study of its inducing potential in man seemed important.

Nine healthy volunteers (1 female), aged 20–30 years, participated in the study. Antipyrine half-lives ($T_{\frac{1}{2}}$) were determined by plasma sampling (6 samples) up to 30 h after an oral load of 600 mg, using the method of Brodie, Axelrod & others (1949). 24-h urinary excretion rates of D-glucaric acid were measured as described by Hunter, Maxwell & others (1971). When control measurements of these parameters had been made, spironolactone 50 mg three times daily was administered for 7 days. Further measurements were started on the day following the end of treatment. After an interval of at least 4 weeks, eight of the subjects received phenobarbitone 120 mg orally each night for seven consecutive nights, following which antipyrine $T_{\frac{1}{2}}$ estimates were repeated.

The results of the experiments are shown in Table 1. In four of the nine subjects there was significant reduction in antipyrine $T_{\frac{1}{2}}$ after spironolactone as assessed by comparison of the slopes of the regression lines. Using paired data for the whole

group there was no significant change in antipyrine $T_{\frac{1}{2}}$ ($t = 1{\cdot}05$, $P > 0{\cdot}1$), apparent antipyrine distribution volume ($t = 0{\cdot}26$, $P > 0{\cdot}1$) or D-glucaric acid excretion rate ($t = 1{\cdot}82$, $P > 0{\cdot}05$). After phenobarbitone treatment, five subjects showed significant reduction in antiyprine $T_{\frac{1}{2}}$ (see Table 1) and in the group as a whole this change was significant ($t = 2{\cdot}35$, $P < 0{\cdot}05$). There was no change in the antipyrine distribution volume ($t = 1{\cdot}40$, $P > 0{\cdot}1$).

Table 1. *Effects of spironolactone and phenobarbitone on antipyrine half-life and* D-*glucaric acid excretion.*

	Control		After spironolactone		After phenobarbitone
Subject	Antipyrine $T_{\frac{1}{2}}$ (h)	D-Glucaric acid excretion (μmol/24 h)	Antipyrine $T_{\frac{1}{2}}$ (h)	D-Glucaric acid excretion (μmol/24 h)	Antipyrine $T_{\frac{1}{2}}$ (h)
I	8·9	0	10·6	19	7·6
II	23·5	31	11·1*	35	10·8*
III	10·5	17	10·1	11	8·5*
IV	14·8	18	12·6*	9	9·7*
V	12·3	4	14·0	14	14·1
VI	13·3	5	13·5	8	11·8*
VII	13·8	1	16·8	23	12·0
VIII	12·8	10	9·9*	23	4·0*
IX	20·8	24	17·9*	25	—

* Significantly less than control ($P < 0{\cdot}05$).

On the basis of the changes in antipyrine $T_{\frac{1}{2}}$, the results suggest that spironolactone enhances drug oxidation in some individuals. In particular, subject II, who had the longest control antipyrine $T_{\frac{1}{2}}$, showed the greatest response to spironolactone administration. Of the five subjects who failed to respond to spironolactone treatment, three (I, V, VII) were also unaffected by phenobarbitone, a finding which suggests that they were already under the influence of environmental inducing agents.

The results are not directly comparable with published animal data because of the difference in spironolactone dosage (2 mg/kg in the present experiments as against 100 mg/kg in animal experiments). It is possible that larger doses would have produced larger effects. Our findings suggest that spironolactone is a weak enzyme inducer in man.

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Departments of Pharmacology and Medicine,
St. Thomas's Hospital Medical School,
London, S.E.1, U.K.

SHIRLEY A. TAYLOR
M. D. RAWLINS
S. E. SMITH

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