Br. J. Pharmac. (1972), **44**, 89–99.

Analysis of the inhibition of pethidine N-demethylation by monoamine oxidase inhibitors and some other drugs with special reference to drug interactions in man

B. CLARK* AND J. W. THOMPSON
with the technical assistance of
G. WIDDRINGTON

Department of Pharmacology, Medical School, University of Newcastle upon Tyne, NE1 7RU

Summary

1. N-Demethylation of pethidine was studied in microsomal suspensions from unstarved male rat liver and the N-demethylase identified as belonging to the class of hepatic microsomal mixed function oxidases.

2. A study of the structure/action relationships of compounds inhibiting pethidine N-demethylase revealed that hydrazine derivatives including phenylhydrazine, methylphenylhydrazine and mebanazine were all potent competitive inhibitors.

3. Pethidine N-demethylase was only slightly inhibited by histamine and amphetamine but not by adrenaline and ephedrine nor by several miscellaneous compounds including piperidine, N-ethylpiperidine, N-methylpiperidine, N-methylammonium, hydrallazine or pethidinic acid.

4. Several psychotropic drugs were all found to be potent competitive inhibitors of pethidine N-demethylase. These included monoaminoxidase inhibitors (the most active being nialamide and phenoxypropazine [K_i=0·01 mM]; the least active iproniazid [K_i=1·05 mM]); the tranquillizers promazine, propiomazine and chlorpromazine and tricyclic antidepressants (opipramol [K_i=0·01 mM], imipramine [K_i=0·03 mM], desipramine [K_i=0·03 mM] and amitryptyline [K_i=0·03 mM]). Hydrocortisone [K_i=0·3 mM], prednisolone [2·8 mM] and nalorphine [0·07 mM] were also inhibitors, whilst SKF 525A was the most active of all [K_i=0·002 mM].

5. These results are discussed in relation to the clinically observed drug interactions which may occur between monoamineoxidase inhibitors and pethidine. It is concluded that since many different groups of drugs, including monoamineoxidase inhibitors, tranquillizers, tricyclic antidepressants, steroids, nalorphine, SKF 525A and barbiturates compete for cytochrome P_{450} reductase, it is possible that this mechanism may account, at least in part, for the observed interactions of these various drugs in man.

* Present address: Department of Biochemistry, Research and Development Laboratories, Fisons Ltd., Pharmaceutical Division, Loughborough, Leics.

Introduction

In 1958 Papp & Benaim reported that a serious drug interaction may occur when patients taking a monoamine oxidase inhibitor (MAOI) are given pethidine. Since then, it has become recognized that the combination of an MAOI with certain other drugs may be hazardous and potentially lethal. The incidence of interactions between MAOI's and pethidine is not known, but the literature contains more than a dozen references on this subject (Papp & Benaim, 1958; Palmer, 1960; Shee, 1960; Craig, 1962; Dally, 1962; Denton, Borelli & Edwards, 1962; London & Milne, 1962; Mason, 1962; Pells Cocks & Passmore-Rowe, 1962; Taylor, 1962; Bradley & Francis, 1963; Brownlee & Williams, 1963a; Nymark & Nielson, 1963; Myron Vigran, 1964; Loveless & Maxwell, 1965). In spite of this, only five cases have been reported to the Committee on Safety of Drugs (W. H. Inman, personal communication) although the total number of cases which have actually occurred may be considerably larger. This may well be yet another example of the very poor response by doctors to report adverse drug reactions to the Committee on Safety of Drugs.

It is important to study the mechanism underlying this drug interaction in order to prevent and treat this and similar types of drug interaction. This paper reports the results of experiments designed to investigate the effects of different MAOI's on the metabolism of pethidine. The actions of other centrally active drugs including major tranquillizers, tricyclic antidepressants, steroids, barbiturates, nalorphine and SKF 525A on the metabolism of pethidine have also been examined. Although several biochemical mechanisms have been suggested to explain these interactions, this appears to be the first attempt to examine the problem experimentally. The results reported in this paper represent an extension of some earlier work (Clark & Thompson, 1966; Clark, 1967).

Methods

Enzyme preparations

Microsomal suspensions from unstarved male rat liver were prepared as described previously (Clark, 1967).

N-demethylations

The assay system for the N-demethylation of pethidine has been described in detail in a previous publication (Clark, 1967). Except in those cases where K_i values have been given when substrate concentrations were done over the range 0–3·33 mM, the pethidine concentration throughout was 3·33 mM and other drugs were added to the system as described in **Results**. Inhibitor concentration curves were done for those drugs shown in Table 4, from which the concentrations required to produce 50% inhibition of pethidine N-demethylation were determined (see **Discussion**).

To determine K_i

As given in Tables 2, 4 and 5: $1/V$ against $1/S$ plots in the presence and absence of known inhibitor concentrations were obtained. From the intercepts on the x axis the apparent K_m (K_{app}, in the presence of inhibitor) and the K_m (K_m, substrate only)

were determined. For competitive inhibition, the inhibitor constant K_i is given by the equation:

$$K_i = \frac{i}{\left[\frac{K_{app}}{K_m} - 1\right]}$$

where i is the inhibitor concentration and K_{app} and K_m are the apparent K_m in the presence of inhibitor and K_m for substrate alone, respectively.

Drugs

The following drugs were used and expressed as mM: L-adrenaline bitartrate monohydrate, amitriptyline (Tryptizol), (+)-amphetamine sulphate, amylobarbitone sodium, barbitone sodium, chlorpromazine hydrochloride, desipramine (Pertofran), ephedrine hydrochloride, histamine acid phosphate, hydrallazine (Apresoline), hydrocortisone hemisuccinate (Efcortelan), imipramine hydrochloride (Tofranil), iproniazid (Marsilid), isocarboxazid (Marplan), mebanazine oxalate (Actomol), morphine sulphate, nalorphine hydrobromide (Lethidrone), nialamide hydrochloride (Niamid), opipramol hydrochloride (Insidon), pargyline hydrochloride (Butonyl), pentobarbitone sodium, pethidine hydrochloride, phenelzine sulphate (Nardil), phenobarbitone sodium, phenoxypropazine (Drazine), pivazide (Tersavid), prednisolone disodium phosphate (Predsol), promazine hydrochloride (Sparine), propiomazine hydrochloride (Largon), SKF 525A, thiopentone sodium, tranylcypromine sulphate (Parnate). Other materials used were of analar grade or laboratory reagents of high purity.

Results

Identification of the pethidine N-demethylating system

Table 1 lists the inhibitory effects produced by several miscellaneous agents. Cyanide was not a powerful inhibitor of this system, compared with its action on cytochrome oxidase where 0·1 mM abolished all activity. Carbon monoxide (as coal gas) produced a large inhibition, probably due to the formation of a reversible complex with cytochrome P_{450}, thus preventing the pigment from reacting with oxygen. Oxidizing agents such as potassium ferricyanide and hydrogen peroxide and also reducing agents; for example, sodium dithionite, caused inhibition of pethidine demethylation. From these results, it was concluded that the N-demethylase responsible belongs to the class of hepatic microsomal mixed function oxidases (Roth & Bukovsky, 1961; Clouet, 1964).

TABLE 1. *Effect of inhibitors of microsomal mixed function oxidase on pethidine N-demethylase*

Compound	% Inhibition
KCN (0·33 mM)	25
(0·66 mM)	35
CO (coal gas for 20 s)	50–70
Potassium ferricyanide (0·33 mM)	50
H_2O_2 (33 mM)	58
(66 mM)	65
Sodium dithionite (2 mg)	100

Structure/action relationships of compounds inhibiting pethidine N-demethylase

Table 2 shows the relationship between the structure of several compounds and their ability to inhibit pethidine N-demethylase. The predominantly competitive nature of the inhibitions was indicated by the form of the $1/S$ against $1/V$ plots based on results of experiments obtained in the presence or absence of each inhibitor (Clark, 1967).

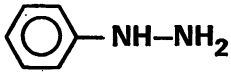
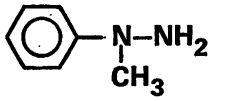
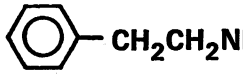
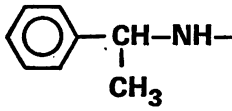
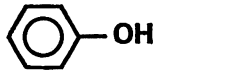
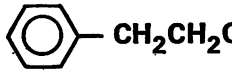
Phenethylalcohol did not inhibit in concentrations up to 1·0 mM, nor did it reverse the strong inhibition caused by phenelzine. Phenol was a weak inhibitor as also was hydrazine. By contrast hydrazine derivatives including phenylhydrazine, methylphenylhydrazine and mebanazine were all potent inhibitors.

Effects of some amines on pethidine N-demethylase

The effects of four amines on pethidine N-demethylase are shown in Table 3. Adrenaline and ephedrine failed to produce significant inhibition at 3·33 mM whilst histamine and amphetamine at the same concentrations gave only small inhibitions of 13% and 28%, respectively. On the basis of these experiments it was not known whether the inhibitions were competitive or non-competitive, but the results of Eade & Renton (1970) suggest that they belong to the former group.

Several miscellaneous compounds, some related to pethidine, were tested and found to be inactive. These included piperidine, N-ethyl piperidine, N-methylpiperidine and N-methylammonium. Hydrallazine produced no inhibition up to

TABLE 2. *Structure/action relationships of compounds inhibiting pethidine N-demethylase*

Compound		K_i(m M)
Phenylhydrazine		.01
Methylphenylhydrazine		.03
Phenelzine		.07 ± .05 (S.D. 6 expts.)
Mebanazine		.07
Hydrazine		.61
Phenol		1.66
Phenethylalcohol*		No inhibition up to 1 m M

* Phenethylalcohol did not reverse the inhibition caused by phenelzine.

0·66 mM (Table 4) whilst pethidinic acid was inactive up to 3·33 mM and was not itself demethylated, in agreement with the results of Brodie (1962).

Effects of psychotropic and other drugs

Several psychotropic drugs were tested for their effects on pethidine demethylation and were all found to be inhibitors to varying degrees (Tables 4 and 5), with the exception of barbitone. The inhibitions were mainly competitive in nature as judged by the form of the $1/S$ against $1/V$ plots from results obtained in the presence or absence of the drugs.

All the MAOI's tested were inhibitors of pethidine N-demethylase, although the potency range was considerable. For example, nialamide was a potent inhibitor, whilst iproniazid was a weak inhibitor as also was isoniazid. It seems unlikely that the enzyme inhibition was due to the reducing power of the compounds tested be-

TABLE 3. *Effect of some amines on pethidine N-demethylase*

Compound	% Activity
None	100
Adrenaline (3·33 mM)	106
Ephedrine (3·33 mM)	98
Amphetamine (3·33 mM)	72
Histamine (3·33 mM)	87

TABLE 4. *Competitive inhibitors of pethidine N-demethylase*

	K_I (mM)
Monoamine oxidase inhibitors	
Nialamide	0·01
Phenoxypropazine	0·01
Isocarboxazid	0·02
Clorgyline	0·04
Mebanazine	0·07
Phenelzine	0·07
Pargyline	0·07
Tranylcypromine	0·14
Pivazide	0·80
Iproniazid	1·05
Isoniazid (antituberculous)	1·31
Tranquillizers	
Promazine	0·05
Propiomazine	0·09
Chlorpromazine	0·05
Antihypertensive	
Hydrallazine	No inhibition up to 0·66 mM
Tricyclic antidepressants	
Opipramol	0·01
Imipramine	0·03
Desipramine	0·03
Amitryptyline	0·03
Steroids	
Hydrocortisone	0·30
Prednisolone	2·80
Morphine antagonists	
Nalorphine	0·07
Experimental	
SKF 525A	0·002

cause there was no correlation between these two properties. Three tranquillizers and five tricyclic antidepressants tested were also potent inhibitors. Two steroids, hydrocortisone and prednisolone, were tested because these had been found to give apparently beneficial results in the treatment of patients who had collapsed following a pethidine-MAOI reaction. Both steroids were weak inhibitors and failed to reverse the inhibition of pethidine N-demethylation produced by phenelzine (Table 4).

SKF 525A, which is a potent inhibitor of hepatic microsomal drug metabolizing enzymes was a potent inhibitor of pethidine N-demethylation, as also was the morphine antagonist, nalorphine.

The inhibitory potency of barbiturates was clearly correlated with their partition coefficients. Sodium thiopentone as the most lipid soluble was also the most potent whilst sodium barbitone, the least lipid soluble, produced no effect at concentrations up to 3·33 mM.

Lack of chemical interaction between pethidine and MAOI's

Using thin layer chromatography, paper electrophoresis and spectrophotometry there was no indication of any complex formation between iproniazid or phenelzine with pethidine.

Discussion

Several suggestions have been made by other authors to account for the observed dangerous interaction between certain MAOI's and pethidine in some patients receiving both drugs. Shee (1960), reporting on the dangerous potentiation of pethidine by iproniazid postulated that the toxic effect was due to a chemical combination between pethidine and iproniazid or a metabolite. In the present study, evidence of the formation of a complex was looked for but was not obtained.

Nymark & Nielson (1963) reported that rabbits pretreated with intramuscular injections of β-p-chlorphenylmercaptoethyl hydrazine (a potent MAOI) showed violent reactions to intravenous pethidine, most of them dying within an hour of receiving the analgesic. The cardinal signs of the reaction were hyperpyrexia, hyperexcitability, motor restlessness, erect ears, dilated pupils, exophthalmos, forced superficial respiration, clonic convulsions and extreme licking with strongly contracted lips. These authors suggested that the effects were due to central sympathetic and psychic over-stimulation caused by repeated administration of MAOI's causing a rise in the concentration of brain monoamines and precipitated by pethidine.

TABLE 5. *Effect of barbiturates on pethidine N-demethylation*

Barbiturate	K_i (mM)	Partition coefficient C*
Thiopentone sodium	0·04	580
Amylobarbitone sodium	0·15	42
Pentobarbitone sodium	0·42	39
Phenobarbitone sodium	1·02	3
Barbitone sodium	No inhibition up to 3·33 mM	1

* Data of M. T. Bush (1963) $C = \frac{\text{concentration in methylene chloride}}{\text{concentration in water}}$ at 25° of the unionized form.

Loveless & Maxwell (1965) similarly accounted for the fatal hyperpyrexia they observed after injections of pethidine into rabbits which had previously received tranylcypromine or nialamide. A mechanism of this nature could well account for the adrenergic effects of the interaction of MAOI's and pethidine in man, but probably does not explain adequately those effects closely resembling pethidine overdosage, that is coma and respiratory failure.

In the light of reports showing that iproniazid and other MAOI's prolonged the hexobarbitone-induced hypnosis in animals (Fouts & Brodie, 1956), Papp & Benaim (1958), London & Milne (1962) and Brownlee & Williams (1963b) have speculated that the potentiation of pethidine was due to the inhibition of its metabolism by MAOI's. Although there was no direct experimental evidence for such a mechanism, it has been widely accepted (Editorial, 1963 ; *British National Formulary*, 1968).

The results reported in this paper indicate that all of the MAOI's tested (Table 4) are inhibitors of the N-demethylation of pethidine. Unpublished results show that all the inhibitions were competitive in nature. N-Demethylation is a key reaction in the metabolism of pethidine in rats (Axelrod, 1956 ; Roth & Bukovsky, 1961 ; Clouet, 1964) and in man (Burns, Berger, Lief, Wollack, Papper & Brodie, 1955 ; Plotnikoff, Leong Way & Elliott, 1956). Analysis of the inhibition caused by phenelzine (Clark, 1967) has shown that this MAOI interferes with the end of a chain of enzyme reactions leading to the oxidative metabolism of a number of drugs (Omura, Sato, Cooper, Rosenthal & Esterbrook, 1965) including pethidine. It is likely that there are common pathways for the oxidative metabolism of drugs, foreign compounds and certain steroids which are hydroxylated in the liver with each competing for the same ' active oxygen ' donor supply (Brodie, 1962 ; but see Gillette, 1969). N-Demethylations, for example of pethidine, are believed to occur (Brodie, 1962) by the breakdown, either spontaneous or enzyme-induced, of the primary oxidized product thus:

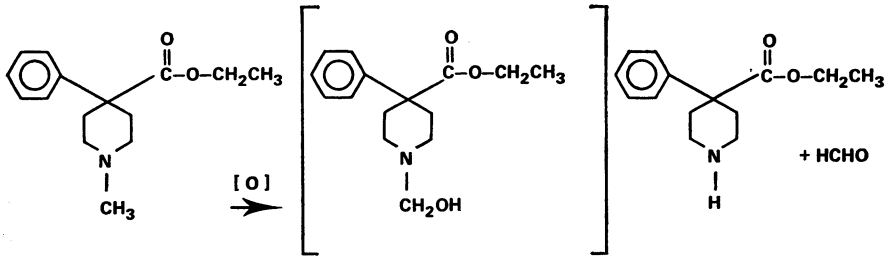


FIG. 1.

A variety of drugs have been tested for their effect on the N-demethylation of pethidine (Tables 2–5) and surprisingly it was found that many of these were moderately potent inhibitors, for example, 50% inhibition at mM concentrations.

The assay system used in the present experiments measured the activity of the whole system from NADPH through to the production of norpethidine. If this system is common (except in the final steps) to all groups of drugs which are oxidatively metabolized by hepatic microsomes, then mutual competitive inhibition might occur. Drugs undergoing such oxidative metabolism would compete either for the N-demethylase itself (in the case of those drugs which are N-demethylated) or for the active oxygen donor. The inhibitions would be significant if the amount of the active oxygen donor formed from cytochrome P_{450} was the rate limiting factor in

the system. Phenobarbitone and many other drugs induce the drug-metabolizing enzymes in hepatic microsomes (Ernster & Orrenius, 1965) and the rise in enzyme activity is closely paralleled by the rise in the content of cytochrome P_{450} reductase activity (Orrenius & Ernster, 1964 ; Ernster & Orrenius, 1965 ; Long, 1969). Therefore competition for cytochrome P_{450} reductase could satisfactorily explain the observed inhibitions produced by tranquillizers, tricyclic antidepressants, steroids, nalorphine, SKF 525A and barbiturates. This type of mutually competitive inhibition has already been reported (Axelrod & Cochin, 1956 ; Anders & Mannering, 1966a, b, & c). Whether or not a compound can be metabolized by the hepatic system depends to a large extent on its lipid solubility (Brodie, 1962). Table 5 shows that there is a similar correlation between the inhibitory potency of certain barbiturates and their lipid solubility.

Table 2 shows the structure activity relationships for a number of inhibitory compounds. Phenelzine itself is very lipid soluble, due to the phenethyl group. That it is not this group which is bringing about the inhibition is shown by the fact that phenethyl alcohol, which is equally lipid soluble, does not inhibit to any significant extent ; nor did it reverse the inhibition caused by phenelzine. On the other hand, hydrazine, the other group in the phenelzine molecule produced a significant, if small, inhibition. As expected, phenylhydrazine was also a potent inhibitor whilst the corresponding alcohol, phenol, had a much lower inhibitory potency. Substitution of the hydrazine part of the molecule, as in N-methyl phenylhydrazine, although not significantly affecting the lipid solubility, decreased the inhibitory power. Mebanazine, an analogue of phenelzine had a similar inhibitory potency to the latter drug. This strengthens the view that the hydrazine part of the molecule is important for inhibition, whereas the aromatic group confers the necessary lipid solubility.

Drugs which are low in lipid solubility and which are poorly metabolized by the hepatic system might be excepted to be weak inhibitors of the N-demethylation of pethidine and the results of experiments obtained with a number of amines were consistent with this hypothesis (Table 3).

The monoamine oxidase inhibitors (Table 4) were all inhibitors of the N-demethylation of pethidine but the potency was not simply related to the lipid solubility of the drugs, although this is of some importance. Nor does it seem to be directly related to the degree to which these drugs are metabolized in the liver by the microsomal oxidative system. Although little is known about the detailed metabolism of many of these drugs, it is clear that there are substantial differences (see, for example, Sotoh & Moroi, 1971 on isocarboxazid).

The literature contains several references to the *in vitro* inhibition of the metabolism of one drug by another. For example, chlorpromazine, imipramine and iproniazid inhibit pentobarbitone metabolism (Kato, Chiesara & Vassanelli, 1964) and 2,4-dichloro-6-phenyl phenoxyethylamine inhibits the N-demethylation of pethidine (McMahon & Easton, 1962).

Thus interference by one drug of another drug's metabolism would appear to be a common phenomenon *in vitro* but has this any significance *in vivo*? Prolongation of hypnotic-induced sleeping times in small animals by other drugs, for example by *p*-aminosalicylate (Rogers, Alcantara & Fouts, 1963), SKF 525A, iproniazid, nialamide (Laroche & Brodie, 1960) and imipramine (Kato, Chiesara & Vassanelli, 1963).

Many drug interactions in man might be explicable by this type of mechanism. For example, the delay of recovery from thiopentone anaesthesia caused by chlorpromazine, amitriptyline, hydroxyzine, thiethylperazine and thioridazine (Dobkin, Israel & Criswich, 1962) might be due to a reduction in the rate of metabolic destruction of the thiobarbiturate. Desipramine increases the urinary excretion of amphetamine by reducing its rate of hydroxylation in the liver (Consolo, Dolfini, Garattini & Valzelli, 1967) and this might account for the potentiation and prolongation of the effect of the sympathomimetic by the antidepressant. In a similar way one might explain the fact that pethidine-induced respiratory depression may be enhanced by antidepressants of the imipramine type (Goodman & Gilman, 1970) and by chlorpromazine (Lambertson, Wendel & Longenhagen, 1961). In addition to the mechanisms already discussed, other factors may be involved in the production of MAOI-pethidine interaction such as distribution, rate of destruction, rate of excretion and the time interval between taking it and receiving pethidine and the length of time over which the antidepressant had been used.

In conclusion, a large number of drugs of various types inhibit the N-demethylation of pethidine *in vitro* in preparations of rat liver microsomes. All of those drugs which are known to have potentiated or prolonged the effect of pethidine in man and those which have been tested were shown to be inhibitors of this system. Because of this, it is possible that this mechanism might account, in part at least, for the observed interactions of these various types of drugs in man. The possibility of interactions between a great many other drugs ought to be considered in relation to the common clinical practice of prescribing several drugs at once.

We are grateful to the Medical Research Council for generous financial support. We should also like to thank Mrs. H. M. Cairns and Mrs. M. Cheek for secretarial assistance and also Mrs. E. Lewis, Graphics Section. Dept. of Photography and Teaching Aids, for making the diagrams. Generous gifts of the following drugs are gratefully acknowledged: amitriptyline (Tryptizol), Merck, Sharp & Dohme Ltd.; clorgyline (M & B 9302), May & Baker Ltd.; desipramine (Pertofran), Geigy (U.K.) Ltd.; hydrallazine (Apresoline), Ciba Laboratories Ltd.; hydrocortisone hemisuccinate (Efcortelan), Glaxo Laboratories Ltd.; imipramine hydrochloride (Tofranil), Geigy (U.K.) Ltd.; iproniazid (Marsilid), Roche Products Ltd.; isocarboxazid (Marplan), Roche Products Ltd.; mebanazine oxalate (Actomol), I.C.I. Ltd.; nalorphine hydrobromide (Lethidrone), Burroughs Wellcome Ltd.; nialamide hydrochloride (Niamid), Harvey Pharmaceuticals Department of Pfizer Ltd.; opipramol hydrochloride (Insidon), Geigy (U.K.) Ltd.; pargyline hydrochloride (Eutonyl), Abbot Laboratories Ltd.; phenelzine sulphate (Nardil), W. R. Warner & Co. Ltd.; phenoxypropazine (Drazine), Smith & Nephew Pharmaceuticals Ltd.; pivazide (Tersavid), Roche Products Ltd.; prednisolone disodium phosphate (Predsol), Glaxo Laboratories Ltd.; promazine hydrochloride (Sparine), John Wyeth & Brother Ltd.; propiomazine hydrochloride (Largon), John Wyeth & Brother Ltd.; SKF 525A, Smith, Kline & French Laboratories Ltd.; tranylcypromine sulphate (Parnate), Smith, Kline & French Laboratories Ltd.

REFERENCES

ANDERS, M. W. & MANNERING, G. J. (1966a). Inhibition of drug metabolism. I. Kinetics of the inhibition of N-demethylation of ethylmorphine by SKF 525A and related compounds. *Mol. Pharm.*, **2**, 319–327.

ANDERS, M. W. & MANNERING, G. J. (1966b). Inhibition of drug metabolism. II. Metabolism of 2-diethylaminoethyl 2,2-diphenyl valerate HCl (SKF 525A). *Mol. Pharm.*, **2**, 328–340.

ANDERS, M. W. & MANNERING, G. J. (1966c). Inhibition of drug metabolism. IV. Induction of drug metabolism of SKF 525A and Lilly 18947 and the effect of induction on the inhibitory properties of SKF 525A and type compounds. *Mol. Pharm.*, **2**, 341–346.

AXELROD, J. (1956). The enzymatic N-demethylation of narcotic drugs. *J. Pharmac. exp. Ther.*, **117**, 322–330.

AXELROD, J. & COCHIN, J. (1956). Inhibitory action of N-allylnormorphine on enzymatic demethylation of narcotic drugs. *Fedn Proc.*, **15**, 395.

BRADLEY, J. J. & FRANCIS, J. G. (1963). Reactions to pethidine or opium derivatives in patients receiving monoamine oxidase inhibitors. *Lancet*, **i**, 386.

British National Formulary (1968). London: The British Medical Association, The Pharmaceutical Society of Great Britain, p. 79.

BRODIE, B. B. (1962). In: *Ciba Symposium on Enzymes and Drug Action*, ed. Mongar, J. L. & deReuck, A. V. S., pp. 317–343. London: Churchill.

BROWNLEE, G. & WILLIAMS, G. W. (1963a). Potentiation of amphetamine and pethidine by monoamineoxidase inhibitors. *Lancet*, **i**, 669.

BROWNLEE, G. & WILLIAMS, G. W. (1963b). Monoamineoxidase inhibitors. *Lancet*, **i**, 1323.

BUSH, M. T. (1963). Sedatives and hypnotics. I. Metabolism, fate and excretion. In: *Physiological Pharmacology*, Vol. **1**, ed. Root, W. S. & Hofmann, F. G., pp. 185–218. N.Y.: Academic Press.

BURNS, J. J., BERGER, B. L., LIEF, P. A., WOLLACK, A., PAPPER, E. M. & BRODIE, B. B. (1955). The physiological disposition and fate of Meperidine (Demerol) in man and a method for its estimation in plasma. *J. Pharmac. exp. Ther.*, **114**, 289.

CLARK, B. (1967). The *in vitro* inhibition of the N-demethylation of pethidine by phenelzine (Phenelhydrazine). *Biochem. Pharmac.*, **16**, 2369–2385.

CLARK, B. & THOMPSON, J. W. (1966). Inhibition of pethidine metabolism by monoamine oxidase inhibitors. *Fedn Eur. Biochem. Soc. 3rd Meeting, Warsaw* (Abstract F. 247).

CLOUET, D. H. (1964). Meperidine N-demethylase activity in rat liver. *J. Pharmac. exp. Ther.*, **144**, 354–361.

CONSOLO, S., DOLFINI, E., GARATTINI, S. & VALZELLI, L. (1967). Desipramine and amphetamine metabolism. *J. Pharm. Pharmac.*, **19**, 253–256.

CRAIG, D. D. H. (1962). Reactions to pethidine in patients on phenelzine. *Lancet*, **ii**, 559.

DALLY, P. (1962). Fatal reactions associated with tranylcypromine and methylamphetamine. *Lancet*, **i**, 1235–1236.

DENTON, P. H., BORELLI, V. M. & EDWARDS, N. V. (1962). Dangers of monoamine inhibitors. *Br. med. J.*, **2**, 1752–1753.

DOBKIN, A. B., ISRAEL, J. S. & CRISWICH, V. G. (1962). Prolongation of thiopental anaesthesia with hydroxyzine, SA 97, thiethylperazine, and thioridazine. *Can. Anaes. Soc. J.*, **9**, 342–346.

EADE, N. R. & RENTON, K. W. (1970). Effect of monoamine oxidase inhibitors on the N-demethylation and hydrolysis of meperidine. *Biochem. Pharmac.*, **19**, 2243–2250.

Editorial (1963). Pethidine poisoning. *Br. med. J.*, **ii**, 822.

ERNSTER, L. & ORRENIUS, S. (1965). Substrate-induced synthesis of the hydroxylating enzyme system of liver microsomes. *Fedn Proc.*, **24**, 1190–1199.

FOUTS, J. R. & BRODIE, B. B. (1956). On the mechanism of drug potentiation by iproniazid (2-isopropyl-1-isonicotinyl hydrazine). *J. Pharmac. exp. Ther.*, **116**, 480–485.

GILLETTE J. R. (1969). Mechanisms of oxidation by enzymes in the endoplasmic reticulum. In: *Biochemical Aspects of Antimetabolites of Drug Hydroxylation*, ed. Shugar, D., pp. 109–124. N.Y.: Academic Press.

GOODMAN, L. S. & GILLMAN A. (1970). *The Pharmacological Basis of Therapeutics*, 4th edn. p. 259. London: Collier-Macmillan.

KATO, R., CHIESARA, E. & VASSANELLI, P. (1963). Mechanisms of potentiation of barbiturate and meprobamate actions by imipramine. *Biochem. Pharmac.*, **12**, 357–364.

KATO, R., CHIESARA, E. & VASSANELLI, P. (1964). Further studies on the inhibition and stimulation of microsomal drug-metabolizing enzymes of rat liver by various compounds. *Biochem. Pharmac.*, **13**, 69–83.

LAMBERTSON, C. J. WENDEL, H. & LONGENHAGEN, J. B. (1961). The separate and combined respiratory effects of chlorpromazine and meperidine in normal men controlled at 45 mm Hg alveolar pCO_2. *J. Pharm. exp. Ther.* **131**, 381–393.

LAROCHE, M. J. & BRODIE, B. B. (1960). Lack of relationship between inhibition of monoamine oxidase and potentiation of hexobarbital hypnosis. *J. Pharmac. exp. Ther.*, **130**, 134–137.

LONDON, D. R. & MILNE, M. D. (1962). Dangers of monoamine oxidase inhibitors. *Br. med. J.*, **2**, 1752.

LOVELESS, A. H. & MAXWELL, D. R. (1965). A comparison of the effects of imipramine trimipramine and some other drugs in rabbits treated with a monoamine oxidase inhibitor. *Br. J. Pharmac. Chemother.*, **25**, 158–170.

LONG, R. F. (1969). Induction of drug-metabolising enzymes and cytochrome P-450. *Biochem. J.*, **115**, 26*P*.

MCMAHON, R. E. & EASTON, N. R. (1962). The N-demethylation of butyramine. *J. Pharmac. exp. Ther.*, **135**, 128–133.

MASON, A. (1962). Fatal reaction associated with tranylcypromine and methylamphetamine. *Lancet*, **i**, 1073.

MYRON VIGRAN, I. (1964). Dangerous potentiation of meperidine hydrochloride by pargyline hydrochloride. *J. Am. med. Ass.*, **187**, 953–954.

NYMARK, M. & NIELSON, I. M. (1963). Reactions due to the combination of monoamine oxidase inhibitors with thymoleptics, pethidine or methylamphetamine. *Lancet*, **2**, 524–525.

OMURA, T., SATO, R., COOPER, D. Y., ROSENTHAL, O. & ESTERBROOK, R. W. (1965). Function of cytochrome P-450 of microsomes. *Fedn Proc.*, **24**, 1181–1189.

ORRENIUS, S. & ERNSTER, L. (1964). Phenobarbital-induced synthesis of the oxidative demethylating enzymes of rat liver microsomes. *Biochem. J.*, **92**, 37.

PALMER, H. (1960). Potentiation of pethidine. *Br. med. J.*, **ii**, 944.

PAPP, C. & BENAIM, S. (1958). Toxic effects of iproniazid in a patient with angina. *Br. med. J.*, **ii**, 1070–1072.

PELLS COCKS, D. & PASSMORE-ROWE, A. (1962). Dangers of monoamine oxidase inhibitors. *Br. med. J.*, **ii**, 1545–1546.

PLOTNIKOFF, N. P., LEONG WAY, E. & ELLIOTT, H. W. (1956). Biotransformation products of meperidine excreted in the urine of man. *J. Pharmac. exp. Ther.*, **117**, 414–419.

ROGERS, L. A., ALCANTARA, G. A. & FOUTS, J. R. (1963). p-Aminosalicylic acid induced prolongation of hexobarbital sleeping time. *J. Pharm. exp. Ther.*, **142**, 242–247.

ROTH, J. S. & BUKOVSKY, J. (1961). Studies on an n-demethylating system in rat liver microsomes. *J. Pharmac. exp. Ther.*, **131**, 275–281.

SHEE, J. C. (1960). Dangerous potentiation of pethidine by iproniazid, and its treatment. *Br. med. J.* **ii**, 507–509.

SOTOH, T. & MOROI, K. (1971). Enzymatic hydrolysis of isocarboxazid by rat tissues. *Biochem. Pharmac.*, **20**, 504–507.

TAYLOR, D. C. (1962). Alarming reaction to pethidine in patients on phenelzine. *Lancet*, **ii**, 401–402.

(*Received June* 23, 1971)