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The interaction between monoamine oxidase inhibitors and narcotic analgesics in mice

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1. The administration of either iproniazid or tranylcypromine to mice potentiates the acute toxicity of pethidine, morphine, pentazocine and phenazocine.

2. Blood levels of pentazocine in mice pretreated with tranylcypromine do not differ from the levels in animals not receiving the monoamine oxidase (MAO) inhibitor.

3. There is no correlation between changes in brain and liver MAO activity and the increased pethidine toxicity.

4. A comparison is made between the change in pethidine toxicity and the changes in the concentration of cerebral noradrenaline, dopamine and 5-hydroxytryptamine following the injection of tranylcypromine.

5. It is concluded that the increased toxicity of potent analgesics in combination with MAO inhibitors is not due to a decelerated metabolism of the analgesic drug, but is related to an increased concentration of cerebral 5-hydroxytryptamine. A critical level of this monoamine, in the brain, may be necessary before the drug interaction will take place.

Monoamine oxidase (MAO) inhibitors are known to potentiate the effects of a wide variety of pharmacological agents, and severe toxic reactions have been observed when certain drugs have been given to patients receiving MAO inhibitors for the treatment of depressive states. This group of drug interactions has been the subject of reviews by Goldberg (1964) and Sjöquist (1965). The majority of the adverse reactions are caused by agents which, like MAO inhibitors, exert an effect on monoaminergic neurotransmission. Some drugs, however, interact with MAO inhibitors by mechanisms which remain to be fully elucidated. The narcotic analgesics, and in particular pethidine, provide an example.

The adverse reaction to pethidine is said to be due to a decelerated breakdown of the analgesic drug, since MAO inhibitors are known to exert non-specific effects on detoxifying enzyme systems in the liver. A decelerated breakdown of pethidine would explain an exaggeration of the normal response to this drug, namely hypotension and respiratory depression, but it does not explain other reported effects such as hypertension and hyperpyrexia, effects which occur soon after the administration of pethidine to patients receiving MAO inhibitors (Rogers, Jepson, Kilpatrick & Thornton, unpublished). Furthermore, although the toxicity of other potent

analgesics is assumed to be potentiated in a similar fashion, there is no supporting evidence for this assumption.

This paper describes some experiments carried out on mice to determine whether or not the toxicity of analgesic drugs other than pethidine is potentiated by MAO inhibitors, and also to examine the possible mechanisms involved.

Methods

Animals and drugs

The experiments were carried out on male albino mice weighing between 18 and 25 g.

Drugs used were tranylcypromine sulphate; iproniazid phosphate; morphine sulphate; pethidine hydrochloride; pentazocine hydrochloride and phenazocine hydrobromide. Phenazocine was dissolved in dimethyl sulphoxide (3 volumes) and further diluted with 0·9% sodium chloride solution (7 volumes). The remaining compounds were dissolved in physiological saline.

In each experiment control mice were given the same amount of saline solution or organic solvent as the experimental animals. All drugs were administered by the intraperitoneal route.

Acute toxicity

The LD50s, and their 95% confidence limits were determined by the method of Litchfield & Wilcoxon (1949) on groups of ten mice at an ambient temperature of 23° C and observed for 2 hr.

Determination of pentazocine concentration in blood

Mice were killed by decapitation and the blood from five animals was pooled in a beaker containing sodium oxalate crystals. Oxalate was used as the anticoagulant because heparin was found to interfere with the subsequent assay.

A 2·5 ml. aliquot of blood was shaken for 5 min, in a stoppered tube containing 1 ml. of borate buffer pH 9·2 and 10 ml. of benzene. After centrifugation, 7·5 ml. of the benzene layer was withdrawn and added to 2·5 ml of 0·2N hydrochloric acid. Shaking for 5 min sufficed to pass the pentazocine from the organic phase into the aqueous phase, and after centrifugation, 2 ml. of the hydrochloric acid was recovered. The fluorescence was measured in a spectrophotofluorimeter, with an excitation wavelength of 280 mμ and a fluorescence wavelength of 305 mμ (uncorrected values).

A standard curve of pentazocine concentration in blood was constructed.

Measurement of monoamine oxidase activity

The MAO activity of brain and liver homogenates was determined by measuring the appearance of 4-hydroxyquinoline formed by the oxidative deamination of kynuramine (Krajl, 1965).

Measurement of brain monoamines

Mice were killed by decapitation and the brains from two animals were pooled and homogenized with 3 ml. of ice-cold 0·01 N hydrochloric acid. The monoamines

were extracted simultaneously from the homogenates using the method of Magnus, Krause & Riedel (1964). Aliquots of the final acid extract were used for the assay of noradrenaline (Shore & Olin, 1958), dopamine (Costa, Gessa, Kuntzman & Brodie, 1962) and 5-hydroxytryptamine (Bogdanski, Pletscher, Brodie & Udenfriend, 1956). The mean concentrations of noradrenaline, dopamine and 5-hydroxytryptamine (5-HT) in the brains of control mice were 0·44 μg/g, 0·86 μg/g and 0·54 μg/g respectively.

Results

Acute toxicity

The LD50s of the analgesic drugs were determined in control mice and in mice pretreated with either tranylcypromine 15 mg/kg (4 hr) or iproniazid 500 mg/kg (6 hr) (Table 1).

The toxicity of the analgesic drugs was increased by approximately 40–50% in mice pretreated with the monoamine oxidase inhibitors. The increase in toxicity was similar after both inhibitors except in the case of phenazocine. Dimethyl sulphoxide was used as the injection vehicle for phenazocine which may have some bearing on the different changes in the toxicity of this compound. This possibility is being investigated further.

The analgesics appeared to produce a greater degree of central excitation in mice pretreated with MAO inhibitors. This was difficult to assess with morphine or pethidine because of the excitement evoked by these drugs in the normal mouse. However, control mice given pentazocine or phenazocine died from depression and respiratory failure, whereas in animals pretreated with MAO inhibitors the analgesics caused increased locomotor activity and opisthotonos before the respiratory failure and death.

Blood levels of pentazocine

The blood levels of pentazocine in mice pretreated with tranylcypromine were determined over a period of 30 min following the injection of a sub-lethal dose of the analgesic drug. Pentazocine was chosen because a simple fluorimetric method is available for its determination in blood. Iproniazid was found to interfere with this fluorescence assay procedure.

TABLE 1. *Acute toxicity of potent analgesic drugs in mice pretreated with monoamine oxidase inhibitors*

	Saline-pretreated LD50 (mg/kg)	Tranylcypromine-pretreated		Iproniazid-pretreated	
		LD50 (mg/kg)	%increase in toxicity	LD50 (mg/kg)	%increase in toxicity
Pethidine	160 (144–178)	75 (68–86)	53%	71 (65–78)	56%
Morphine	576 (495–673)	333 (266–417)	42%	299 (252–359)	48%
Pentazocine	101 (92–111)	57 (49–67)	44%	56 (47–67)	45%
Phenazocine	75 (62–89)	18 (12–26)	76%	50 (42–64)	33%

95% confidence limits in parenthesis.

The blood concentration of pentazocine was maximal approximately 7·5 min after injection (Fig. 1) and in mice pretreated with tranylcypromine did not differ significantly from that of mice not receiving the MAO inhibitor.

Pethidine toxicity, MAO inhibition and brain monoamine levels following the injection of tranylcypromine

The results of this study (Figs. 2 and 3) are expressed as a percentage of control. It is therefore not possible to give standard errors in the figures.

In one series of experiments the LD50 of pethidine was determined in groups of mice 2, 4, 8, 16 and 24 hr after the injection of tranylcypromine (15 mg/kg). Mice similarly treated with tranylcypromine were used for the determination of cerebral monoamine levels and for the measurement of brain and liver MAO activity. A comparison of the results obtained is shown in Fig. 2.

Following the injection of the single dose of tranylcypromine, the toxicity of pethidine was found to increase to a maximum at approximately 4 hr, whereas brain and liver MAO were maximally inhibited by 2 hr. Increases in the concentration of cerebral 5-HT and dopamine followed much the same time course as the changes in pethidine toxicity, peak levels occurring with 5-HT at 4 hr and with dopamine at 2–8 hr. The concentration of noradrenaline did not reach a maximum until 8 hr after the injection of tranylcypromine.

In a second series of experiments, the same parameters were measured, but doses

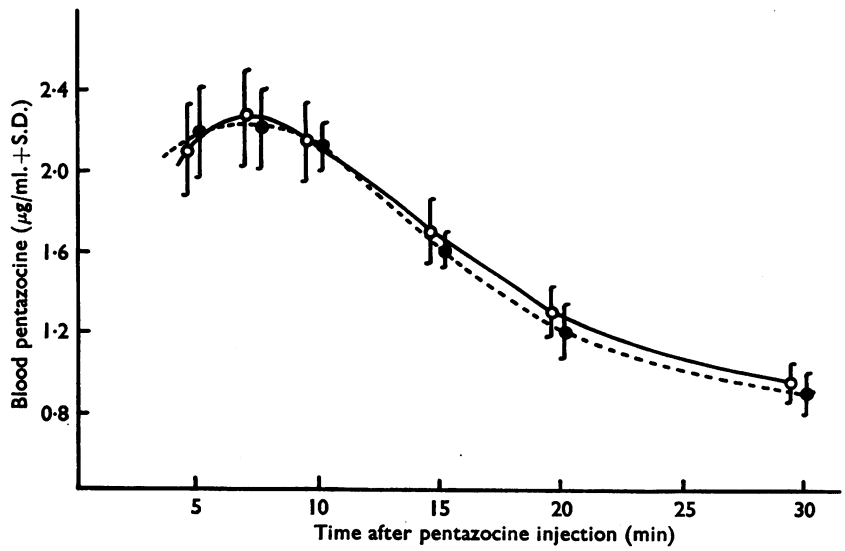

FIG. 1. Effect of tranylcypromine pretreatment on the blood levels of pentazocine in mice. Groups of five animals were treated with saline or with tranylcypromine 15 mg/kg. Four hours later, pentazocine (40 mg/kg) was injected intraperitoneally to the control mice (●- - -●) and to the tranylcypromine-treated mice (○——○). Each point is an average from five groups.

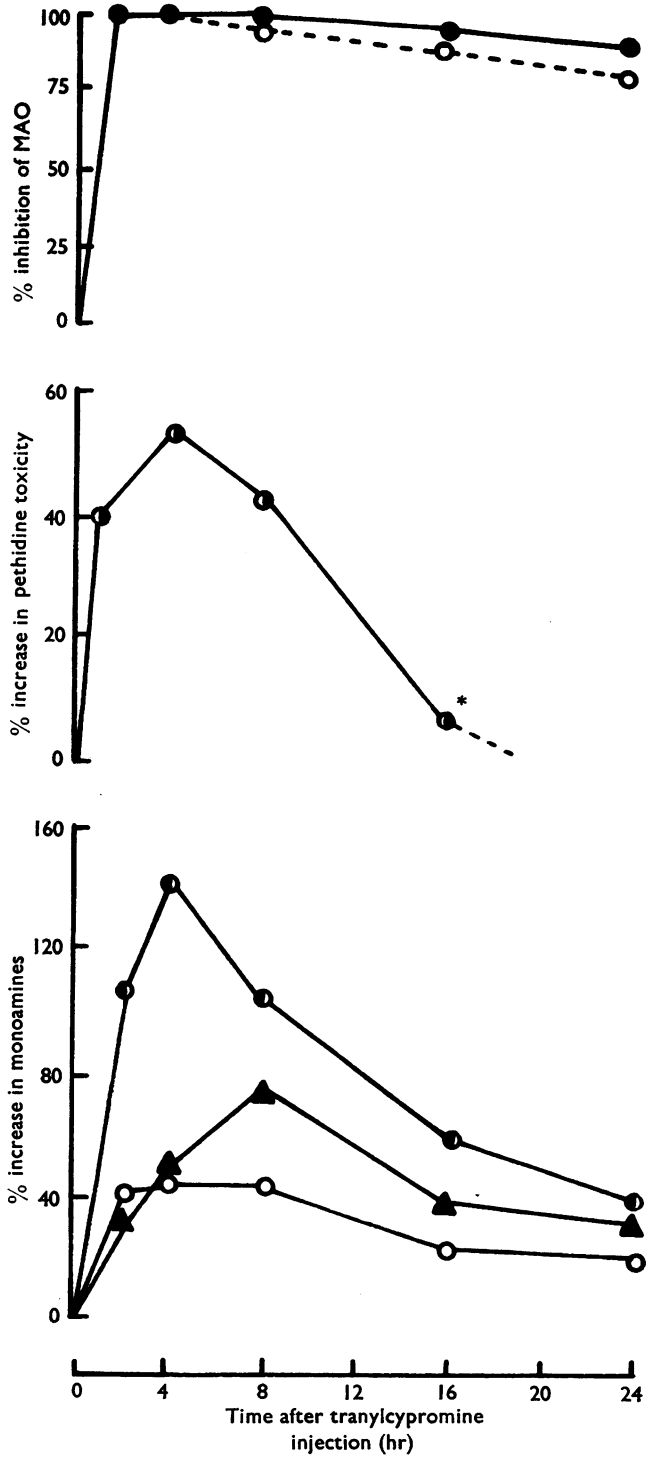

FIG. 2. Time course of the effect of tranylcypromine (15 mg/kg intraperitoneally) on the brain (●——●) and liver (○- - - -○) monoamine oxidase activity, acute pethidine toxicity (◑ ——◑) and on the brain concentration of 5-hydroxytryptamine (◐ —— ◐), noradrenaline (▲——▲) and dopamine (○——○) in mice. In the biochemical studies each point is an average from five experiments. The acute toxicity was determined using groups of ten mice, as described in **Methods**. All values with the exception of that marked with an asterisk are significantly higher than the controls ($P<0{\cdot}05$).

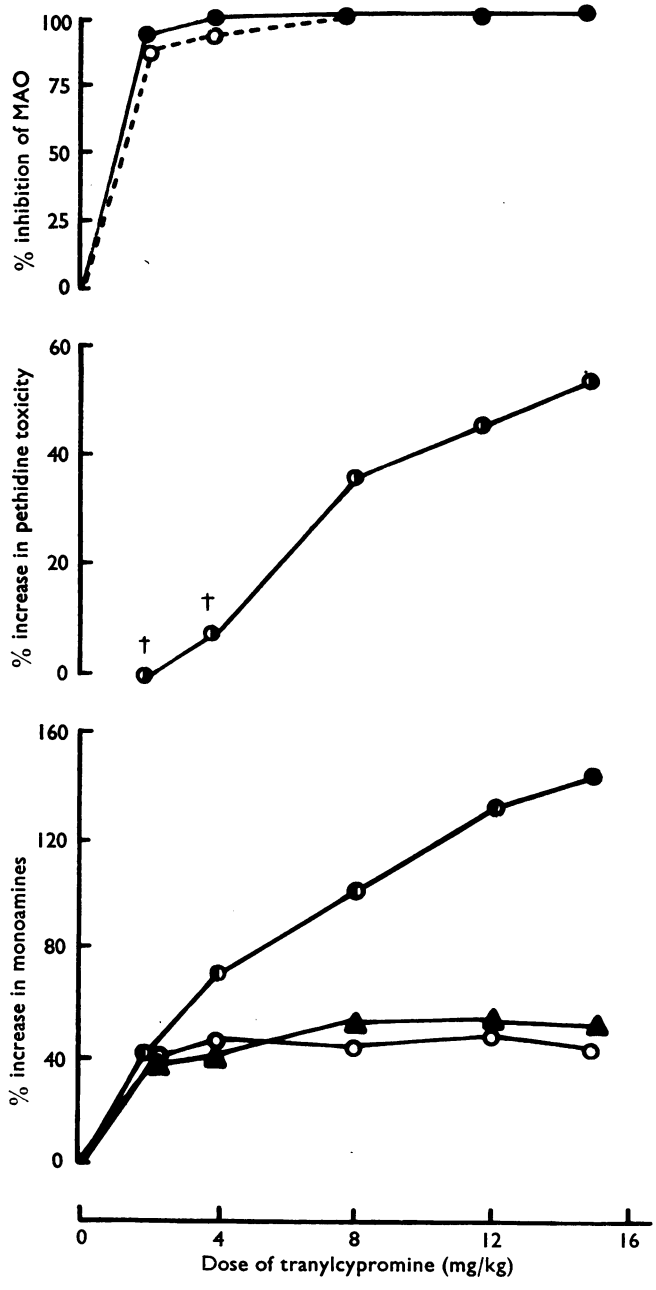

FIG. 3. Effect of different doses of tranylcypromine on the brain (●——●) and liver (○- - - -○) monoamine oxidase activity, acute pethidine toxicity (◑ —— ◑) and on the brain concentration of 5-hydroxytryptamine (◐ —— ◐), noradrenaline (▲——▲) and dopamine (○——○) in mice. The animals were killed 4 hr after the intraperitoneal injection of tranylcypromine. In the biochemical studies each point is an average from five experiments. The acute toxicity was determined using groups of ten mice, as described in **Methods**. All values with the exception of those marked with a dagger are significantly higher than the controls ($P<0{\cdot}05$).

of 2, 4, 8 and 12 mg/kg tranylcypromine were administered to different groups of mice and the duration of the drug pretreatment was maintained constant at 4 hr. The results are presented in Fig. 3. Included with these results are the values for tranylcypromine 15 mg/kg obtained in the previous experiment.

Over the range 2–15 mg/kg tranylcypromine, the toxicity of pethidine was increased in a linear fashion with increasing doses of the MAO inhibitor. There was a similar linear increase in the concentration of cerebral 5-HT whereas the noradrenaline and dopamine levels reached a maximum following tranylcypromine 2 mg/kg and showed no further increase with increasing doses of the drug. Brain and liver MAO were maximally inhibited by 4 mg/kg of tranylcypromine.

The over-all results presented in Fig. 2 and 3 indicated that the increases in pethidine toxicity might be closely related to the increased concentration of cerebral 5-HT. Correlation coefficients were therefore calculated and the results are presented in Fig. 4. There was no significant correlation between increased pethidine toxicity and percentage increase in either noradrenaline ($r=0.44$) or dopamine ($r=0{\cdot}56$), whereas, in the case of 5-HT the correlation was highly significant ($r=0{\cdot}957$, $P<0{\cdot}001$).

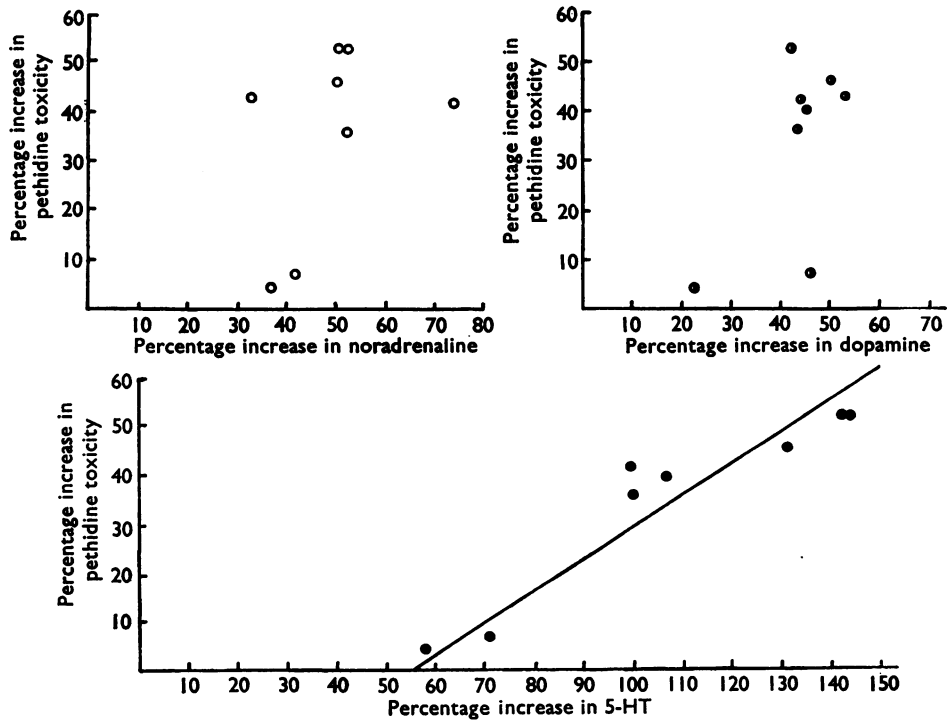

FIG. 4. Changes in pethidine toxicity and brain monoamine levels in mice treated with tranylcypromine. Relation between percentage increase in pethidine toxicity and percentage increase in brain levels of noradrenaline (○) dopamine (◑) and 5-hydroxytryptamine (●). Correlation coefficients: noradrenaline $r=0{\cdot}44$ $P>0{\cdot}2$; dopamine $r=0{\cdot}56$ $P>0{\cdot}1$; 5-hydroxytryptamine $r=0{\cdot}957$ $P<0{\cdot}001$.

Discussion

Pethidine is the only potent analgesic for which there is good evidence that a severe toxic reaction may occur if the analgesic drug is administered to subjects undergoing long term treatment with MAO inhibitors (Rogers, Jepson, Kilpatrick & Thornton, unpublished). In cases where morphine has been used in similar conditions no complications have occurred. Animal experiments with rabbits (Nymark & Nielsen, 1963 ; Loveless & Maxwell, 1965) and with mice (Brownlee & Williams, 1963) have also showed that the acute toxicity of pethidine is markedly increased by the prior administration of a MAO inhibitor. Once again, there is no evidence implicating analgesics other than pethidine. The results presented in this paper (Table 1) demonstrate that pretreatment of mice with either tranylcypromine or iproniazid increases the mortality not only from pethidine but also from the three other " narcotic " analgesic drugs tested (morphine, pentazocine and phenazocine). Therefore, if this response bears any relationship to the reaction seen in humans, it clearly remains advisable that the precautions already taken in medical practice should be maintained when any potent analgesic is being administered to patients receiving MAO inhibitors.

The pethidine/MAO interaction has been attributed to a decreased metabolism of the analgesic drug resulting from inactivation of detoxifying enzymes in the liver (London & Milne, 1962 ; Brownlee & Williams, 1963). It is well known that MAO inhibitors inhibit microsomal enzyme systems in the liver cells and thus reduce drug metabolism (Fouts & Brodie, 1956 ; Laroche & Brodie, 1960 ; Kato, Chiesara & Vasanelli, 1964). The metabolism of ethylmorphine (Anders & Mannering, 1966) and pethidine (Clark, 1967) is inhibited *in vitro* by iproniazid and by phenelzine respectively. Nevertheless, there is a considerable body of evidence arguing against the hypothesis that *in vivo* the analgesic/MAO inhibitor interaction is due to this mechanism. For example, inhibition of the detoxifying enzymes occurs only in the presence of the MAO inhibitor (Laroche & Brodie, 1960 ; Serrone & Fujimoto, 1962) and yet the injection of pethidine has caused adverse reactions in man when more than 36 hr have elapsed since the last dose of MAO inhibitor. (Papp & Benaim, 1958 ; Shee, 1960). Furthermore, in patients with hepatic dysfunction, the toxic effects of pethidine develop slowly and only after repeated doses (Dundee & Tinckler, 1952) whereas the onset of the toxic symptoms occurs within a few minutes of pethidine administration to patients receiving MAO inhibitors.

In an attempt to clarify this conflicting evidence, it was decided to examine the blood levels of an analgesic in normal mice and in mice pretreated with a MAO inhibitor. Following the intraperitoneal injection of these analgesic drugs, death in the mice occurs largely within the first 30 min ; mice surviving for 1 hr usually recovered. If decelerated metabolism of the analgesic plays an important part in the increased toxicity, then the blood levels of the drug might be expected to be elevated in mice pretreated with MAO inhibitor. The results presented in Fig. 1 show that the blood levels of pentazocine, in tranylcypromine-treated animals, do not differ significantly from the levels in control mice. Thus, at a time when toxic symptoms are at their maximum, any decrease in metabolism of the analgesic drug is not apparent. In addition, measurement of the MAO activity in the brain and liver of mice treated with tranylcypromine revealed that the ability of this drug to potentiate pethidine toxicity is not related to MAO inhibitory activity since the dose-response and the time-effect relationships are completely different (Figs. 2 and 3).

The symptoms evoked in humans by the pethidine/MAO inhibitor interaction suggest central stimulation, rather than the depression which occurs when detoxification of pethidine is impaired. In our investigations we noted that the toxic effects produced in mice by the combination of analgesic drug with MAO inhibitor were characterized by a greater degree of central excitation than those produced in mice injected with analgesic alone. Similar observations have also been made regarding the pethidine/MAO inhibitor reaction in rabbits (Nymark & Nielsen, 1963 ; Loveless & Maxwell, 1965). In view of these observations it seemed likely that the drug interaction might be related to the accumulation of monoamines in the central nervous system, resulting from MAO inhibition.

Over the 24 hr period following a single dose of tranylcypromine, the changes in pethidine toxicity were found to follow a similar time course to the increased monoamine levels (Fig. 2). It is of interest that although the cerebral MAO was inhibited by 90% or more for up to 24 hr, the levels of monoamines in the brain were returning towards control values during the latter part of this period. This finding is in agreement with other reports that MAO must be inhibited to at least 85% before the monoamine content of brain increases (Chessin, Dubnick, Leeson & Scott, 1959 ; Gey & Pletscher, 1961).

When different doses of tranylcypromine were injected and the mice killed 4 hr after injection, the catecholamine levels reached a maximum following 2 mg/kg of the MAO inhibitor, but showed no further increase with larger doses (Fig. 3). On the other hand, the 5-HT content of the brain continued to increase in response to larger doses of tranylcypromine. These results are in accord with other reports (Dubnick, Leeson & Phillips, 1962 ; Funderburk, Finger, Drakontides & Schneider, 1962) that doses of MAO inhibitors which exceed the dose required for complete MAO inhibition may induce an additional rise in cerebral 5-HT.

The results presented in Fig. 2 and 3 indicated that the increase in pethidine toxicity might be closely correlated with the changes in the concentration of brain 5-HT. Statistical analysis did, in fact, show that the correlation between these two parameters was highly significant ($r=0{\cdot}957$, $P<0{\cdot}001$). The results therefore signify that the increased pethidine toxicity in animals treated with MAO inhibitors may well be related specifically to increased levels of 5-HT within the brain.

Since the acute toxicity of pethidine was not potentiated until the 5-HT content of the brain was some 60% above control values (Fig. 4) it is possible that a critical level of the monoamine, within the brain, is necessary before the potentiation is displayed. That critical levels of cerebral monoamines may be necessary is supported by the case report of Taylor (1962) in which a patient receiving a MAO inhibitor reacted normally on one occasion, but reacted abnormally on a second occasion when the dose of MAO inhibitor had been increased.

Amphetamine releases noradrenaline from nerve terminals within the brain (Glowinski & Axelrod, 1965) and this drug evokes toxic central stimulation in man and animals previously treated with MAO inhibitors (Brownlee & Williams, 1963 ; Goldberg, 1964 ; Sjöquist, 1965). It is tempting to speculate that the narcotic analgesics may cause a release of 5-HT in a similar manner. Pethidine, morphine and other potent analgesics have been shown to release 5-HT from peripheral tissues (Bhattacharya & Lewis, 1956 ; Burks & Long, 1967). Release of 5-HT by morphine from the brain of cats has also been reported (Türker & Akcasu, 1962) although this effect was not observed in dog, rat and rabbit brain (Maynert, Kling-

man & Kaji, 1962 ; Sloan, Brooks, Eisenman & Martin, 1962). It may be, however, that the storage vesicles of the cerebral 5-HT must be suitably " primed " by MAO inhibition before the rapid release of the monoamine is possible.

Further aspects of the relationship between changes in the toxicity of potent analgesics and the metabolism of cerebral monoamines are currently under investigation.

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