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THE EXCRETION OF PETHIDINE AND ITS DERIVATIVES

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The excretion of pethidine and its metabolite norpethidine is increased in acid urine and decreased in alkaline urine. Excretion of these two bases is the main route of removal of pethidine from the body if the urine is highly acid. If the urine is alkaline, excretion of the hydrolysis products meperidinic and normeperidinic acids, both as free acids and as conjugates, is the more important means of elimination of the drug. Acidification of the urine with ammonium chloride is indicated in the therapy of cases of pethidine poisoning in patients with reduced metabolic breakdown of the drug by the microsomal enzyme systems within liver cells. Reversed-phase chromatography of the dinitrophenyl derivative of norpethidine may prove to be of forensic importance in the diagnosis of pethidine poisoning or of pethidine addiction. Norpethidine can be detected in the urine by this method for at least 3 days after the last dose of pethidine. Analytical sensitivity is increased by acidification of the urine which produces a temporary rise of the excretion rate.

Pethidine (meperidine), first introduced 23 years ago (Eisleb & Schaumann, 1939), is still by far the most widely used synthetic potent analgesic drug (Murphree, 1962). Previous studies (Lehman & Aitken, 1943 ; Oberst, 1943 ; Bernheim & Bernheim, 1945 ; Way, Swanson & Gimble, 1947 ; Way, Gimble, McKelway, Ross, Sung & Ellsworth, 1949 ; Plotnikoff, Elliott & Way, 1952 ; Burns, Berger, Lief, Wollack, Papper & Brodie, 1955 ; Plotnikoff, Way & Elliott, 1956) have shown that in man the major part of the drug is metabolized and that only a small fraction is excreted unchanged in the urine. All these workers have, however, ignored the effect of acid–base changes on pethidine excretion. Pethidine is a weak base with a high partition coefficient between lipoid solvents and water when in the un-ionized form. The clearance and excretion of the drug is, therefore, likely to be influenced by variation in urinary *p*H (Milne, Scribner & Crawford, 1958). We have extended the earlier work by investigating the fate of pethidine in man during states of mild metabolic acidosis and alkalosis with urinary *p*H at the extremes of the physiological range. Similar studies were made on the less-active analgesic, ethoheptazine, in which the piperidine ring of pethidine is replaced by a seven-membered ring. The results are shown to be of both pharmacological and forensic importance.

METHODS

Pethidine hydrochloride (100 mg) was given by subcutaneous injection to patients requiring moderate analgesia but who showed no evidence of hepatic or renal disease. Either ammonium

chloride (4 g as a loading dose followed by 2 g four times daily) or sodium bicarbonate (4 g as a loading dose followed by 2 g six times daily) was given on the previous day and throughout the days of the test. Similar studies were made of the excretion of norpethidine (ethyl 4-phenylpiperidine-4-carboxylate) carbonate (50 mg by mouth) and of ethoheptazine citrate (75 mg by mouth). As these substances are non-addictive, studies were made with normal subjects not requiring analgesics. Each drug was given at 9 a.m. Urine was collected at 7, 9 and 11 a.m., 1, 3, 5, 7 and 9 p.m. on the first day and at 9 a.m., 1, 5 and 9 p.m. on the second day. Further samples were obtained at 9 a.m. on the third and fourth days, giving a total collection period of 72 hr after administration of the drugs.

Chemical methods

Estimation of pethidine and metabolites in urine was by the method of Burns *et al.* (1955). This method was satisfactory for the estimation of pethidine and norpethidine. The chemical processes involved in the conversion of meperidinic and normeperidinic acids and their conjugates to the lipid-soluble esters, pethidine and norpethidine, cause some degradation of the molecule, and recoveries are somewhat low. The error is more serious in estimations of conjugated acid as the autoclaving involved in hydrolysis causes considerable breakdown of the molecule. Fractionation of ethoheptazine and norethoheptazine (ethyl 4-phenylazacycloheptane-4-carboxylate) by this method was not attempted as a pure sample of norethoheptazine was not available for reference. The specificity of the methyl-orange method of Burns *et al.* (1955) was compared by strip chromatography with a general method for urinary amines

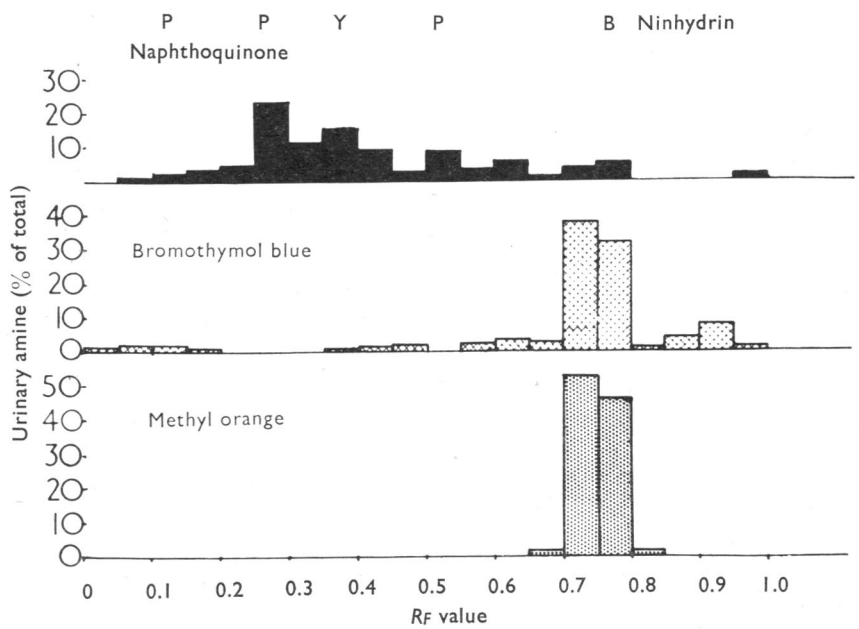

Fig. 1. Strip chromatograms of chloroform-soluble amines from urine of a patient after injection of 100 mg of pethidine hydrochloride. Butanol: acetic acid: water. Ninhydrin spray shows five spots (colour indicated at top): purple (P) spot at R_F 0·10=methylamine; purple spot at R_F 0·30=dimethylamine; yellow (Y) spot, red fluorescence in ultra-violet light, at R_F 0·40=pyrrolidine; purple spot, red fluorescence in ultra-violet light, at R_F 0·55=piperidine; blue (B) spot, red fluorescence in ultra-violet light, at R_F 0·75=norpethidine. Analysis of the chromatographic strips shows that the naphthoquinone method is more sensitive for endogenous urinary amines, whereas the two dye-complexing methods are relatively insensitive to these amines. Of the two methods, the methyl-orange method is preferable.

(Milne, Asatoor, Edwards & Loughridge, 1961) and the thymol-blue method for pethidine and its derivatives used by Lehman & Aitken (1943) and Oberst (1943) (Fig. 1). The methyl-orange method is unaffected by naturally occurring urinary amines, whereas the other methods are considerably less specific.

Chromatography of dinitrophenyl derivatives of norpethidine and norethoheptazine was by the method of Asatoor (1960) and Asatoor & Kerr (1961), modified as follows:

A volume of urine passed in 4 min was treated as described by Asatoor & Kerr (1961), omitting the preliminary treatment for the removal of ammonia. An aliquot (8 ml.) of the cyclohexane extract was evaporated to dryness and the residue was dissolved in a small volume of ethanol. Half the volume of the ethanolic solution was used for chromatography on paraffin-treated paper (Asatoor, 1960).

For direct chromatography of pethidine, ethoheptazine and nor-derivatives a chloroform extraction was made from alkaline urine. The chromotography was in a butanol:acetic acid:water (120:30:50) mixture. A ninhydrin spray was used for nor-derivatives. The colour obtained with the nor-derivatives of the drugs and other urinary heterocyclic amines gives a characteristic dull-red fluorescence in ultraviolet light, whereas that obtained with other urinary amines gives no fluorescence. A platinic iodide spray was used for unchanged drugs.

RESULTS

Pethidine is metabolized as shown in Fig. 2 (Burns *et al.*, 1955 ; Plotnikoff *et al.*, 1956). The drug is either demethylated to norpethidine, or the ester linkage is hydrolysed with formation of meperidinic acid (1-methyl-4-phenylpiperidine-4-carboxylic acid). Norpethidine is also hydrolysed to the corresponding normeperidinic acid (4-phenylpiperidine-4-carboxylic acid), but meperidinic acid itself cannot

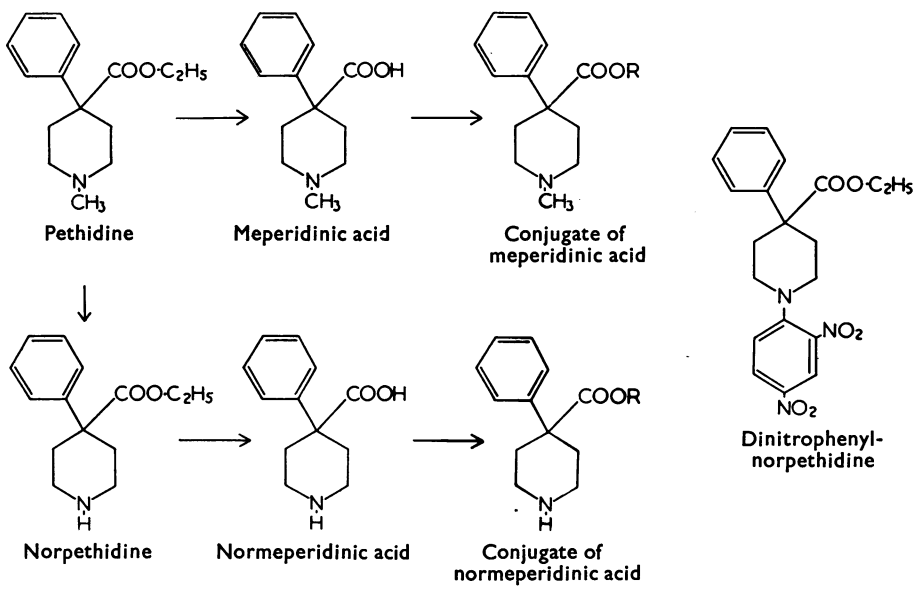

Fig. 2. Metabolism of pethidine by microsomal enzyme systems within liver cells. The drug is either hydrolysed to meperidinic acid, or demethylated to norpethidine with subsequent hydrolysis to normeperidinic acid. The two acids are either excreted unchanged or as conjugates of unknown composition. Norpethidine reacts with 2,4-dinitrofluorobenzene to form dinitrophenyl (DNP) norpethidine.

be demethylated in the body. Both meperidinic acid and normeperidinic acid form conjugates of unknown composition which are hydrolysed by autoclaving with mineral acid.

Fig. 3 gives the mean rates of excretion of pethidine and norpethidine in acid urine after a single subcutaneous injection of 100 mg of pethidine hydrochloride.

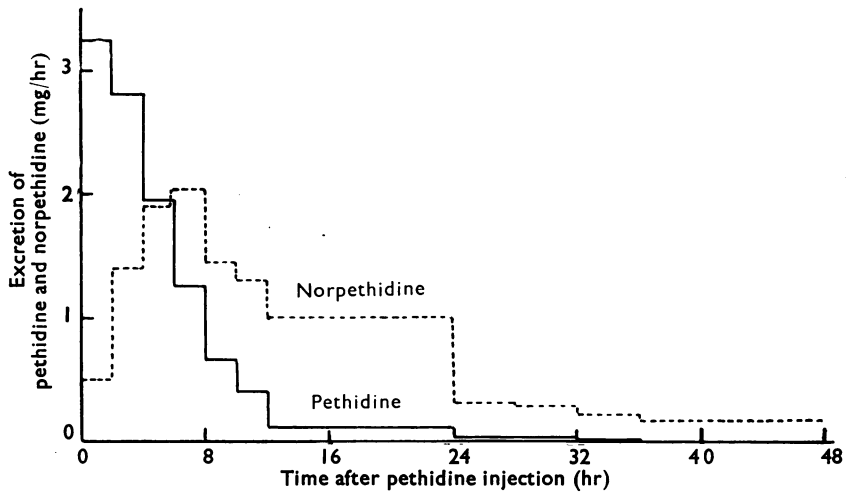

Fig. 3. Excretion of pethidine and norpethidine (ordinate) in highly acid urine during a 48 hr period after injection of 100 mg of pethidine hydrochloride. Pethidine output falls logarithmically, and is small after 12 hr. Norpethidine output rises to a maximum 4 to 8 hr after the injection, and subsequently falls. Significant amounts are excreted after 48 hr. Results are the means of values from six subjects.

Pethidine output is highest in the first 2 hr after injection and thereafter falls logarithmically. The excretion of unchanged drug is negligible after 12 hr, and is below the level of chemical detection after 36 hr. In the first 4 hr after pethidine injection the rate of formation of norpethidine exceeds the rate of its elimination from the body, and the excretion of the metabolite therefore rises to a maximum value 4 to 8 hr after the injection. The excretion then gradually falls and is negligible in amount after 48 hr, although it can be detected chemically during the third and occasionally the fourth day.

Fig. 4 gives the corresponding mean cumulative outputs of pethidine and norpethidine both in acid and in alkaline urine. When the urine is highly acid the mean output of the unchanged drug is 22% of the injected dose, and that of norpethidine over 34% of the dose. By contrast, in alkaline urine, the mean cumulative excretion of both pethidine and norpethidine amounts to only 4% of the dose, the difference from the output in acid urine being highly significant statistically ($t=8.8$, $P<0.001$).

The analytical methods for separate determination of pethidine and norpethidine are inaccurate at low excretion levels, but the results suggested that less than 25% of the total output in alkaline urine was in the form of the unchanged drug. Fig. 5 gives the partition between pethidine and norpethidine in highly acid urine as a

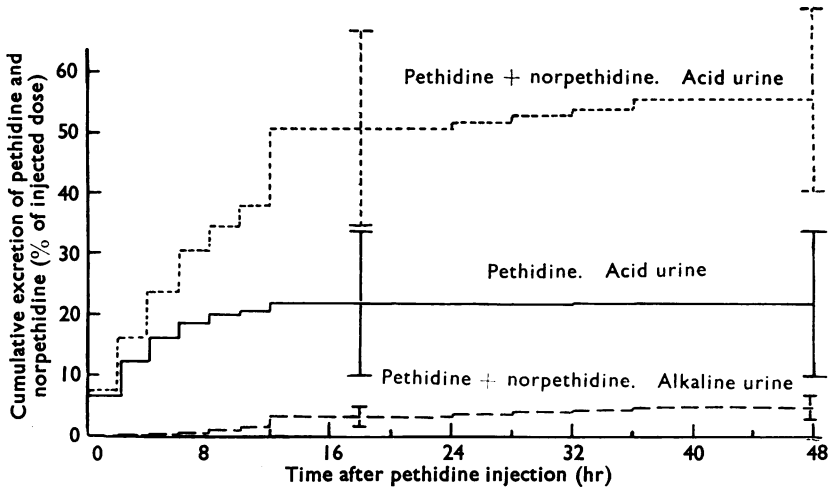

Fig. 4. Cumulative excretion of pethidine and norpethidine (ordinate, as percentage of injected dose) in highly acid urine and in alkaline urine during 48 hr period after injection of 100 mg of pethidine hydrochloride. Each line gives the means of results from six normal subjects. (The vertical lines give the standard deviations of excretion at 24 and 48 hr.)

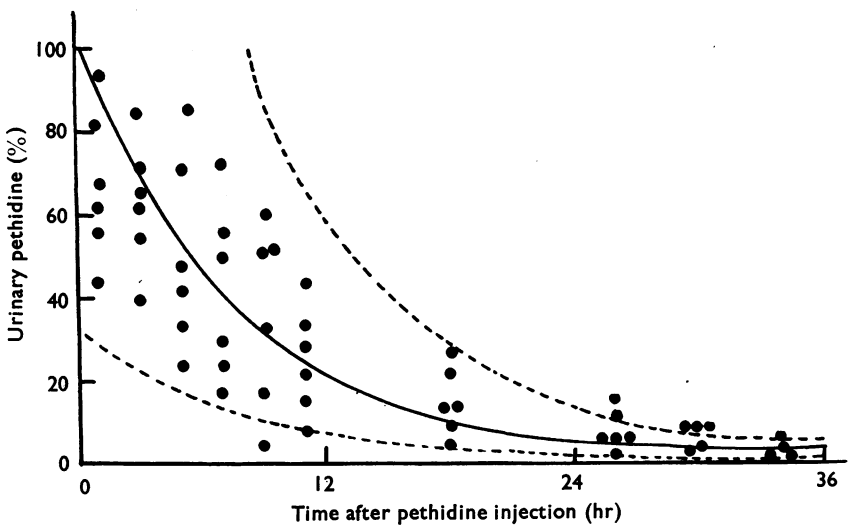

Fig. 5. Pethidine output in acid urine (ordinate) expressed as a percentage of the total urinary pethidine and norpethidine, during 36 hr after injection of 100 mg of pethidine hydrochloride. The pethidine fraction falls logarithmically and is small after 12 hr from the injection. The dotted lines give the limits at twice the standard deviation.

function of the time after the injection. In the first few hours the greater proportion is of unchanged drug, but this rapidly falls and is very low after 18 hr from the time of injection.

The difference between the excretion rates of norpethidine in acid and alkaline urines is shown in the chromatograms of Figs. 6 and 7. The following naturally

occurring amines are invariably present in normal urine: piperidine, pyrrolidine, ethylamine, dimethylamine and methylamine. In addition, ammonia forms a dinitrophenyl derivative which has an R_F value higher than that of the urinary amines. The excretion of the endogenous urinary amines is not affected by changes of urinary *p*H, but ammonia is excreted in much greater amount in acid urine (Pitts, 1948). Norpethidine, with an R_F value of its dinitrophenyl derivative less than that of the naturally occurring amines, is also excreted in greater quantity in acid urine.

Fig. 8 gives the mean excretion of norpethidine in both acid and alkaline urines after ingestion of norpethidine carbonate. Owing to slight delay in absorption from the gut, the peak output is in the 2 to 4 hr period after ingestion of the drug, but otherwise the results are similar to those after injection of pethidine. Fig. 9 gives the corresponding mean cumulative excretion of the drug. Output of the unchanged

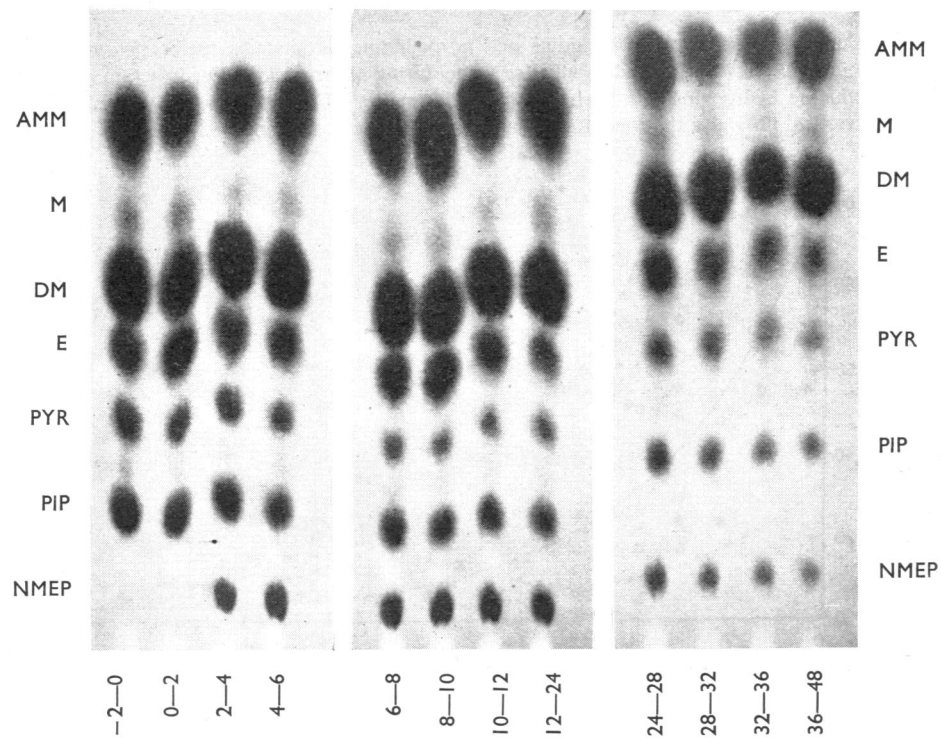

Fig. 6. Chromatograms of twelve urine fractions before, and up to 48 hr after, injection of 100 mg of pethidine hydrochloride during acidosis with highly acid urine. Output of norpethidine is high from 2 to 24 hr after the injection but progressively falls from 24 to 48 hr. Reversed-phase chromatography of dinitrophenyl derivatives of urinary amines and ammonia extracted by cyclohexane. Chloroform : methanol : water : liquid paraffin as solvent. Dinitrophenyl derivatives photographed in ultra-violet light. From the origin the spots are dinitrophenyl derivatives of norpethidine (NMEP), piperidine (PIP), pyrrolidine (PYR), ethylamine (E), dimethylamine (DM), methylamine (M), and ammonia (AMM). Values under the chromatogram refer to times in hours.

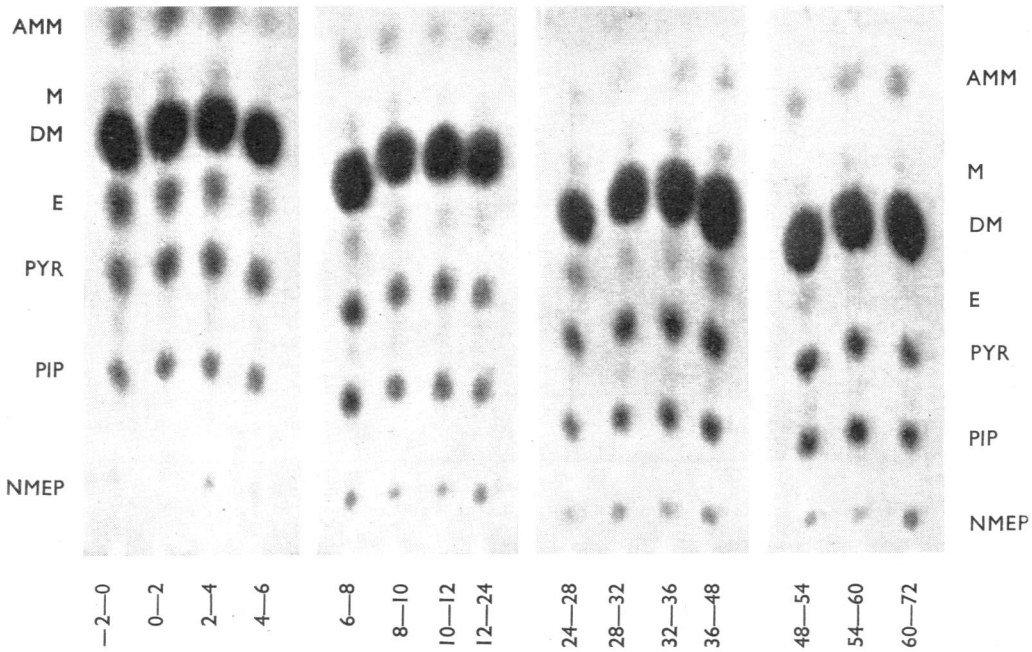

Fig. 7. Chromatograms of sixteen urine fractions before and up to 72 hr after injection of 100 mg of pethidine hydrochloride during alkalosis with highly alkaline urine. Technique and abbreviations as in Fig. 6. Excretion of both norpethidine and ammonia but not of endogenous urinary amines is much less than in acid urine (Fig. 6). Norpethidine output changes very little from 2 to 72 hr after ingestion.

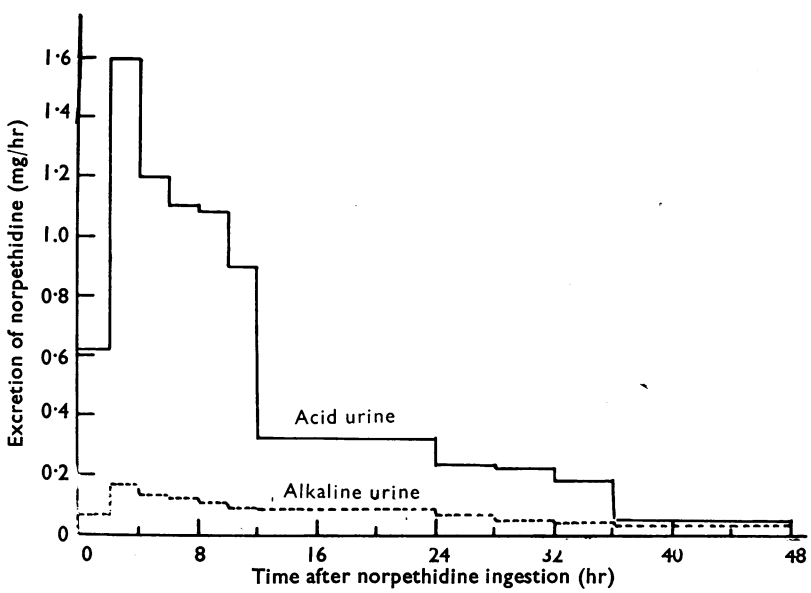

Fig. 8. Rate of excretion of norpethidine during 48 hr after ingestion of 50 mg of norpethidine carbonate. The output is highest from 2 to 4 hr afterwards and thereafter falls logarithmically. Excretion is much greater in acid than in alkaline urine. Each line gives the means of six collection periods.

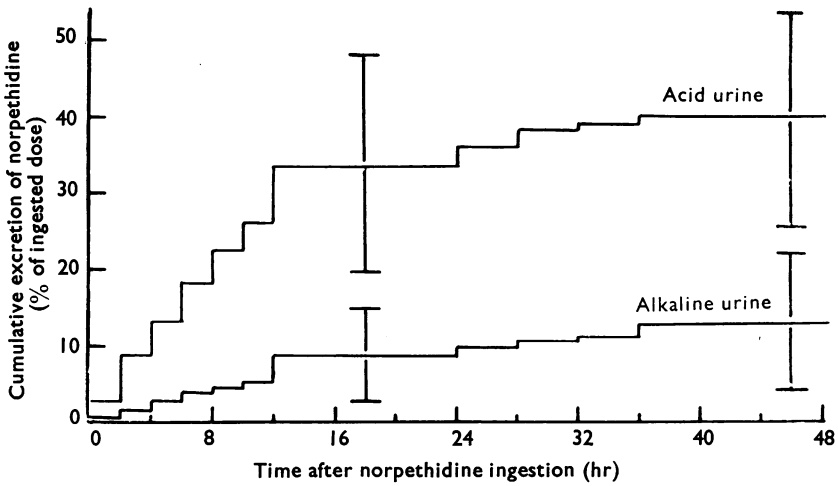

Fig. 9. Cumulative excretion of norpethidine (ordinate, as percentage of ingested dose) during 48 hr after ingestion of 50 mg of norpethidine carbonate. The output is much higher in acid than in alkaline urine. Each line gives the means of six collection periods; the vertical lines give the standard deviations at 24 and 48 hr.

drug in acid urine is about four times the amount excreted if the urine is alkaline. The difference is statistically significant ($t=4.1$, $P<0.01$). Chromatograms of serial urine specimens after ingestion of norpethidine carbonate gave results similar to those shown in Figs. 6 and 7.

Separate determinations of ethoheptazine and norethoheptazine were not carried out as no reference sample of the latter compound was available. The methyl-orange method seemed satisfactory as a means of determining the sum of the two substances. Neither compound could be detected in alkaline urine after ethoheptazine ingestion. A mean total of 3.2 mg was excreted in highly acid urine within 12 hr, and 70% of this was excreted in the first 6 hr. Neither amine was detectable in urine after 12 hr, showing that ethoheptazine is more rapidly degraded than pethidine or norpethidine. The results of the dye-complexing method were confirmed by chromatography of the dinitrophenyl derivative of norethoheptazine.

Table 1 gives the partition of unchanged drug and metabolites in urine after administration of pethidine, norpethidine and ethoheptazine. The excretion of meperidinic and normeperidinic acids and conjugates agrees well with previously reported data (Burns *et al.*, 1955; Plotnikoff *et al.*, 1956). The true range of output of pethidine and norpethidine is greater than that found by previous workers who did not explore the excretion at the extremes of urinary *p*H. Table 1 shows that excretion of the lipid-soluble esters is the main route of disposal of the drug in acid urine, whilst excretion of the water-soluble free acids or their conjugates is more important in alkaline urine. The figures given for excretion of the acids, especially of the conjugated acids, are probably falsely low, as the chemical methods result in some breakdown of the molecule.

TABLE 1

PARTITION OF URINARY EXCRETION PRODUCTS AFTER INJECTION OF 100 MG OF PETHIDINE HYDROCHLORIDE OR INGESTION OF 50 MG OF NORPETHIDINE CARBONATE OR 75 MG OF ETHOHEPTAZINE CITRATE

Values are percentages of the doses of the drugs given. * See text

Pethidine

Patient	Day after administration of drug	*p*H of urine	Excretion product: Unchanged drug	Nor-pethidine	Meperidinic acid	Normeperidinic acid	Conjugate of meperidinic acid	Conjugate of normeperidinic acid
1	1st	Acid	22	29	30	4	Not measured	
2	1st	Acid	20	26	11	12	Not measured	
3	1st	Acid	26	24	7	9	7	8
4	1st	Alkaline	0·3	1	22	17	5	3
5	1st	Alkaline	1	2	10	5	2	13
	2nd		0	0·3	4	1	1	0
Previous data*	1st	Not controlled	2·4–7·9	2·2–14·6	10·3–40·9	2·7–28·3	0–16·1	3·8–22·3

Norpethidine

Patient	Day after administration of drug	*p*H of urine	Excretion product: Unchanged drug	Normeperidinic acid	Conjugate of normeperidinic acid
1	1st	Acid	33	9	4
	2nd		5	6	3
2	1st	Alkaline	8	11	29
	2nd		2	8	18

Ethoheptazine (24 hr excretion)

Patient	*p*H of urine	Excretion product: Ethoheptazine and nor-compound	Corresponding acids	Conjugates of acids
1	Acid	4	4	3
2	Alkaline	0	5	4

DISCUSSION

The results show that the amines pethidine, ethoheptazine and their nor-derivatives are excreted much more rapidly in acid than in alkaline urine. Table 2 lists the weak bases and acids which are excreted at different rates and clearances with variation in urinary *p*H. Such substances are excreted by a three-component system (Weiner, Washington & Mudge, 1959): filtration of both the ionized and the un-

TABLE 2

DRUGS SHOWING *p*H-DEPENDENT EXCRETION

Drug	Metabolites not showing *p*H-dependent excretion	Species investigated	References
Acidic drugs: urinary output greater in alkaline urine			
5,5-Dimethyl-2,4-oxazolidinedione (chief metabolite of troxidone)	Probably excreted unchanged	Man, dog	Waddell & Butler (1957b)
Gentisic acid	Ethereal sulphate and glucuronide	Man	Batterman & Sommer (1953)
Indolylacetic and other indolic acids	Indolylacetylglutamine if even number of carbon atoms in side-chain. Indolylacrylglycine if odd number	Man, dog, rat	Milne, Crawford, Girao & Loughridge (1960)
Nitrofurantoin	Unknown metabolites	Dog	Woodruff, Malvin & Thompson (1961)
Phenylbutazone	Hydroxyl derivatives. Both phenol and alcohol hydroxylation	Man, dog	Gutman, Dayton, Yü, Berger, Chen, Sicam & Burns (1960)
Phenobarbitone	*p*-Hydroxyphenobarbitone	Man, dog	Waddell & Butler (1957a)
Probenecid	Ester glucuronide	Dog	Weiner, Washington & Mudge (1960)
Salicylic acid	Salicyluric acid and acyl and phenolic glucuronides	Man, dog, rabbit	Smith, Gleason, Stoll & Ogorzalek (1946); Gutman, Yü & Sirota (1955); Weiner *et al.* (1959)
Basic drugs: urinary output greater in acid urine			
Chloroquine and other derivatives of aminoquinoline	Unknown metabolites	Man	Jailer, Rosenfeld & Shannon (1947)
5-Hydroxytryptamine	5-Hydroxyindolylacetic acid. *N*-Acetyl-5-hydroxytryptamine and glucuronide	Rat	Sandler & Spector (1961)
Mecamylamine	Probably excreted unchanged	Man, dog, rat	Baer, Paulson, Russo & Beyer (1956); Milne, Rowe, Somers, Muehrcke & Crawford (1957)
Mepacrine and other acridine derivatives	Demethylated product and other metabolites	Man	Jailer *et al.* (1947)
Nicotine	Nornicotine and γ-(3-pyridyl)-γ-methylaminobutyric acid	Man	Haag & Larson (1942)
Pempidine	Probably excreted unchanged	Man, dog	Harington, Kincaid-Smith & Milne (1958); Torretti, Weiner & Mudge (1962)
Pethidine and norpethidine	Meperidinic and normeperidinic acids and conjugates	Man	This paper
Procaine	*p*-Aminobenzoic acid and diethylaminoethanol	Dog, rabbit	Terp (1951)
Quinine	Derivatives by oxidation	Man, dog	Haag, Larson & Schwartz (1943); Torretti *et al.* (1962)
Tolazoline	Probably excreted unchanged	Dog	Torretti *et al.* (1962)

ionized forms at the glomerulus, secretion of the ionized fraction by the proximal renal tubule, and back-diffusion of the un-ionized portion in the distal tubule. Back-diffusion is greatly influenced by urinary *p*H, weak acids diffusing out of an acid urine and weak bases from an alkaline urine.

At equilibrium the concentration of a diffusible base within the distal tubular fluid should be less than that in the peritubular blood plasma if the urine is highly alkaline. Conversely, the concentration should be higher if the urine is highly acid. Expressed mathematically,

$$R=\frac{1+10\,(p\mathrm{Ka}-p\mathrm{Hu})}{1+10\,(p\mathrm{Ka}-p\mathrm{Hp})}$$

where R is the concentration ratio between tubular fluid and plasma at equilibrium, *p*Ka is the negative logarithm of the dissociation constant of the diffusing base and *p*Hu and *p*Hp are the *p*H values of tubular fluid and plasma respectively (Milne *et al.*, 1958). The graphical representation of this equation is given in Fig. 10, the *p*H of plasma being taken as 7.4. It is seen that in the case of bases with *p*Ka above 7.0, R varies within the whole *p*H range of urine, whereas if the base has a *p*Ka value below 6.0 R only varies if the urine is acidic. The *p*Ka of pethidine is 8.63 and that of norpethidine is 9.68, and therefore variation in excretion with urinary

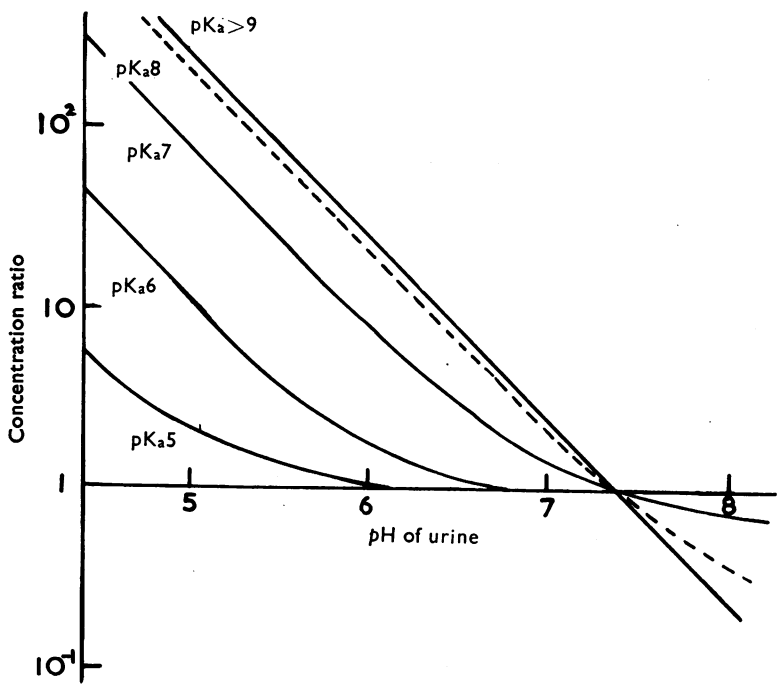

Fig. 10. Graphs of equation $R=\frac{1+10\,(p\mathrm{Ka}-p\mathrm{Hu})}{1+10\,(p\mathrm{Ka}-7{\cdot}4)}$. The concentration ratio between tubular fluid and plasma (R, ordinate) increases with rising acidity throughout the whole *p*H range of urine if the *p*Ka of the diffusing base is above 7·0. If the *p*Ka is below 6·0, R increases only in the urine *p*H range 4·5 to 6·5.

*p*H is continuous throughout the whole physiological range of *p*H from 4.5 to 8.0. Since the plasma-protein binding of pethidine is greater than that of norpethidine, more of the unchanged drug must diffuse from alkaline urine to produce an equivalent concentration gradient to that of the metabolite. Therefore, pethidine would theoretically be expected to be in especially low concentration in alkaline urine, as was found experimentally. The hydrolysis products, meperidinic and normeperidinic acids and their conjugates, are less lipid soluble and are amphoteric substances possessing both acidic and basic radicles. Their excretion is, therefore, uninfluenced by variation in urinary *p*H.

Table 1 shows that excretion of the hydrolysis products is the main method of elimination of pethidine from the body if the urine is alkaline. By contrast, excretion of the bases pethidine and norpethidine is more important if the urine is highly acid. Since excretion of the metabolites continues for several days after ingestion of a single dose of the drug and existing analytical methods underestimate the amount of metabolites, there is no necessity to postulate other pathways of pethidine metabolism than those shown in Fig. 2. Burns *et al.* (1955) analysed urine specimens collected over only 24 hr after pethidine ingestion and erroneously considered that their low recoveries suggested alternative pathways of degradation. Recoveries of ethoheptazine and its derivatives are, however, considerably lower than those of pethidine, indicating some alternative route of metabolism.

Ammonia is more closely related in physical and chemical properties to the endogenous urinary amines than to the lipid-soluble bases listed in Table 2. There is, however, an important physiological difference; ammonia is synthesized within the distal tubule cells, and therefore diffuses from the cell water into highly acid fluid within the tubular lumen (Orloff & Berliner, 1956). By contrast, the other organic bases showing *p*H-dependent excretion diffuse across the cell from the lumen into the peritubular blood, and have to cross both the juxta-luminal and the juxta-capillary cell membranes. Methylamine, dimethylamine, pyrrolidine and piperidine are too strong bases for their renal clearances to vary with urinary *p*H, the lowest *p*Ka value being 10.7 in the case of methylamine. Milne *et al.* (1958) have shown that the optimum range of *p*Ka for bases to be excreted by a *p*H-dependent mechanism is 6.5 to 10.0. Pethidine, norpethidine and ammonia (*p*Ka = 9.3) are all within this optimum range. The only known bases with *p*Ka's above 10, in which the clearances vary with urinary *p*H, are mecamylamine, pempidine, tolazoline and closely allied compounds. For each of these drugs the un-ionized component is much more lipid soluble than that of the endogenous urinary amines.

This investigation may prove to be of practical as well as theoretical importance. Pethidine is a classical example of a drug removed from the body by metabolic conversion to non-toxic derivatives by the microsomal enzyme systems of the liver (Fouts & Brodie, 1956). At the usual values of urinary *p*H, or more particularly if the urine is alkaline, urinary excretion of the unchanged drug is negligible in comparison with metabolic degradation. Burns *et al.* (1955) have shown that the rate of disappearance of pethidine from plasma averages 17% per hour. The results shown in Fig. 3 suggest that removal of the unchanged drug by excretion in highly

acid urines would amount to a plasma clearance rate of 4% per hour, a much smaller, but not a negligible, amount. Several papers report serious toxic effects from pethidine in patients with hepatic insufficiency (Dundee & Tinckler, 1952), or after therapy with drugs which inhibit hepatic microsomal enzyme systems, such as iproniazid and phenelzine (Mitchell, 1955; Papp & Benaim, 1958; Palmer, 1960; Shee, 1960; Taylor, 1962; Clement & Benazon, 1962; Reid & Jones, 1962). Prompt acidification of the urine in such cases would greatly increase the rate of elimination of pethidine by the kidney. The use of reversed-phase chromatography of the dinitrophenyl derivative of norpethidine is more specific than other methods of identification and is applicable to blood and tissues as well as to urine. It may, therefore, be of forensic importance in cases of suspected pethidine poisoning or of addiction to the drug. In the diagnosis of pethidine addiction, acidification of the urine by ammonium chloride would temporarily increase the output of both unchanged pethidine and of the nor-derivative and would thus increase the chance of analytical detection of both compounds. Ethoheptazine disappears from urine, and therefore presumably from plasma, more rapidly than does pethidine. This partly explains the much weaker analgesic properties of ethoheptazine as compared to pethidine (Murphree, 1962).

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