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SPECIES DIFFERENCES IN DRUG METABOLISM

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INTRODUCTION

The importance of species differences in drug metabolism in understanding the mechanism of action of many drugs has become increasingly evident. Several reviews and articles on the overall topic of drug metabolism have covered aspects of it (1–17). In addition, discussion of species differences in drug metabolism formed an important segment of a recent symposium, the proceedings of which contain a number of very informative papers (18–24).

It would appear that the increasing interest in the subject stems from the premise that improved understanding and broader knowledge of species differences in drug metabolism will greatly improve our abilities to predict the pharmacologic and toxicologic properties of a given compound in man from experimental data obtained in animals. It should also be pointed out that such studies, even when only indirectly related to drug therapy, have yielded valuable new biochemical information of quite fundamental nature. Examples of this type concern acetyl CoA, the role of pyridine nucleotides in oxygen incorporation, mechanisms of enzyme adaptation, human genetics, phylogenetic and ontogenetic enzyme development, intracellular structure, organ and membrane function, and biosynthesis of vitamin C (25). The increased interest is also probably correlated with recent technological advances that will possibly enable one to study the physiological disposition and metabolic fate of a compound in several species within a relatively short period of time.

If the above comments sound encouraging, they may also be unduly optimistic, at least insofar as prediction is concerned. For example, Williams (19) stated that aromatic hydroxylation varies quantitatively and qualitatively in haphazard fashion among species, and that one can not, at present, draw definite conclusions about the relationship between drugs, species, and metabolic routes. Brodie (23) is equally discouraging in another sense, namely, the possibility of discovering an animal species, that, drug-metabolism-wise, is greatly similar to man. It should be pointed out here, however, that very little work of this type has been done with the higher nonhuman primates, i.e., the chimpanzee, gorilla, and orang-utan. The reader should also beware of the catchall name "monkey" since in many papers it refers to

the rhesus monkey *Macaca mulatta,* and metabolism in the anthropoid apes may be quite different.

Needed, then, are new ideas and new approaches to the better understanding of species differences in drug metabolism. If higher primates fail to yield drug metabolism results comparable to man, it might be possible to modify the microsomal enzymes in animals, through the use of inhibitors or inducers, to give metabolic patterns that are more similar to the human. Another possibility is that, in some cases at least, urinary excretion patterns of metabolites in several species are not truly reflecting the metabolic differences at the site of action (pharmacologic or toxicologic) since certain metabolic reactions are known to be reversible, e.g., acetylation/deacetylation, hydroxylation/dehydroxylation. Gillette (20) has alluded to this possibility in a thought-provoking commentary, especially in regard to drugs that are converted to active metabolites. His comments are worth quoting: "It is therefore obvious that species variations in the pattern of urinary metabolites will provide only indirect clues to the pattern of metabolites in blood plasma and tissues and thus to the pharmacologic action of the drug and its metabolites." The studies of Gillette and others described below on the metabolism of imipramine are pertinent in this regard. A similar recent example is a brief report on the metabolism of the tricyclic antidepressant, doxepin, 11-(3-dimethylaminopropylidene)-6H-dibenz[b, e]-oxepin (26). Although numerous metabolites of doxepin, resulting from demethylation, N-oxidation, and hydroxylation were found in rat liver and dog and rat urine, only doxepin and desmethyldoxepin were found in rat brain.

This review, therefore, will concentrate chiefly on more recent papers (1963 to 1969) containing new ideas or unusual findings, or data that relate to the above comments, rather than attempt to be a comprehensive summary of the field. The effects of species variations in absorption, excretion, and a host of other factors (diet, sex, enzymic induction, inhibition, etc.) on drug metabolism are not considered per se here, but are, of course, recommended for the reader's attention. The dose employed, in the author's experience [see also Levy (27)] can also greatly influence metabolic patterns, and should always be considered. Results of certain *in vitro* studies are also included where they seemed pertinent and well controlled (28).

Factors in Species Differences in Metabolism

Many variables, excluding the external environment, must be considered as important factors in species differences in drug metabolism. Among these are differences in binding, either to tissues or to plasma components, such as albumin. Large variations in binding have been reported for the same drug with different species (29–33). More obvious are two other factors, the concentration and types of drug-metabolizing enzymes in each species. Marked species variations have been shown in both K_m and V_{max} for the metabolism of ethylmorphine (34) in liver microsomes of rats, mice, guinea pigs, rabbits, and monkeys (African green). Thus, it would be a mistake to assume

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that species variations in drug metabolism are caused solely by differences in the amount of enzyme present in liver microsomes.

Likewise, although there still seems to be some uncertainty, several investigators (35–39) have reported that the amount of cytochrome P_{450} in microsomes of various species does not differ enough between species to be correlated with large differences in rates of metabolism between species. It is possible, however, that microsomes of different species may contain a different form of cytochrome P_{450} having different affinities for drugs and other foreign compounds. The rate-limiting factor for drug metabolism in each species may be NADPH cytochrome-P_{450} reductase. Good correlation has been obtained between the amount of this enzyme present and O-demethylation of *p*-nitroanisole, hydroxylation of aniline, and N-dealkylation of ethylmorphine. The various substrates may, in turn, increase or decrease the rate of cytochrome-P_{450} reduction in liver microsomes (40) of the various species.

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N-Heterocyclics

Imipramine.—Metabolism of the antidepressant drug, imipramine, a dibenzazepin derivative, has been extensively studied. It was suggested (41, 42) that the demethylated metabolite, DMI, is at least partially responsible for the antidepressant activity of imipramine. Rats, rabbits, and mice metabolized imipramine by N-demethylation but the rate of metabolism of DMI was much slower in rats, a species in which imipramine was more active. Perhaps the dog also metabolizes DMI slowly since it was recently reported (43) that imipramine disappeared rapidly from dog plasma but DMI levels remained fairly constant. No pharmacologic data on dogs is apparently available. Recently it was claimed (44) that demethylation of imipramine was not essential for the response seen in the catalepsy test with tetrabenazine, since the rat brains were found to contain no DMI. Bickel & Weder (45), however, confirmed the original reports of the appearance of DMI in rats given imipramine, but also confirmed the negative results of Michaelis & Stille in a separate group of rats. It was proposed that the opposite results may have been caused by the intraperitoneal injection technique employed, since the route of administration greatly affected the resulting DMI brain levels. Perhaps the same conclusion would apply to the report (46) that DMI was detectable in rat brain only after 4 hours and not earlier, in contrast to the findings (41) that DMI levels were maximal at 30 minutes.

It has also been shown (47) that methylation of DMI to imipramine was catalyzed by an enzyme present in lungs of rabbits, but not in those of rats, a finding that also may have significance for pharmacologic species differences.

Diazepam.—The minor tranquilizer, diazepam, 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepam-2-one was metabolized in the dog and man chiefly by N-demethylation and C-3 hydroxylation (48, 49). In

the rat C-3 and 5-phenyl hydroxylation were the most important pathways (50).

The longer anticonvulsant activity of diazepam in mice compared to rats may be caused by the higher level of N-demethylated metabolites in mouse brain (51). Mouse adipose tissue was also found to contain higher levels of N-demethylated metabolites of diazepam than adipose tissue of rats or humans (52).

Oxazepam.—Metabolism of oxazepam, 7-chloro-1,3-dihydro-3-hydroxy-5-phenyl-2H-1,4-benzodiazepam-2-one, a hydroxy desmethyl analogue of diazepam, has been studied in man, dog, rat, and pig (53). It was excreted almost entirely as the O-glucuronide in man, dog, and pig, but was extensively metabolized in the rat.

Chlordiazepoxide.—Metabolism of chlordiazepoxide, 7-chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine-4-oxide, was studied in man, dog, rat (54, 55), and mouse (56). The major metabolic pathways were similar in man and dog, but different in the rat. In man and dog, hydrolytic cleavage of the C-2 methylamino group gave the corresponding lactam metabolite, which was further cleaved to the corresponding amino acid. More recently, chlordiazepoxide was reported to be also metabolized in the dog by hydroxylation at C-3 and N-oxide reduction, i.e., converted to oxazepam (57). In the rat, *para* hydroxylation of the 5-phenyl ring was the major pathway, along with stepwise degradation of the C-2 methylamino moiety. Of interest also in the rat was the presence of a metabolite in which the N-oxide group was reduced. A similar process has been reported for imipramine N-oxide (58).

Aminopyrine.—As measured under carefully controlled (optimal) conditions the activity of rat liver enzyme preparations in N-dealkylation of aminopyrine was about 15 times that of the trout (59). It was suggested that "relating the different levels of drug-metabolizing activity in two totally different species, like the homiothermous rat and the poikilothermous fish to a basic parameter, such as resting metabolism—which in turn is related to food intake and therewith to the degree of exposure to body-foreign compounds—might greatly reduce the difference in detoxificating capacity reported."

Chloroquine.—The metabolism of chloroquine, 7-chloro-4-(4-diethylamino-1-methylbutylamino)quinoline, has been extensively studied. Recently (60–62) metabolism in the rhesus monkey was shown to differ from that in man in two respects. The principal metabolite in monkeys, but not in man, was the carboxylic acid resulting from oxidative deamination of chloroquine. In addition, there was a gradual shift in urinary metabolites in the monkey from unchanged drug to desethylchloroquine, whereas in man these constituents remained in a ratio of 3:1, both during and following an extended medication period.

Quinaldic Acid.—Quinaldic acid, quinoline-2-carboxylic acid, is a metabolite of kynurenic acid which exhibits marked species differences in its me-

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tabolism. Cats given quinaldic acid excreted quinaldyl-glycyltaurine and minor amounts of quinaldylglycylglycine (63, 64) whereas rabbits excreted only unchanged compound (65) and rats excreted both unchanged acid and its glycine conjugate (66). Metabolism of quinaldylglycyltaurine itself was also species-dependent (67). Rats hydrolyzed it to quinaldic acid and quinaldylglycine, cats excreted it unchanged, and as the glycylglycine conjugate, and rabbits given the compound orally excreted it as quinaldic acid but unchanged if administered parenterally (was this due to gut bacterial action?).

Tremorine.—It has been shown that tremorine, 1,4-bis-(pyrrolidino)-butyne-2, produces tremor and spasticity in several species (68). The pharmacologic action has been shown to be exerted by two active metabolites, oxotremorine, 1-pyrrolidino-4-(2-oxo-pyrrolidine)2-butyne (69) and N-(4-pyrrolidine-2-butynyl)-γ-aminobutyric acid (70). The species difference in pharmacologic activity between rat and mouse may result from different rates of metabolism of tremorine and oxotremorine in the two species (71).

Phencyclidine.—This anesthetic agent, 1-(1-phenylcyclohexyl) piperidine (Sernylan) was metabolized principally by mono- and dihydroxylation of the piperidine ring. The relative concentrations of unchanged drug and the two metabolites differed widely between species (72, 73). The amount of dihydroxy metabolite varied from 0 per cent in cat, man, dog, cow, and horse to 75 per cent in the pigeon and rat, with intermediate amounts (25 to 55 per cent) in mouse, sheep, and monkey (rhesus). The amount of monohydroxy metabolite was low in the rat, pigeon, and cat (5 to 14 per cent), intermediate in monkey, sheep, mouse, and man (29 to 68 per cent) and high in the dog, cow, and horse (85 to 100 per cent). It was suggested that the deficiency in hydroxylation in the cat may explain the high susceptibility of the cat to the drug. The drug was apparently more toxic to those species in which dihydroxylation did not occur.

Phenylbutazone.—Marked species differences were noted in the rate of metabolism of phenylbutazone (74, 75). The biologic half-life was six hours in the dog, three hours in the rabbit, six hours in the rat, six hours in the horse, eight hours in the monkey, five hours in the guinea pig, and 72 hours in man. Piperno et al. (76) recently showed that the half-life in horses was dose-dependent, a factor of some importance for equine medicine. At therapeutic dose levels, the half-life was found to be 3.5 hours.

Perel et al. (77) showed that the biologic half-life of many phenylbutazone analogues varied widely between man and dog. A direct relationship existed between pK_a and half-life in man, but not in the dog.

Pyrimidines.—The deamination of the cytostatic agent 6-azacytidine to yield 6-azauridine was found to be extremely low in rats (78) compared to the mouse, cat, dog, guinea pig, rabbit, and man. The view that 6-azacytidine acts mainly through its deamination product, 6-azauridine, was supported by the finding that 6-azacytidine produces almost no neurotropic effects in the rat (79). Thus, the rat would have had no predictive value for

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the action of 6-azacytidine in man, a species in which deamination is extensive. Species differences in deamination by various organs was also revealed; multiorgan deamination occurred in some species, but in the dog was restricted to the liver.

Ethers, Epoxides

The oxidation of the side-chain in *n*-butyl-*p*-nitrophenyl ether was found to be species dependent (80). Rabbits and guinea pigs metabolized the compound mainly by (ω-1)-hydroxylation, whereas rats and mice metabolized more through α and ω-oxidation; the latter oxidation was followed by β-oxidation.

Studies (81) with cyclodiene epoxide insecticide enantiomers have indicated that pig liver microsomes metabolized one enantiomer by hydrolytic epoxide cleavage (NADPH not required) and the other by oxidative attack (NADPH and oxygen required). An interesting consequence of these findings (if reflected *in vivo*) is that the housefly apparently metabolizes the compounds by oxidative mechanisms, which are susceptible to inhibition by insecticide synergists of the 1,3-benzodioxole type. Thus, the pig may be partially protected against synergist combinations of this type by the apparent ability of its microsomes to metabolize half the insecticide by a hydrolytic process unaffected by these synergists. In addition, synergist combinations with those enantiomers that are rapidly hydrolyzed by pig liver microsomes should be toxic to the housefly and innocuous to the pig. Comparative metabolic studies thus may indicate possible pathways to selective toxicity.

Carbamates

Metabolism of several compounds in this series has been well studied in several species. Tetraethylthiuram disulfide (disulfiram) is of interest since, although it itself was inactive as a radioprotective agent, a major metabolite of the drug in rat urine (82) was the S-glucuronide of the free thiol, diethyldithiocarbamate, an active radioprotective agent. Prolonged absorption of the disulfide apparently prevented accumulation of radioprotective levels of thiol in plasma, since it was later shown (83) that administration of the disulfide gave plasma and liver thiol concentrations in mice that were markedly lower than those seen after thiol administration. The S-glucuronide was also shown to be a metabolite of disulfiram in rats (82) and also in man (84).

Species differences in the metabolism of the insecticide 1-naphthyl-N-methyl carbamate (carbaryl) were found, since the dog formed none of the metabolites identified in rat and guinea pig urine (85, 86). The metabolites identified were 4-(methylcarbamoyloxy)-1-naphthyl glucuronide, 1-naphthyl glucuronide, 4-(methylcarbamoyloxy-1-naphthyl sulfate, and 1-naphthyl sulfate. Human urinary metabolites were identified as 1-naphthyl glucuronide and sulfate. The major difference between the animal species studied was the extent to which carbaryl was hydrolyzed to yield 1-naphthol.

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Little or no hydrolysis of carbaryl occurred in the monkey (rhesus) and pig as opposed to the ewe and man (87).

Species differences in the metabolism of benzyl N-benzyl carbethoxyhydroxamate, an agent affecting lipid metabolism, have also been observed (88). An unusual metabolite, the O-benzyl benzaldoxine was formed by man and the rat, but not by monkey, cat, or guinea pig.

Amides, Imides

A new metabolite of acetophenetidine was isolated from human urine and shown to be S-(1-acetamido-4-hydroxyphenyl)-cysteine (89). The new metabolite represents the unacetylated precursor of the mercapturic acid; excretion of such compounds does not seem to have been previously studied. The results suggested that man, like the guinea pig (90), may have a low capacity to acetylate aliphatic amino groups. The degree of conversion of acetophenetidine to free amines by different species appeared to be correlated with the liability of the species to methaemoglobinaemia (91).

Monkeys (rhesus) were reported (92) to metabolize 2-acetylaminofluorene (2-AAF) to the 7-hydroxy derivative rather than by N-hydroxylation. The latter is a metabolite of 2-AAF in the rat, rabbit, hamster (93), dog, and human, species in which 2-AAF is carcinogenic. 2-AAF is not, however, carcinogenic in the rhesus monkey. Guinea pigs are also refractory to the carcinogenic action of 2-AAF although N-hydroxylation occurs (94). The findings in the guinea pig may be related to their ability to rapidly deacetylate N-hydroxy-2-AAF (95).

Man was unique in forming an unusual metabolite, the azoxybenzene, of a new analgesic, antiphlogistic agent, 2-(2-methoxyethoxy)-5-acetaminoacetophenone (96). The metabolite was not found in rats or dogs.

Thalidomide.—The teratogenic action of thalidomide appears to be caused by the compound itself rather than by one or more of its hydrolysis products (97). It has been suggested (98, 99) that hydroxythalidomides could be teratogenic metabolites of thalidomide, since synthetic 3- and 4-hydroxy-thalidomides produce abnormalities in chicks (100). Since aromatic hydroxylation is known to vary widely between species, perhaps lack of this process in the hamster is related to the lack of teratogenicity in this species, as opposed to many others. The lack of teratogenic effect in the hamster is not caused by inability of thalidomide to penetrate the conceptus (101). Others (102) have suggested that species differences in teratogenicity may be the result of differences in the rate of acetylation of an unknown substance which controls organ development.

O-Heterocyclics

Benzodioxanes.—Marked species differences have been observed in the metabolism of a series of benzodioxane central nervous system depressants (103–105). Butamoxane, 2-butylaminomethyl-1,4-benzodioxane, was metabolized in both the rat and dog through ring hydroxylation at the 6- or 7-

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position. However, ethoxybutamoxane, 2-butylaminomethyl-8-ethoxy-1,4-benzodioxane was metabolized in the dog by oxidation of the butylaminomethyl sidechain to yield 2-carboxy-8-ethoxy-1,4-benzodioxane and in the rat by ether cleavage to the 8-hydroxy analogue. In man, metabolism apparently proceeded via ring hydroxylation.

The third member of the series studied was chlorethoxybutamoxane, the 5-chloro analogue of ethoxybutamoxane. In mice, rat, and guinea pigs, the main route of metabolism was cleavage of the ether linkage; in the dog and rabbit, the major pathway was side-chain oxidation.

Coumarin.—Coumarin was found to be more extensively metabolized by ring opening in rats than in rabbits (106). It was suggested that this could explain the difference in toxicity, coumarin being more toxic to rabbits. More recently, evidence was presented which suggested that the difference in coumarin metabolism may reflect differences in the gastrointestinal flora of the animals used (107). Species differences have been reported in the 7-hydroxylation of coumarin by liver microsomes (108, 109). Recently, Shilling et al. (110) have shown that a major metabolite of coumarin in man was the 7-hydroxy derivative, which was a minor metabolite in the rat and rabbit (106). O-hydroxyphenylacetic acid, a major metabolite of coumarin in rats and rabbits, but not 7-hydroxycoumarin, inhibited liver glucose-6-phosphatase (111), the relative activity of which may reflect hepatoxicity of the drug (111). Shilling et al. suggested on this basis that attempted evaluation of the toxicity of coumarin to man based on toxicity data for rats or rabbits was of doubtful validity.

Rotenone.—Metabolism of the natural product insecticide, rotenone, involved ring hydroxylation, side-chain hydroxylation, and probably epoxidation of the isopropenyl side chain. The ratio of metabolic product varied with species and it was suggested that the selective toxic action of rotenone may result from this variation in case of biodegradation between species (112).

Griseofulvin.—Rabbits (113) and dogs (114) metabolized the antifungal agent griseofulvin, 7-chloro-4,6,2′-trimethoxy-6′-methylgris-2′-en-3,4′-dione, by 6-demethylation, whereas the rat formed primarily the 4′-desmethyl derivative.

AMINES

Amphetamine.—Amphetamine metabolism has been extensively investigated by several groups over a number of years. Axelrod (115) reported that *p*-hydroxylation was the primary route of metabolism in the dog and rat but not in rabbits and guinea pigs. It was suggested that the drug was metabolized principally by oxidative deamination in the rabbit (116). More recently, Ellison et al. (117), using labeled drug, reported that oxidative deamination was also the major route of metabolism in the squirrel monkey. These authors found that in the dog (beagle), oxidative deamination and *p*-hydroxylation were equally important major routes. Dring et al. (118),

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however, stated that deamination is the major reaction in the dog (greyhound). It is possible that a strain difference in metabolism is responsible for the discrepancy or conceivably, urinary pH may have influenced excretion of metabolites since it is known to affect excretion of unchanged amphetamine (119, 120). Dring et al. (118) and Ellison et al. (121) also found that man metabolized the drug principally by deamination, like the rabbit and dog.

It has since been reported (122) that benzoylmethyl ketone, an intermediate of oxidative deamination, is excreted as the enol sulfate of the ketone, i.e., $C_6H_5CH=C(OSO_3H)CH_3$, in rabbits, but only as traces in man and dog. The ketone was not found in mouse, guinea pig, or rhesus monkey urine, which suggests that amphetamine was not metabolized by deamination in these species. If so, as stated above, the squirrel monkey uses this route as a major metabolic pathway.

Diphenhydramine.—Metabolism of diphenhydramine, 2-(diphenylmethoxy)-N,N-dimethylethyl amine, is of interest here chiefly because it is metabolized in the rhesus monkey (123) to diphenylmethoxyacetic acid which is excreted as the glutamine conjugate. This report and those of others (8, 124) demonstrate that glutamine conjugation is not a pathway limited to man and the chimpanzee as once proposed (125).

Tyramine.—Because of the extensive use of tyramine in pharmacologic research, the species differences observed for the conversion of tyramine to dopamine should be of interest (126). Liver microsomes from guinea pigs, rats, and mice had only a fraction of the activity seen in rabbit preparations, the mouse being lowest.

Naphthylamine.—2-Formamido-1-naphthyl hydrogen sulfate was reported (127) as a new metabolite of 2-naphthylamine in the dog and rat, but not in the guinea pig or hamster, species which excreted only small amounts of 2-amino-1-naphthyl hydrogen sulfate. The dog is the only experimental animal in which bladder tumors have been induced by feeding naphthylamine. The dog also excreted the highest fraction of the dose of 2-naphthylamine-^{14}C in the urine, compared to the guinea pig, mouse, and rabbit (128).

The dog (129) and human (130) but not the guinea pig, hamster, rabbit, or rat, excreted 2-naphthyl hydroxylamine as a metabolite of 2-naphthylamine. It was suggested (129) that the occurrence of this metabolite (a carcinogen) may account for the carcinogenic activity of 2-naphthylamine in the bladders of men and dogs.

Phenolic Amines.—The ratio of *p* to *o*-aminophenol excreted in the urine of various animal species dosed with aniline was: gerbil, 15; guinea pig, 11; golden hamster, 10; rabbit, 6; rat, 6 (male) and 2.5 (female); chicken, 4; mouse, 3; ferret, 1; dog, 0.5; cat, 0.4 (131). N-hydroxylation of p-chloroaniline by liver microsomes was carefully studied (132). When the maximal velocities of microsomal reactions were compared, the order between species was: guinea pig > mouse > chicken > rabbit > rat > cat > pig. However,

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a different order was observed when activity was expressed on the basis of microsomal protein. Large species differences in the half-life of N-hydroxyarylamines have been reported (133).

Thio Compounds

An interesting species difference has been reported in the metabolism of 2,2-dichloro-N-[β-hydroxy-α-(hydroxymethyl)-*p*-(methyl-sulfinyl)phenethyl] acetamide, an antibacterial agent (134). In the mouse, the sulfoxide group was reduced to the sulfide, but in the rat and monkey (rhesus), the sulfoxide was both reduced, and oxidized to the sulfone. Reduction and deactylation occurred in the dog. Both the sulfide and sulfone were pharmacologically active.

Thioxanthene.—The thioxanthene derivative 'Miracil D', a schistosomicidal agent, is believed to act through an active metabolite. However, the sulfone, sulfoxide, and sulfoxide-polypeptide complex, metabolites of the drug in mouse, monkey, and man were inactive (135). Evidence has been reported (136) that the hydroxymethyl derivative is the important biologically active metabolite (isolated from monkey urine). Therapeutically, 'Miracil D' was less active in mice than monkeys, and the mouse was found to excrete much less of the hydroxymethyl metabolite. The 6-chloro derivative of 'Miracil D', on the other hand, was active in mice but not in monkeys. In keeping with the above hypothesis that the hydroxymethyl derivative is the active metabolite, the glucuronide of the chlorohydroxymethyl derivative was present as a major metabolite in mouse urine, but only in trace amounts in monkey urine. To complete this beautiful series of observations on the relation of species differences in metabolism to therapeutic activity, the presence of a 4-methyl group was known (137) to be an absolute requirement for biological activity. The reason for this is now abundantly clear, as a result of the studies of Rosi and co-workers (136).

Chlopromazine.—The metabolism of chlorpromazine is exceedingly complex and perhaps for this reason no adequate species comparisons have been made. Studies that have been reported suggest that species differences in metabolism do exist (138, 139). Reports have been made on the determination of chlorpromazine and several of its metabolites in human plasma (140–142). Perhaps if these studies are extended to animals, more meaningful comparisons between species might be made than is possible from the complex array of urinary metabolites. Such comparisons might be important, since evidence exists for the relevance of metabolism to toxic effects of chlorpromazine (143, 144).

4,4'-Diaminodiphenylsulfone.—Species differences in metabolism of this anti-leprotic agent (dapsone) were not readily apparent in urinary metabolites, in that metabolites in man, rabbit, and monkey (rhesus) were similar: free drug, N-acetyl dapsone, the mono-acetylated N-glucuronide, and sulfamate (145–147). Recently, however, the ratio of free to acetylated drug was found to be 1:20 in monkey plasma, compared to 1:1 in human plasma

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(145). Monkey and rabbit were shown to be fast acetylators *in vitro,* man and rat were slow acetylators.

With different compounds (isoniazid and sulfamethazine), Gordon et al. (148) have reported that squirrel monkeys, however, acetylated only one-half to one-fourth as well as rhesus monkeys. This apparently was because squirrel monkeys possess a competing deacetylation mechanism whereas rhesus monkeys do not.

Alkaloids

Lysergic Acid Diethylamide.—Considerable species differences in the rate of metabolism of lysergic acid diethylamide (LSD) have been reported (149) which may reflect differences in metabolic pathways. The biologic half-life of LSD in the mouse, monkey (Macaca mulatta), cat, and man (150) was 7, 100, 130, and 175 minutes, respectively. Metabolism *in vitro* (liver microsomes) apparently produced different hydroxylation products, the 2-hydroxy derivative in the case of the guinea pig (149) and the 13-hydroxy (corresponding to the five-position of the indole nucleus) in rats (151). Rat bile was reported (152) to contain two hydroxylation products, substitution having occurred apparently in the benzene ring of the indole nucleus.

Morphine.—A major metabolite of morphine in the chicken and cat is the ethereal sulfate (153, 154). Methods have been worked out for its isolation from urine and an important species difference might be found by examination of human, rabbit, and dog urine for this metabolite, since the 3-glucuronide is the only conjugate identified thus far in these species (155–157).

Atropine.—Data suggesting that species differences (qualitative or quantitative) in metabolism of atropine may explain species differences in pharmacologic sensitivity of atropine have been reported. Urine of dogs given atropine contained a high per cent as unchanged drug (158). The mouse, however, metabolized atropine more rapidly, by hydrolysis, hydroxylation at the 4'-carbon, and demethylation at C-9 (159, 160). Dogs are about ten times more sensitive than mice or rats with regard to atropine effects on the central nervous system (161).

Esters

Acetylsalicyclic Acid.—A study (162) of the rate of hydrolysis of aspirin by serum of several species revealed that cats and rabbits approximated the human rate while dogs had a much slower, and rats a much faster rate than man. Harris & Riegelman (163) claimed that the human rate is probably much faster, if undiluted serum (or plasma) and therapeutic aspirin levels are used. It would also be of interest to determine if the species differences disappear if the results were given on the basis of protein nitrogen in the samples.

Procaine.—Benohr et al. (164) found wide species variations in the hy-

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drolysis of procaine, tributyrin, and phenacetin by liver microsomes. Guinea pigs showed the highest procaine esterase, of interest since Livett & Lee (165) reported that procaine was hydrolyzed much more slowly than several procaine analogues by guinea pig liver homogenates. It was earlier reported (166) that human plasma hydrolyzed procaine much more rapidly than other species.

Mercapturic Acids

Guinea pigs excreted considerably less mercapturic acid from precursors than did rats and rabbits (167). The reason appeared to be caused by difficulty in N-acetylation of S-substituted cysteines by this species. Low acetylation capacity in the guinea pig does not appear to be as general as in the dog.

1-Bromobutane was metabolized by mercapturic acid formation, i.e., replacement of the halogen by N-acetylcysteine. Both the rat and rabbit excreted the (3-hydroxybutyl)-mercapturic acid, representing hydroxylation at the expected penultimate position (168). The rat, however, excreted (2-hydroxybutyl)-mercapturic acid (only a trace was found in rabbits), representing hydroxylation at a more unusual position (169).

Nitro Compounds

Considerable species difference in mammalian nitro reduction was reported (170), the enzyme being highly active in mice, guinea pigs, and rabbits, and less so in rats and dogs. These *in vitro* studies were extended (171, 172) and included avian, reptilian, and piscine species. The liver nitroreductase activity correlated with species differences in toxicity in some cases, but not in others. When nitroreductase activity was expressed in terms of microsomal protein (173), the order of activity was mouse > rat > rabbit as opposed to that given above. These same authors presented evidence that reduction was mediated by microsomal cytochrome P_{450}. The possibility that differences in capacities of human and rodent placental homogenates to reduce p-nitrobenzoic acid may be caused by differences in flavin content was demonstrated by Juchau (174).

Sulfonamides

The medium to long-acting sulfonamides, sulphadimethoxine (2,4-dimethoxy-6-sulfanilamidopyrimidine), and sulfamethomidine (the 4-methoxy-2-methyl analogue) show a remarkable species difference in metabolism (175–178) in that they are excreted in man and other primates (rhesus monkey) but not in certain lower animals (rabbit, dog, guinea pig, rat) primarily as the N^1-glucuronide. However, the 5-; 2,4-; 2,5-; and 4,5-analogues were shown (176) to be mainly excreted unchanged, or as N^4-acetyl derivatives in all species.

A further instance of lack of acetylation capabilities of the dog was illustrated by work on sulfasomizole (5-*p*-aminobenzenesulfonamido-3-

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methylisothiazole) which is acetylated in man, rat, and rabbit, but not in the dog (179).

Indoles

O-Demethylation of isomeric methoxyoxindoles was observed with liver microsomal preparations of rabbit, but not those of rat or guinea pig (180). These observations may be explained by the presence of heat-labile inhibitors in liver extracts of rat, and guinea pig, but not of rabbit (181). O-Demethylating microsomal enzymes have also been shown to be much less stable than N-demethylating enzymes with respect to codeine (182) and it is possible that these enzymes were less stable in rat and guinea pig preparations.

Indomethacin.—Marked species differences in the metabolism of the antiinflammatory agent indomethacin, 1-(*p*-chlorobenzoyl)-5-methoxy-2-methyl-indole-3-acetic acid, have been reported (183). Man excreted the drug entirely in the form of the ester glucuronide as did the rabbit, to the extent of 44 per cent of the urinary metabolites. The rat, rabbit, guinea pig, and rhesus monkey also metabolized the drug by O-demethylation and N-debenzoylation. The dog excreted only a minor fraction of the dose of drug in the urine.

Others (184) showed that the dog, like man, converted indomethacin to the acyl glucuronide, but, unlike man, excreted the drug primarily in the feces. Biliary excretion was extensive in all species but the dog was unique in its inability to excrete the glucuronide in urine, apparently because of inefficient hepatic/blood clearance of the glucuronide. Glucuronide excreted in dog bile was shown to be hydrolyzed in the gut, reabsorbed as free drug, and reexcreted in the bile. This cycle evidently continued until the eventual elimination of the drug in feces. Indomethacin glucuronide administered intravenously to dogs was not extensively excreted in urine, indicating that inefficient renal, as well as hepatic/blood clearance of the drug, may be important in explaining the results in dogs. Thus, with indomethacin, the observed species differences in urinary metabolites may depend on a combination of the nature of the metabolite, the extent of biliary excretion, and reabsorption and the renal clearance in the various species.

A second type of species variation in indomethacin metabolism was seen in the distribution in tissues of rats and guinea pigs. In the rat, concentrations of radioactivity (labeled drug administered) in all tissues were lower at all times than plasma values. In the guinea pig, however, radioactivity was concentrated, relative to plasma, in liver, kidney, and small intestine. This may represent a true species-dependent tissue affinity, since the urinary metabolites in the two species were qualitatively similar. Localization of the same compound in tissues is apparently seldom different in different species (44). Attempts to correlate levels of radioactivity in animal tissues following administration of labeled indomethacin with drug-related manifestations of toxicity were unsuccessful.

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Metabolism of the dimethylamino analogue of indomethacin was similar in all species examined, at least insofar as deacylation was concerned. p-Chlorohippuric acid was the major metabolite of the drug in man, mouse, rat, and dog (185).

Findings analogous in some respects to those with indomethacin have been reported for the antiinflammatory agents, mefenamic acid, N-(2,3-xylyl)anthranilic acid, and flufenamic acid, N-(α,α,α-trifluoro-m-tolyl) anthranilic acid (186–188). These compounds were excreted in feces of dog, but in urine of monkeys and man, after biliary excretion. The compounds were also extensively metabolized by side chain oxidation and ring hydroxylation, respectively, in man and monkey, but not in the dog.

Miscellaneous Structures

Quinic Acid.—Aromatization of quinic acid to benzoic acid was reported (189) to occur in man (70 per cent) and old-world monkeys (40 to 70 per cent), but there was little or no aromatization in new-world monkeys, the lorisform lemurs, or the tree shrew.

DDT.—The insecticide DDT, 1,1-di(*p*-chlorophenyl)-2,2,2-trichloroethane was metabolized in pigeons to 1,1-di(*p*-chlorophenyl)-2,2-dichloroethylene (DDE) and 1,1-di(*p*-chlorophenyl)-2,2-dichloroethane(DDD) (190). Only the latter compound is highly toxic and it was suggested that its storage may be more harmful than previously suspected, in view of species differences known to exist in response to DDT and its metabolites (191). It was further suggested that the toxicity of DDT in the various species may depend on the relative amounts of these two metabolites formed.

Amantadine.—The antiviral agent amantadine was excreted partly as the N-methyl derivative in dogs (192) but not by man, monkey (African green), or the mouse.

Biphenyl.—Liver preparations (10,000x *g* supernatant) from 11 species converted biphenyl into 4-hydroxybiphenyl, but the extent of conversion was widely variable (193). Preparations from rabbits, rats, guinea pigs, hens, trout, and fox (1) did not form 2-hydroxybiphenyl, whereas this isomer was formed by livers of mouse, hamster, cat, coypu, and frog. Age-linked differences were also seen. It should be pointed out that the incubation temperature of 37° C was probably not optimal for trout (59).

Ethylene Glycol.—An interesting consequence of species variation in metabolism was seen with ethylene glycol (194) which is metabolized to carbon dioxide, oxalic acid, glyoxylic acid, and urea. The extent of formation of oxalic acid increased much more rapidly with dose in cats than in rabbits and rats or guinea pigs, which correlated with the toxicity of ethylene glycol in these species. Ethylene glycol was more toxic to the species which excreted the most oxalate (cats) and was least toxic to the species which were more able to oxidize it to carbon dioxide.

Pemoline.—This CNS stimulant (2-imino-5-phenyl-4-oxazolidinone), under investigation as an adjunct in the development of learning and mem-

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ory, showed wide differences between species in extent and pathway of metabolism (195). In the rabbit, hydrolysis of the imino group to give pemoline-dione occurred, but no dione was found in the dog, rat, or man. Little metabolism of the drug occurred in the dog, whereas over 50 per cent of the drug was metabolized in the rabbit and human. The heterocyclic ring was apparently cleaved in rabbits.

N,N-Diallylmelamine.—The metabolism of the peripheral vasodilator triazine derivative, N,N-diallylmelamine, is a dramatic example of the importance of species differences in metabolism. The compound lowered blood pressure, after a delayed onset, in rats and dogs, but was inactive in humans. Zins et al. (196) showed that the pharmacologic activity depended almost entirely on conversion to an active metabolite, in which the parent drug was hydroxylated on the triazine ring. This metabolite was not found in man, which explained the lack of pharmacologic activity of the drug in this species. Administration of the metabolite, however, lowered blood pressure for prolonged periods in human subjects.

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Conclusions

As indicated in this review, it is not yet possible to predict, in other than a few instances, the metabolic fate of drugs in various species. Most studies in the field of drug metabolism have been descriptive in nature and almost no work on the detailed mechanism involved has been reported. Prediction of species differences of this type no doubt will depend on our understanding of the process of metabolism itself. Several groups are actively pursuing the latter goal and one may hope for progress in this direction. Only a relatively few years have passed since the basic discovery of the essential role of liver microsomes and cofactors in drug metabolism. Thus, we should not be overly impatient for a comprehensive tool of universal predictive value, especially since the mechanisms themselves may involve subtle alterations in molecular conformations and interactions. Other aspects awaiting further exploration are comparative metabolism studies in the higher primates and interspecies comparison of drug metabolite levels at the site of action.

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