EXTRARENAL EXCRETION OF DRUGS AND CHEMICALS[1,2]

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In addition to renal mechanisms for the excretion of drugs, which have been reviewed by Weiner (1), a number of other organ systems are also capable of excreting chemicals. Because of the multiplicity of these extrarenal organ systems, an attempt will be made to summarize the factual information available for each route and to include, where possible, the present-day concepts regarding mechanisms.

Bile

The excretion of chemical substances into bile has been the subject of a number of reviews (2–5). The recent review by Smith (5) is by far the most comprehensive and detailed survey of our current knowledge.

Brauer (3) originally divided the substances which are excreted into bile into three classes according to their bile/plasma concentration ratios. Substances of Class A are those whose ratio is nearly one (glucose, Na^+, K^+, and Cl^+). Class B includes substances whose bile/blood ratios usually range from 10 to 1000 (bile salts, sulfobromophthalein, fluorescein, rose bengal, bilirubin glucuronide, and creatinine). Class C compounds consist of those in which the ratio is less than one (inulin, sucrose, phosphates, cholesterol, and mucoproteins).

Much of the work that has been carried out has dealt primarily with those compounds contained in Class B. It appears that the transport of these substances across the biliary epithelium into bile requires some kind of active secretory process. Characteristically, these substances compete for transport, and the transport mechanism can be saturated by an excess of compound. Hypothermia was shown to decrease the excretory rate of some of these substances (3, 6).

Little is known about the mechanism involved in the actual transfer of Class B substances into bile. Since a number of them are organic acids which exist in the ionized state at physiological pH, it has been proposed (2, 4)

[1] The survey of literature pertaining to this review was concluded in June 1967.

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that all acids share a common transport process. While the previous substances studied (sulfobromophthalein, phenol red, fluorescein, *p*-aminohippuric acid, and penicillin) are carboxylic or sulfonic acids, Hart & Schanker (7) recently demonstrated that chlorothiazide, an acid which is neither a sulfonic nor a carboxylic acid, appears to be actively secreted into bile by the same process that secretes the carboxylic and sulfonic acids.

Basic substances can also be excreted into bile in high concentrations. Schanker & Solomon (8) demonstrated that the quaternary ammonium ion, procaine amide ethobromide (PAEB) rapidly appears in the bile of rats in high concentrations, both as unchanged PAEB and as conjugated PAEB. Competition was demonstrated by a number of compounds. Piperphenamine (Darstine), benzomethamine and oxyphenonium were particularly active in this regard, whereas tetraethylammonium, cetyltrimethylammonium, and other substances did not appear to compete for excretion. A number of quaternary ammonium compounds are excreted into the bile of rats, while others are not. Those which are excreted seem to have one characteristic in common (9): a highly polar quaternary amine group at one end of the molecule and one or more nonpolar ring structures at the opposite end. On the other hand, those bases which are poorly excreted lack the nonpolar ring structure at one end of the molecule (9). These data suggest that the transport system does possess a certain degree of specificity. This system appears to be different from the one responsible for the secretion of organic acids in that sulfobromophthalein and glycocholate have no effect on the transport of PAEB (8).

Besides these transport systems, there have been indications of other ways in which substances can pass from the liver into bile. Inulin, sucrose, and mannitol have been shown to transfer from blood to bile (10). The concentrations found in bile, however, were either equal to or less than the conconcentrations in blood. The concentrations were inversely related to their molecular size. It has been proposed (10) that the appearance of these substances in bile suggests transport by simple diffusion and osmotic filtration.

The biliary excretion of a variety of chemical substances, for which quantitative data are available (11–80), is summarized in Table I. Wherever possible, the excretory products have been broken down into parent compound and metabolic products. Williams, Millburn & Smith (24) have studied a series of compounds both for the amounts excreted into bile and the type of products excreted. They have come to some tentative conclusions regarding requirements for biliary excretion. Using aniline and substituted benzoic acids, they propose that substances of low molecular weight (less than 300) would be excreted into bile in small amounts (less than 5 per cent of the dose), even if polar conjugates of the original compound were formed. With various iodinated derivatives of *p*-aminobenzoic acid, they concluded that the increase in molecular weight associated with iodination results in increased biliary secretion. These investigators also found that compounds containing two or more aromatic rings tended to be excreted into the bile if they could be metabolized and conjugated.

TABLE I

EXCRETION OF VARIOUS DRUGS AND CHEMICALS INTO BILE

COMPOUND	SPECIES	DOSE MG/KG	TIME HR	PERCENT OF DOSE EXCRETED			REFERENCE
				TOTAL	PARENT	METABOLITE	
Contrast Media							
Iodopanoic acid	Cat	100	18	75	—	75	11
Phenlodol	Cat	50	6	20	—	—	12
Phenlodol	Dog	100	8	50	—	—	13
Butyryliodopanoic	Cat	100	18	45	—	—	14
Acetyliodopanoic	Cat	100	18	30	—	—	14
Dyes							
Phenolphthalein	Dog	4.8	72	43	—	—	15
Phenolphthalein	Cat	6.6	3	17	—	17	16
Phenol Red	Dog	20	3	3	—	—	17
Bromophenol Blue	Dog	20	3	18	—	—	17
Bromcresol Green	Dog	20	3	32	—	—	17
Sulfobromophthalein	Man	5	2	61	13	48	18
Sulfobromophthalein	Rat	15	1	82	11	71	19
Phenoltetrabromphthalein monosulfonate	Rat	44	2	95	—	95	20
Phenoltetrabromphthalein tetrasulfonate	Rat	63	2	7	7	—	20
Fluorescein	Rat	3	2	14	—	14	21
Tetrabromofluorescein	Rat	3	2	63	63	—	21
Indocyanine Green	Dog	1	5	97	97	—	22
Evans Blue	Dog	1	5	4	—	—	23
Sulfonamides							
Sulfanilamide	Rat	50	24	4	3	1	24
Sulfacetamide	Rat	50	24	0.5	0.5	—	24
Sulfapyridine	Rat	50	24	11	—	11	5
Sulfadiazine	Rat	50	24	2	2	—	24
Sulfathiazole	Rat	50	24	2	2	—	5
Sulfamethoxypyridazine	Rat	50	24	8	—	8	24
Sulfadimethoxine	Rat	50	24	11	—	11	24
Sulfadimethoxine glucuronide	Rat	100	24	78	78	—	24
Hormones							
Thyroxine	Rat	0.028	24	24	1	23	25
Thyroxine	Man	0.3[a]	96	10	—	—	26
Triiodothyronine	Dog	0.001	24	27	3	24	27
Progesterone	Rabbit	0.020	5	40	—	40	28
Progesterone	Man	—	—	36	—	36	29
Estrone	Man	0.37[a]	48	50		50	30
Estradiol	Man	0.37[a]	48	50	—	50	30
Testosterone	Man	1	24	13	—	13	31
Norethynodrel	Rabbit	5	7	33	0.3	32.7	32
Norethynodrel	Man	5[a]	24	30	—	—	33
Stilbestrol	Rat	10	24	94	3	91	34
Corticosterone	Cat	0.04	240	86	—	86	35
Corticosterone	Man	—	—	25	—	25	29
Cortisone	Man	—	—	3	—	3	29
Hydrocortisone	Rat	0.25	3	83	—	83	36
Cardiac Glycosides							
Lanatoside A&C	Rat	1	5	70	70	—	37
Digoxin	Rat	1	5	40	11	29	37
Digoxin	Dog	0.1	108	15	1	14	38
Digitoxin	Rat	1	5	10	6	4	37
Digitoxin	Dog	0.05	8	39	3	36	39
Ouabain	Rat	120	4	85	—	—	40
Scillaren A	Rat	1	6	84	84	—	41

[a] Total dose

Compound	Species	Dose mg/kg	Time hr	Percent of Dose Excreted			Reference
				Total	Parent	Metabolite	
Antibiotics							
Methicillin	Rat	300	24	4	—	—	42
Methicillin	Dog	50	24	22	—	—	43
Ampicillin	Rat	100	18	15		—	44
Ampicillin	Rat	100	24	2	—	—	45
Penicillin-V	Rat	100	6	5	—	—	45
Penicillin-T	Rat	100	2.5	20		—	46
Penicillin-G	Dog	50	24	9	—	—	43
Nafcillin	Dog	50	24	97	—	—	43
Cloxacillin	Rat	100	3	21		—	47
Metacycline	Dog	10	24	3	—	—	48
Oxytetracycline	Dog	10	22	2	—	—	48
Demethylchlortetracycline	Dog	10	24	2	—	—	48
Erythromycin	Rat	66	2	15	7	8	49
Erythromycin	Rat	100	4	1	—	—	50
Erythromycin	Man	250[a]	20	13		—	51
Rifomycin	Dog	-	—	70	—	—	5
Oleandomycin	Rat	100	4	10	—		50
Carbomycin	Rat	100	4	0.3	—	—	50
Chloramphenicol	Rat	100	4	30	—	—	52
Chloramphenicol	Man	1000[a]	20	3	—	—	52
Autonomic Agents							
Epinephrine	Rat	0.032	7	10		10	53
Norepinephrine	Rat	0.0005	8	14	—	14	54
Isoproterenol	Rat	0.0005	8	38	—	38	54
Atropine	Rat	1	4	50	—	50	55
Neostigmine	Rat	0.2	6	2.6	0.1	2.5	56
Analgetics							
Morphine	Dog	30	12	40	0.2	39.8	57
Morphine	Monkey	30	4	12	0.1	11.9	58
Methadone	Rat	3	1	20	—	—	59
Methadone	Rat	15	24	9	1.5	7.5	60
Methadone	Dog	10	5	4	1.6	2.4	60
Codeine	Rat	40	3	10	—	10	61
Nalorphine	Dog	30	4	6	0.6	5.4	62
Salicylic acid	Rat	50	24	2	—	2	24
Diuretics							
Chlorothiazide	Dog	20	4	41	—	—	63
Hydrochlorothiazide	Dog	2	1	4	—	—	64
Tranquilizers							
Thioridazine	Rat	100	72	80	0.1	79.9	65
Thiethylperazine	Rat	20	48	87	—	—	66
Prochlorperazine	Rat	25	24	37	—		67
Prochlorperazine	Dog	10	10	63		—	68
Chlorpromazine	Dog	20	10	22	—		68
Trifluoperazine	Dog	2.5	10	72		—	68
CNS Agents							
Amitriptyline	Rat	0.8	6	50	—	50	69
Phenyramidol	Dog	25	7	2		2	70
Carbenoxolone	Rat	50		50		—	71
Methohexital	Rat	10	8	75	—		72
Methohexital	Dog	10	8	20		-	72
Glutethimide	Rat	40	15	60	3	57	73
Miscellaneous Agents							
Coumarin	Rat	50	24	50	—	50	24
Hydroxycoumarin	Rat	50	24	0.2	—	—	24

Compound	Species	Dose mg/kg	Time hr	Percent of Dose Excreted			Reference
				Total	Parent	Metabolite	
Dichloromethotrexate	Rat	24	4	48	—	—	74
Dichloromethotrexate	Rabbit	7.5	4	38	—	—	74
Dichloromethotrexate	Dog	10	4	74	—	—	74
Orphenadrine	Rat	50	2.5	25	—	25	75
Imidazolin chloroterephthalanilide	Rat	0.7	24	10	—	—	76
p-Aminobenzoic acid	Rat	105	24	3	—	—	24
p-Aminohippuric acid	Rat	134	24	2.1	0.4	1.7	24
Anthranilic acid	Rat	101	24	5	—	—	24
Indole	Rat	20	24	7	—	7	24
Phlorizin	Dog	30	6	66	—	—	77
DDT	Rat	146	76	20		20	78
Methoxychlor	Rat	3	6	48	—	48	79
Retinol	Rat	0.25	24	9	1	8	80
Glycyrrhetic acid	Rat	25	24	100	—	100	24
Thiambutosine	Rat	50	24	33	—	33	24

Cox & Wright (37) studied the relative excretion rates of a series of digitalis glycosides in rats and came to the conclusion that the presence of very polar groups enhanced the excretion of these compounds. Lanatosides A and C were both excreted unchanged in bile to the extent of 70 to 80 per cent of the dose within five hours after injection. The presence of glucose in these molecules makes these substances more polar than derivatives devoid of glucose (digitoxin and digoxin). Digoxin is more polar than digitoxin and was excreted to a greater extent. The least polar derivative (digitoxin) was excreted only to the extent of 10 per cent of the administered dose. The role of conjugation was also evident in this work, since with the relatively less polar digoxin and digitoxin, the major portion of the material excreted in the bile was composed of conjugated products.

There are a number of exceptions to some of these generalizations. With the phthalein derivatives, conjugation is presumably necessary for biliary excretion because the two most widely investigated derivatives, phenolphthalein and sulphobromophthalein, are conjugated prior to excretion. However, the tri- and tetra-halogenated fluoresceins and the tetrachlorotetrabromo-derivative are excreted to a major extent in rat bile (greater than 50 per cent in two hours) and in forms which are indistinguishable from the parent compound (21). The dibrominated analogue of sulfobromophthalein is excreted into bile in an unchanged form; at the end of two hours, 83 per cent of this substance is recovered from bile in comparison to 87 per cent for sulfobromophthalein (81). The maximal biliary excretory rate for the dibrominated analogue of sulfobromophthalein is comparable to that found for sulfobromophthalein (82). Indocyanine green (a nonphthalein dye) is also excreted into bile in an unchanged form (22).

Correlation between polarity and excretion into bile might be questioned.

The relative excretion rates of a series of chelated iron complexes was studied by Haddock et al. (83). They found that those chelates possessing a net neutral charge and lipid solubility were excreted more extensively than those possessing a charged anionic site. They felt that the preference for biliary excretion over urinary excretion was due to the relative nonpolar nature of the derivatives themselves.

Species variations in capacity to excrete these substances do seem to exist. (See Table I.) Unfortunately, few comparative studies have been performed with species variation as the parameter being tested. A preliminary report (84) indicates that as far as small aromatic molecules are concerned, little species variation is observed; however, with high molecular weight substances, considerable variation seems evident. With sulfobromophthalein and its dibrominated analogue, the dog has a much lower biliary excretory maximum than does the rat or rabbit (82, 85).

Some of the implications involved in the biliary excretion of chemicals should be mentioned. First of all, following drug content in the feces as an index of oral absorption is not necessarily a valid criteria. Secondly, the presence of an enterohepatic circulation can have a marked effect on the persistence of a drug in the body as was demonstrated with glutethimide in rats (73). The half-life for glutethimide in normal rats was about 24 hours, while in animals with a biliary fistula, the half-life was only about six hours. Thirdly, the toxicity of substances which depend upon the biliary route for their excretion could be modified if this route becomes unavailable. Gibson & Becker (86) have shown that the lethality of ouabain is markedly increased in mice whose bile ducts have been occluded. A similar effect was obtained in mice treated with α-naphthylisothiocyanate or phenylisothiocyanate, substances which produce intrahepatic cholestasis (87, 88). Biliary excretion could influence toxicity in those situations in which biotransformation reactions yielding toxic products occur in the lower portions of the intestinal tract. Thompson et al. (89) demonstrated that with chloramphenicol, the glucuronide was excreted in the bile of rats, was converted to arylamines in the gut, and that these reabsorbed substances exerted a toxic action on the thyroid. Smith (5) has discussed how an analogous mechanism might explain the intestinal carcinogenic activity of 4-aminodiphenyl and 2-acetamidofluorene.

Gastrointestinal Excretion

Although biliary excretion is probably the major route by which systemically absorbed chemicals enter the gastrointestinal tract, it is possible that other avenues exist. In dogs with bile fistulae, 6 per cent of an intravenously administered dose of digoxin was recovered in feces, suggesting extra-biliary excretion (38). There is also data indicating that diphenylhydantoin may be excreted into the intestinal tract by several routes (90). Williams, Millburn & Smith (24) believe that dieldrin is excreted into the intestine through the gut wall.

Shore, Brodie & Hogben (91) have clearly shown the role of pH gradients in the excretion of weak acids and bases into the gastric contents of dogs prepared with Heidenhain fundic pouches. In these preparations, bases with pK_a values greater than five were secreted in high concentrations, whereas weak acids were not secreted to any extent. Steady-state experiments (92), designed to study intestinal absorption of drugs, also yielded data which were consistent with these findings. Schanker (93) has demonstrated the excretion of quinine into the rat colon in accordance with the pH partition hypothesis.

The secretion of drugs into the lumen of the gastrointestinal tract has its counterpart in ruminants, as recognized by Reid et al. (94), while measuring extracellular volume with antipyrine. In studying methyridine, it was found that this anthelmintic entered all levels of the gastrointestinal tract of sheep in effective concentrations following parenteral administration (95). Another anthelmintic, 2,4-diiodo-nitrophenol is effective parenterally in dogs (96) and turkeys (97) against hookworms and tapeworms, respectively, presumably because the compound is excreted into the gastrointestinal and respiratory tracts.

One question which arises is whether compounds are secreted into the rumen-reticulum directly, or whether they gain access to the rumen contents via saliva, the daily volume of which is approximately 100 liters in cows. Using acutely fistulated calves with ligated esophagi, intravenously administered sulfonamides, antipyrine, and ephedrine were found in bovine rumen-reticular fluid 10 minutes after intravenous injection (98). Non-ionic diffusion was suggested as being responsible. The capacity of the rumen microflora to digest cellulose was significantly depressed following the intravenous injection of sulfamethazine (99). More recently, preliminary experiments were reported which dealt with the diffusion of salicylic acid, benzoic acid, sulfanilamide, antipyrine, aminopyrine, and N-acetyl-4-aminoantipyrine into buffered solutions placed in the rumen (100). Ratios of drug concentration in the rumen to the unbound concentration in plasma were in good agreement with the ratios predicted from nonionic diffusion. Increasing the pH of the rumen contents resulted in increased concentration ratios of benzoic and salicylic acids in the rumen as compared to plasma. From the standpoint of drug distribution, the passage of compounds into the rumen and reticulum represents a dilution factor which approximates the extracellular water space.

Secretion into the other two stomachs of ruminants has not been studied extensively. At the present time there is no known secretory function of the omasum. The abomasum, on the other hand, corresponds to the stomach of non-ruminants, and secretes an acid, pepsin-containing fluid resembling gastric juice, which apparently is stimulated by acetic, propionic and butyric acid, and histamine (101, 102). Non-ionic diffusion presumably would occur as it does in simple-stomached animals (91).

Reference to the salivary excretion of drugs in different species is given

in the comprehensive review by Afonsky (103). Drug passage into saliva was studied by procedures similar to those used for mammary diffusion (104). In the alkaline saliva of goats and cows, weak acids such as sulfadiazine, sulfamethazine, sulfanilamide and several barbiturates were found in concentrations greater than their nonprotein bound levels in plasma. Sulfacetamide did not attain its predicted concentration apparently because of its low lipid solubility. In comparison, the neutral or slightly acid saliva of man contains sulfonamides and barbiturates in concentrations below the unbound fraction in plasma (105). Noach et al. (90) found a high concentration of diphenylhydantoin in the rat salivary gland; in cats, the compound was apparently excreted into the saliva in an unchanged form. These workers point out the possible role of this route of excretion as a factor in the development of gingival hyperplasia.

Penicillin (106–108), dihydrostreptomycin (108), and tetracyclines (108, 109) are also found in saliva. With the penicillins, the appearance varies with time, and with the particular derivative. The methoxyphenyl- and ethoxyphenyl derivatives, and the procaine salt were present in high concentrations; and benzathine penicillin was observed for 24 hours or more at concentrations about one-third of the concurrent serum levels (107). With penicillin G, there is evidence for an active secretory mechanism, since $HgCl_2$ and phenol red, instilled into the gland, reduced penicillin concentrations in saliva. Furthermore, probenecid substantially reduced the penicillin excretion (108), but not the salicylate excretion (110).

Sweat

The excretion of drugs via sweat was reviewed in 1911 by Tachau (111), who noted that interest was expressed in this subject as early as 1844. Prior to 1911, iodine, bromine, benzoic acid, salicylic acid, lead, arsenic, boron, mercury, iron, alcohol, and antipyrine were reputed to appear in human sweat. Tachau (111) claimed that iodine, bromine, boric acid, phenol, salicylic acid, phenyl salicylate, antipyrine, and methylene blue were present, but that arsenic, benzoic and hippuric acids, quinine, acetanilid, and phenolphthalein were not found. Koch (112) reported the presence of thiocyanate, methenamine, and antipyrine in sweat, but not salicylic acid, despite its lipid solubility and presumed ability to traverse biological membranes. With a forensic viewpoint in mind, Weinig & Jahn (113) reviewed the literature on the excretion of ethyl alcohol, antipyrine, arsenic, boric acid, bromine, iodine, mercury, thiocyanate, penicillin, phenol, salicylic acid, phenyl salicylate, methenamine, and sulfonamides in human sweat. They found barbital and sulfonmethane in human sweat. To this must be added quinine and fluorescein (114), sulfanilamide (115), dehydroascorbic acid and nicotinamide (116), methylene blue, and a number of other dyes (117), urea, sulfanilamide, sulfapyridine, sulfathiazole, sulfadiazine and *p*-aminohippuric acid (118), uric acid (119), and histamine (120). The number of

ions which have been found in sweat is equally imposing. Aside from the three of intense research interest (Na^+, K^+, and Cl^-), there are: calcium (121–123), iron (123–125), magnesium, phosphorus, copper, manganese (123), rubidium (126), and zinc (125). From the nutritional standpoint, the loss of iron, calcium, and zinc in sweat may be of substantial concern when the dietary supply of these elements is low, and the environment necessitates profuse sweating. For example, with iron concentrations of 2 to 37 mcg/100 ml, and a total volume of sweat of 10 liters per day, it is possible for cutaneous iron loss to be one of the contributory factors in the genesis of iron deficiency anemia (124). Similar considerations apparently apply to zinc (125) and calcium (121). The chelating agent, deferoxamine, does not increase the excretion of iron in sweat (127).

The question of the mechanism of excretion of drugs and ions in sweat is complicated by the lack of a clear picture of just how the eccrine sweat gland functions. A common view (128) seems to be that the precursor to sweat enters the fundus of the gland from the extracellular fluid. During its passage through the duct to the skin surface, various substances are reabsorbed such as water, and ions, such as Na^+. Recently, a Na-K activated ATPase was demonstrated in the eccrine gland of monkeys (129). Ouabain inhibits this enzyme, and its presence is taken as an enzymatic basis for active transport of Na^+ by the gland. An interesting hypothesis of the mechanism of sweat formation was advanced by Gordon & Cage (130), in which they attempted to explain the high lactate concentration of sweat, Na^+ reabsorption, and the formation of a hypotonic solution.

In man, sweat is usually hypotonic to plasma, while that from the foot pad of the cat is hypertonic (128, 131). The Na^+, and Cl^- content of cat's sweat is higher than man's. Furthermore, cat sweat is mildly alkaline, probably because of its bicarbonate content, while human sweat is normally slightly acid (132). The pH of human sweat also varies considerably depending on whether the flow has been induced by exercise, by heat, or by drugs such as pilocarpine. Thermal stress tends to result in a rise in pH, while pilocarpine- or acetylcholine-induced sweat causes an even greater rise, sometimes to pH levels greater than 7.0 (133). The pH question is important, because most studies involving the secretion of drugs utilize either heat or cholinergic agents to induce sweating. Changing pH values can alter drug ionization and distribution. Other features of sweat gland function which make it difficult to quantify drug excretion are: (*a*) volume of sweat secreted (134); (*b*) gland fatigue (135); and (*c*) endocrine factors (136–138).

Despite the many factors involved, Thaysen & Schwartz (118) showed a relationship in man between the sweat/plasma (S/P) concentration ratios and the pK_a values for several substances (sulfanilamide, sulfapyridine, sulfathiazole, sulfadiazine and *p*-amino hippurate), although the observed S/P ratios were consistently below the theoretically derived ratios. Furthermore, the S/P ratios were not influenced either by fairly wide variations in

the plasma level of the drugs, or by the rate of sweating, and it was inferred that these compounds enter sweat by nonionic diffusion. Unfortunately, the pH of the sweat was not measured in these experiments. In spite of this, the findings were generally consistent with nonionic diffusion.

With ethanol, the S/P ratios for man and cat are about 0.8 to 1.1; for antipyrine, 0.6 to 9.0; creatine, 0.2; thiourea, 0.8; ^{14}C-methylurea and ^{14}C-acetamide, 1.0 to 1.1; and urea, 1 to 1.4 (139). Thaysen & Schwartz found no positive correlation between osmolality of sweat and the S/P ratios for these compounds, and the oil/water solubility ratios showed no clear relationship to the S/P ratios of these substances. From the S/P ratios of 1 to 1.4 for urea, it has been suggested that some back diffusion of water takes place in the gland. However, Brusilow (140) has presented evidence for a possible extra-plasma source of urea, because the S/P ratios of injected ^{14}C-urea were 1.0 in man and the cat, while the S/P ratios for chemically determined urea were 1.2 to 1.4. In studies involving prolonged exercise, the S/P ratio for urea decreased from initial values of 1.5 to 1 over a two to three-hour period, and the ratio was not affected either by a fourfold increase in the plasma urea level, by a doubling of the sweating rate, or by a reduction of plasma Cl^- concentration from 50 to 15 meq/l (141). These workers concluded that urea entered sweat by a process of passive diffusion, and that water reabsorption is unlikely.

Milk

Although the secretion of drugs into milk has been the subject of intermittent study for over 80 years, the principal concerns during the last decade have been the residue problem resulting from pesticide application, the use of antibacterial agents for the treatment of bovine mastitis, and systemic therapy with various drugs. A large number of drugs or their metabolites, such as sulfonamides, sulfones, the antibiotics, nitrofurans, barbiturates, methylpentynol, certain antihistamines, phenolphthalein, isoniazide, phenothiazine, methyridine, pyrimethamine, quinine, phenol, antipyrine, chloral, urea, salicylic and acetylsalicylic acids, phenylbutazone, mandelic acid, atropine, caffeine, coumarin, chlorpromazine, methenamine, theobromine, thiabendazole, aloin, estrogens, and probably certain opiates, gain access to milk following systemic absorption in one or more of the following species: man, cattle, goats, sheep, dogs, and rats (142–145). Of the reports cited, the article by Rasmussen (143) is the most comprehensive, and contains much of his experimental work over the past 11 years. There has also been a series of reviews dealing specifically with various facets of the contamination of milk by antibiotics (146–151).

Extending the concepts of nonionic diffusion (118, 153), Rasmussen (153) demonstrated that the excretion of certain sulfonamides into bovine milk could be explained by this mechanism. Later studies (144, 154–160), indicated that the steady-state concentrations of certain weak organic acids and

bases in cows' or goats' milk were in accord with that predicted by nonionic diffusion. With sulfonamides, penicillin, penethamate, erythromycin, quinine, antipyrine, urea, ethanol, aminopyrine, benzoic and salicylic acids, pentobarbital and phenobarbital, the milk-to-plasma (M/P) ratios of unbound drugs were in close agreement with the theoretically derived ratio (161). These studies also showed that the M/P ratios were independent of the plasma concentration and the volume of milk secreted. Increasing the milk pH, however, increased the M/P ratios for acidic drugs, decreased the ratios for basic drugs, and vice versa (144, 153). In bovine and ovine mastitis, milk pH tends to rise, resulting in an increased level of sulfonamide in the milk (162). It should also be noted that even with complete milking, the fraction of drug excreted via the udder is small compared to the total dose (144).

Although the steady-state approach to studying drug passage into the milk has provided some useful information, it does not rule out other mechanisms, nor does it provide much information regarding the kinetics of drug penetration of the gland. Another problem with this approach is the limitation attainable with toxic compounds. In this regard, mammary gland perfusion would appear to be a useful technique. In addition, the use of inhibitors of active transport processes, or the instillation of $HgCl_2$ and phenol red into the gland might be useful procedures (108, 110).

An apparent exception to nonionic diffusion is oxytetracycline, which appears in milk at concentrations above the values predicted by nonionic diffusion (144), possibly because of calcium chelation. Sulfonamides also present an interesting problem because the acetylated derivatives tend to persist in cows' milk for a longer period than do the parent compounds. Presumably, the presence of acetylated sulfonamides is a result of diffusion from plasma. However, Rasmussen & Linzell (163) found that acetylation of sulfanilamide occurred within the perfused goat udder. If these findings are common to other species, then the distribution and excretion of acetylated derivatives will require more extensive investigation.

As pointed out by Myers (150), the problem of controlling antibiotics in milk is associated with the control of bovine mastitis, which is usually treated by the intramammary infusion of antibacterial solutions and ointments. A novel approach to the practical problem of determining drug retention in the udder is the incorporation of certain triphenylmethane dyes (Food Green 4, Food Blue 2, and Food Blue 3) into antibacterial preparations (164). Such dyes, if they have retention properties similar to an antibacterial agent, would serve as a visible marker, which hopefully would permit reliable assessment of when the udder ceased shedding the compound in the milk. Reasonable agreement was found in the milk between the time-concentration curves for penicillin, oxytetracycline, and sulfonamides on the one hand, and the dyes on the other hand. In each case, the dye was demonstrable in the milk for at least as long as the drugs. However, the percentage

recovery of the dyes from the milk was not in close agreement with the drug recovery, presumably because of different rates of systemic absorption, or "back diffusion," a property which has already been shown to exist (153).

The excretion of insecticides in milk following ingestion or topical application is well known, and is the subject of recent reviews (166–168). Other pesticides have recently been reported in milk, including the benzazamide metabolites of guthion (169), heptachlor epoxide (170), and carbaryl and metabolites (171). While the detailed mechanism of insecticide excretion in milk has not been studied, it seems that the distribution of these compounds is a function of their lipid solubility. For example, Bruce, Link & Decker (170) showed a parallel and linear relationship between the log of the dose of heptachlor epoxide in the diet, and the log of concentration in both body fat and butterfat. With bromide excretion in milk, it was shown that the ratio of bromide in milk to that in the diet was higher when the fumigant, methyl bromide, was fed to cows, than when sodium bromide was fed at the same levels (172). Although the relatively polar compound, hydroxy-DDT, appeared in bovine milk at levels of 1 to 2 ppm in the diet, the amount of hydroxy-DDT present in milk was below that which would be obtained with equivalent levels of DDT; the implication is that the more polar compound would be more water soluble, and therefore less likely to cross the lipid membrane (173). The generalization by Zweig et al. (174) regarding DDT—that the concentration of DDT excreted is proportional to the level of DDT in the ration—might also be applicable to the other chlorinated hydrocarbon insecticides.

An interesting experimental observation regarding insecticides in milk was reported by Street et al. (175) in which it was shown that the administration of DDT would reduce the storage and retention of dieldrin in rats, sheep and swine, and that the feeding of DDT to ewes resulted in a decrease of the amount of dieldrin in the milk by a factor of about one-third. DDT also reduced the dieldrin residue in pork fat.

The use of herbicides in agriculture naturally leads to questions regarding their excretion into milk. There seems to be a paucity of information in this area, although some herbicides at least, do have a fairly high lipid solubility (176). However, on the basis of limited trials, several herbicides, given in a total dose of 454 mg over four days, have been found to be absent (less than 0.05 ppm) from cows' milk (177–179). In another study, ^{14}C-diquat and paraquat were given in single doses (5 to 20 mg/kg) orally to cattle. Less than 0.02 per cent of the radioactivity was excreted in the milk, primarily as metabolic products (180).

Dimethylsulfone has been reported in pasteurized market milk, in concentrations of 5 to 10 mg/l (181). However, whether this substance was actually derived from dimethylsulfoxide is not clear, since dimethylsulfone was found in cows' blood many years ago (182). Dimethylsulfide has also been found in milk, and has been considered one of its flavor constituents

(183). The latter two observations were made long before the recent applications of dimethylsulfoxide.

An interesting example of the toxic principle of a plant being excreted in milk is that of *Eupatorium urticaefolium* (white snakeroot) and *Apolopappus heterophyllus* (rayless goldenrod). These plants contain tremetol, a high molecular weight alcohol, which causes a disease in cattle and man characterized by acidosis and ketosis. Hartmann et al. (184) described three human cases which were traced to cows grazing on snakeroot. Toxic substances from other plants, such as *Colchicum* and *Laburnum sp.*, also may be transmitted into milk (185). Peanuts or groundnuts which are infected by certain strains of *Aspergillus flavus* may contain toxic quantities of aflatoxin. The milk from cows fed contaminated groundnuts contained a substance which produced effects in ducklings identical to those caused by aflatoxin (186). Later studies established the presence of aflatoxin "M," a metabolite of aflatoxin, in the milk (187).

Of gastronomic, if not toxicologic, concern is the observation that benzylthiocyanate, a constituent of the weed *Coronopus didymus* (bitter cress or land cress, Australia) yields off-flavor, unpalatable milk when cattle graze on pastures infested with this plant (188). Apparently, benzylthiocyanate is the responsible agent, since its addition to untainted milk resulted in the characteristic flavor. Although identification and quantification of the compound in milk, blood, or other tissues was not done, the evidence suggests that benzylthiocyanate enters milk. Other plant substances, whose chemical natures have not been elucidated, may discolor milk or alter its taste (189).

Despite the numerous reports of the excretion of various compounds in milk, there has been little attention directed toward colostrum. During the colostral phase, the mammary gland is felt to be more permeable to a number of solutes, and this is borne out by the observations that zinc (190) and iron (191) are present in colostrum at concentrations above those in normal milk.

Tears

The lacrimal fluid is isotonic to normal saline (192), contains Na^+, K^+ and Cl^- as its principal ions (193), and has a pH ranging from 7.1 to 8.0, with a mean of 7.49 (194). The tear/plasma ratio for urea is 1 (193, 195), despite fivefold changes in the rate of tear flow, or a fourfold variation in plasma level, suggesting simple diffusion as the operant process (195). Several workers report the presence of reducing sugars or glucose (193, 196). Increased levels are claimed to be present in diabetics (197), although Balik (198) found that the glucose in lacrimal fluid was only 10 per cent of the blood level, and that the intravenous injection of glucose did not produce an increased level in the tears (199). Sulfonamides also appear in lacrimal fluid at concentrations which are not directly related to the volume of secretion (200). Pilocarpine and atropine increase and decrease the volume of lacrimal

secretion, respectively, and this in turn, alters the concentration of glucose and ions (201, 202). Using bioassay techniques, it was reported that an acetylcholine-like and a sympathin-like substance could be detected in lacrimal fluid, and that the amount of these substances was altered in glaucoma (203).

Lung

Excretion of volatile anesthetics (204, 205), certain alcohols, and other volatile agents via the lung is well known, and no attempt will be made to discuss them here.

Many investigators have observed that dimethylsulfoxide (DMSO) or its metabolites are partly excreted by the lung following systemic administration. In cats, the exhaled gases contained a metabolite, dimethylsulfide, and apparently no DMSO (206). Since the expired air containing the sulfide was collected immediately after intravenous administration of uncontaminated DMSO, there must be a rapid reducing system in this species. In rats, only 6 per cent of a topically applied dose was found in expired air in 24 hours, while less than 1 per cent of an intraperitoneal dose was found in a 3-hour period (207).

Selenium is of interest, since a portion of injected selenate is excreted via the lungs as dimethylselenide. McConnell (208) found in rats that 3 to 10 per cent of administered selenate could be recovered in expired air. The exhaled compound was presumed to be dimethylselenide. Later, McConnell & Portman (209) showed that about 75 per cent of injected dimethylselenide was exhaled within 6 hours, and that the exhaled product resulting from selenate injection was, indeed, the dimethyl derivative. With selenite injection in rats, Schultz & Lewis (210) found 17 to 52 per cent exhaled in 8 hours, while Heinrich & Kelsey (211) noted that 7.5 per cent was exhaled in mice in 48 hours. These workers observed a significant loss of selenium when tissues were dried. From this, they inferred that volatile selenium compounds were present in substantial amounts, the loss of which could lead to analytical errors.

Since tellurium is related to selenium, it has long been presumed to be excreted in the lung as the dimethyl derivative (208, 209). Sandratskaya (212) noted a garlic-like odor to tissues and expired air, following tellurium administration, and found that 2.7 per cent of the orally ingested tellurium was excreted via the respiration. Identification of metabolites apparently was not reported.

Reproductive Tract

Characterization of the luminal fluids of the uterus has received increasing attention in recent years, particularly with regard to ionic composition and pH (213–216). In most species, except the monkey, pilocarpine causes an increase in the volume of luminal secretions (217). Largely as a result of the

interest in teratology, there is considerable information regarding endogenous substances present in uterine "milk" (218).

Reports concerning the presence of systemically administered drugs in semen are sparse; the question of the site of excretion is complicated by the several glands along the male reproductive tract. Ethyl alcohol has long been known to pass into semen (219), as do the sulfonamides (220). Two additional studies show that sulfisoxazole enters the prostatic secretion of men (221) and dogs (222). Several common antibiotics gain access to prostatic fluid and semen (222b).

Homogentisic acid reportedly accumulates in the semen of bulls that have been fed *Litsoca glutinosa*, which contains this compound as a normal constituent (223). Ergothioneine is a normal constituent of seminal plasma of several species, and when S^{35}-ergothioneine was fed to boars, it apparently passed unchanged into the semen in concentrations which were substantially higher than those in blood (224). As in the uterus, pilocarpine increases the volume of prostatic secretions (225); atropine decreases the volume of secretion of boar semen, increases, relatively, the sperm count, and increases the concentration of solutes (226).

LITERATURE CITED

1. Weiner, I. M., *Ann. Rev. Pharmacol.*, **7**, 39–56 (1967)
2. Sperber, I., *Pharmacol. Rev.*, **11**, 109–34 (1959)
3. Brauer, R. W., *J. Am. Med. Assoc.*, **169**, 1462–66 (1959)
4. Schanker, L. S., *Pharmacol. Rev.*, **14**, 501–30 (1962)
5. Smith, R. L., *Progr. Drug Res.*, **9**, 299–360 (1966)
6. Roberts, R. J., Klaassen, C. D., Plaa, G. L., *Proc. Soc. Exptl. Biol. Med.*, **125**, 313–16 (1967)
7. Hart, L. G., Schanker, L. S., *Am. J. Physiol.*, **211**, 643–46 (1966)
8. Schanker, L. S., Solomon, H. M., *Am. J. Physiol.*, **204**, 829–32 (1963)
9. Schanker, L. S., in *The Biliary System*, 469–80 (Taylor, W., Ed., Blackwell, Oxford, 712 pp., 1965)
10. Schanker, L. S., Hogben, C. A. M., *Am. J. Physiol.*, **200**, 1087–90 (1961)
11. McChesney, E. W., Hoppe, J. O., *Arch. Intern. Pharmacodyn.*, **99**, 127–40 (1954)
12. Free, A. A., Page, J. E., Woollett, E. A., *Biochem. J.*, **48**, 490–94 (1951)
13. Crismer, R., *Arch. Intern. Pharmacodyn.*, **72**, 138–60 (1946)
14. McChesney, E. W., Hoppe, J. O., *Arch. Intern. Pharmacodyn.*, **142**, 562–71 (1963)
15. Visek, W. J., Liu, W. C., Roth, L. J., *J. Pharmacol. Exptl. Therap.*, **117**, 347–57 (1956)
16. Pekanmaki, K., Salmi, H. A., *Acta Pharmacol. Toxicol.*, **18**, 133–40 (1961)
17. Kim, J. H., Hong, S. K., *Am. J. Physiol.*, **202**, 174–78 (1962)
18. Monroe, L. S., Kittinger, A. L., *J. Lab. Clin. Med.*, **58**, 468–76 (1961)
19. Krebs, J. S., *Am. J. Physiol.*, **197**, 292–96 (1959)
20. Javitt, N. B., *Am. J. Physiol.*, **208**, 555–62 (1965)
21. Webb, J. N., Fonda, M., Brouwer, E. A., *J. Pharmacol. Exptl. Therap.*, **137**, 141–47 (1962)
22. Wheeler, H. O., Cranston, W. I., Meltzer, J. I., *Proc. Soc. Exptl. Biol. Med.*, **99**, 11–14 (1958)
23. Miller, A. T., Jr., *Am. J. Physiol.*, **151**, 229-33 (1947)
24. Williams, R. T., Millburn, P., Smith, R. L., *Ann. N. Y. Acad. Sci.*, **123**, 110–24 (1965)
25. Flock, E. V., Bollman, J. L., *Biochem. J.*, **84**, 621–26 (1962)
26. Johnson, P. C., Beierwaltes, W. H., *J. Lab. Clin. Med.*, **41**, 676–83 (1953)
27. Flock, E. V., Bollman, J. L., Grindlay, J. H., *Am. J. Physiol.*, **189**, 420–24 (1957)
28. Taylor, W., Scratcherd, T., *Biochem. J.*, **97**, 89–94 (1965)
29. Sandberg, A. A., Slaunwhite, W. R., Jr., *J. Clin. Endocrinol. Metab.*, **16**, 923–24 (1956)
30. Sandberg, A. A., Slaunwhite, W. R., Jr., *J. Clin. Invest.*, **36**, 1266–78 (1957)
31. Sandberg, A. A., Slaunwhite, W. R., Jr., *J. Clin. Invest.*, **35**, 1331–39 (1956)
32. Arai, K., Golab, T., Layne, D. S., Pincus, G., *Endocrinology*, **71**, 639–48 (1962)
33. Layne, D. S., Golab, T., Arai, K., Pincus, G., *Biochem. Pharmacol.*, **12**, 905–11 (1963)
34. Fischer, L. J., Millburn, P., Smith, R. L., Williams, R. T., *Biochem. J.*, **100**, 69P (1966)
35. Taylor, W., Scratcherd, T., *Biochem. J.*, **86**, 114–19 (1963)
36. Wyngaarden, J. B., Peterson, R. E., Wolff, A. R., *J. Biol. Chem.*, **212**, 963–72 (1955)
37. Cox, E., Wright, S. E., *J. Pharmacol. Exptl. Therap.*, **126**, 117–22 (1959)
38. Harrison, C. E., Jr., Brandenberg, R. O., Ongley, P. A., Orvis, A. L., Owen, C. A., Jr., *J. Lab. Clin. Med.*, **67**, 764–77 (1966)
39. Katzung, B. G., Meyers, F. H., *J. Pharmacol. Exptl. Therap.*, **149**, 257–62 (1965)
40. Farah, A., *J. Pharmacol. Exptl. Therap.*, **86**, 248–57 (1946)
41. Simon, M., Wright, S. E., *J. Pharm. Pharmacol.*, **12**, 767–68 (1960)
42. Harrison, P. M., White, J. A., Stewart, G. T., *Brit. J. Pharmacol.*, **15**, 571–73 (1960)
43. Classman, J. M., Warren, G. H., Rosenman, S. B., Agersborg, H. P. K., *Toxicol. Appl. Phamacol.*, **6**, 220–31 (1964)
44. Stewart, G. T., Harrison, P. M., *Brit. J. Pharmacol.*, **17**, 414–19 (1961)
45. Acred, P., Brown, D. M., Turner, D. H., Wilson, M. J., *Brit. J. Pharmacol.*, **18**, 356–69 (1962)
46. Harrison, P. M., Stewart, G. T., *Brit. J. Pharmacol.*, **17**, 420–23 (1961)
47. Acred, P., Brown, D. M., *Brit. J. Pharmacol.*, **21**, 339–54 (1963)

48. Von Wittenau, M. S., Yeary, R., *J. Pharmacol. Exptl. Therap.*, **140**, 258–66 (1963)
49. Lee, C. C., Anderson, R. C., Chen, K. K., *J. Pharmacol. Exptl. Therap.*, **117**, 265–73 (1956)
50. Kazenko, A., Sorenson, O. J., Jr., Wolf, L. M., Dill, W. A., Galbraith, M., Glazko, A. J., *Antibiot. Chemotherapy*, **7**, 410–18 (1957)
51. Takimura, Y., Lopez-Belio, M., *Antibiotic Med.*, **1**, 561–66 (1955)
52. Glazko, A. J., Wolf, L. M., Dill, W. A., Bratton, A. C., Jr., *J. Pharmacol. Exptl. Therap.*, **96**, 445–59 (1949)
53. Hertting, G., La Brosse, E. H., *J. Biol. Chem.*, **237**, 2291–95 (1962)
54. Hertting, G., *Biochem. Pharmacol.*, **13**, 1119–28 (1964)
55. Kalser, S. C., Kelvington, E. J., Randolph, M. M., Santomenna, D. M., *J. Pharmacol. Exptl. Therap.*, **147**, 252–59 (1965)
56. Calvey, T. N., *Brit. J. Pharmacol.*, **28**, 348–59 (1966)
57. Woods, L. A., *J. Pharmacol. Exptl. Therap.*, **112**, 158–75 (1954)
58. Mellett, L. B., Woods, L. A., *J. Pharmacol Exptl. Therap.*, **116**, 77–83 (1956)
59. Elliott, H. W., Elison, C., *J. Pharmacol. Exptl. Therap.*, **131**, 31–37 (1961)
60. Way, E. L., Signorotti, B. T., March, C. H., Peng, C. T., *J. Pharmacol. Exptl. Therap.*, **101**, 249–58 (1951)
61. Latham, M. E., Elliott, H. W., *J. Pharmacol. Exptl. Therap.*, **101**, 259–67 (1951)
62. Woods, L. A., Muehlenbeck, H. E., *J. Pharmacol. Exptl. Therap.*, **120**, 52–57 (1957)
63. Baer, J. E., Leidy, H. L., Brooks, A. V., Beyer, K. H., *J. Pharmacol. Exptl. Therap.*, **125**, 295–302 (1959)
64. Pratt, E. B., Aikawa, J. K., *Am. J. Physiol.*, **202**, 1083–86 (1962)
65. Zehnder, K., Kalberer, F., Kreis, W., Rutschmann, J., *Biochem. Pharmacol.*, **11**, 535–50 (1962)
66. Zehnder, K., Kalberer, F., Rutschmann, J., *Biochem. Pharmacol.*, **11**, 551–56 (1962)
67. Phillips, B. M., Miya, T. S., *J. Pharm. Sci.*, **53**, 1098–1101 (1964)
68. Van Loon, E. J., Flanagan, T. L., Novick, W. J., Maass, A. R., *J. Pharm. Sci.*, **53**, 1211–13 (1964)
69. Cassano, G. B., Sjostrand, S. E., Hansson, E., *Psychopharmacologia*, **8**, 1–11 (1965)
70. Miller, L. D., *Toxicol. Appl. Pharmacol.*, **4**, 190–99 (1962)
71. Iveson, P., Parke, D. V., Williams, R. T., *Biochem. J.*, **100**, 28P (1966)
72. Welles, J. S., McMahon, R. E., Doran, W. J., *J. Pharmacol. Exptl. Therap.*, **139**, 166–71 (1963)
73. Keberle, H., Hoffmann, K., Bernhard, K., *Experientia*, **18**, 105–11 (1962)
74. Oliverio, V. T., Davidson, J. D., *J. Pharmacol. Exptl. Therap.*, **137**, 76–83 (1962)
75. Hespe, W., De Roos, A. M., Nauta, W. T., *Arch. Intern. Pharmacodyn.*, **156**, 180–200 (1965)
76. Kreis, W., Bloch, R., Warkentin, D. L., Burchenal, J. H., *Biochem. Pharmacol.*, **12**, 1165–72 (1963)
77. Jenner, F. A., Smyth, D. H., *J. Physiol. (London)*, **146**, 563–71 (1959)
78. Burns, E. C., Dahm, P. A., Lindquist, D. A., *J. Pharmacol. Exptl. Therap.*, **121**, 55–62 (1957)
79. Weikel, J. H., Jr., *Arch. Intern. Pharmacodyn.*, **110**,, 423–32 (1957)
80. Goodman, D. S., Huang, H. S., Shiratori, T., *J. Lipid Res.*, **6**, 390–96 (1965)
81. Javitt, N. B., *Proc. Soc. Exptl. Biol. Med.*, **117**, 254–57 (1964)
82. Klaassen, C. D., Plaa, G. L., *Pharmacologist*, **9**, 241 (1967)
83. Haddock, E. P., Zapolski, E. J., Rubin, M., Princiotto, J. V., *Proc. Soc. Exptl. Biol. Med.*, **120**, 663–68 (1965)
84. Abou-El-Makarem, M. M., Millburn, P., Smith, R. L., Williams, R. T., *Biochem. J.*, **99**, 3P (1966)
85. Klaassen, C. D., Plaa, G. L., *J. Appl. Physiol.*, **22**, 1151–55 (1967)
86. Gibson, J. D., Becker, B. A., *J. Pharm. Sci.*, **56**, 1503–5 (1967)
87. Becker, B. A., Plaa, G. L., *Toxicol. Appl. Pharmacol.*, **7**, 708–18 (1965)
88. Becker, B. A., Plaa, G. L., *Toxicol. Appl. Pharmacol.*, **7**, 804–11 (1965)
89. Thompson, R. Q., Sturtevant, M., Bird, O. D., Glazko, A. J., *Endocrinology*, **55**, 665–81 (1954)
90. Noach, E. L., Woodbury, D. M., Goodman, L. S., *J. Pharmacol. Exptl. Therap.*, **122**, 301–14 (1958)
91. Shore, P. A., Brodie, B. B., Hogben, C. A. M., *J. Pharmacol. Exptl. Therap.*, **119**, 361–69 (1957)
92. Hogben, C.A.M., Tocco, D. J., Brodie, B. B., Schanker, L. S., *J. Pharmacol. Exptl. Therap.*, **125**, 275–82 (1959)
93. Schanker, L. S., *J. Pharmacol. Exptl. Therap.*, **126**, 283–90 (1959)
94. Reid, J. T., Balch, C. C., Head, M. J., Stroud, J. W., *Nature*, **179**, 1034 (1957)

95. Broome, A. W. J., *Brit. J. Pharmacol.*, **17**, 327–38 (1961)
96. Wood, I. B., Pankavich, J. A., Wallace, W. S., Thorson, R. E., Burkhart, R. L., Waletsky, E., *J. Am. Vet. Med. Assoc.*, **139**, 1101–5 (1961)
97. Boisvenue, R. J., *Am. J. Vet. Res.*, **24**, 1038–43 (1963)
98. Corker, E., Stowe, C., *Federation Proc.*, **26**, 542, #1597 (1967)
99. Egetoft, V., Rasmussen, F., *Nord. Veterinarmed.*, **15**, 313–31 (1963)
100. Miller, G. E., Corker, E. C., Stowe, C. M., *Proc. Am. Dairy Sci. Assoc., 62nd Ann. Meeting*, 76 (1967)
101. Ash, R. W., *J. Physiol. (London)*, **157**, 185–207 (1961)
102. Hill, K. J., in *Physiology of Digestion in the Ruminant, 2nd, Intern. Symp.*, 221–30 (Dougherty, R. W., Ed., Butterworths, Washington, 480 pp., 1965)
103. Afonsky, D., *Saliva and its Relation to Oral Health* (Univ. Alabama Press, University, Alabama, 785 pp., 1961)
104. Rasmussen, F., *Acta Pharmacol Toxicol.*, **21**, 11–19 (1964)
105. Killmann, S. A., Thaysen, J. H., *Scand. J. Clin. Lab. Invest.*, **7**, 86–91 (1955)
106. Bender, I. B., Pressman, R. S., Tashman, S. G., *J. Am. Dental Assoc.*, **46**, 164–70 (1953)
107. Adler-Hradecky, C., Kelentey, B., *Nature*, **198**, 792–93 (1963)
108. Borzelleca, J. F., Cherrick, H. M., *J. Oral Therap. Pharmacol.*, **2**, 180–87 (1965)
109. Radisson, J. J., Bartley, E. E., Fountaine, F. C., Atkeson, F. W., *Science*, **122**, 514–15 (1955)
110. Borzelleca, J. F., Doyle, C. H., *J. Oral Therap. Pharmacol.*, **3**, 104–11 (1966)
111. Tachau, H., *Arch. Exptl. Pathol. Pharmakol.*, 66, 334–46 (1911)
112. Koch, *Arch. Dermatol. Syph.*, **177**, 163–66 (1938)
113. Weinig, E., Jahn, G., *Deut. Z. Ges. Gerichtl. Med.*, **43**, 370–73 (1954)
114. Comaish, J. S., Shelley, W. B., *J. Invest. Dermatol.*, **44**, 279–81 (1965)
115. Cornbleet, T., *Arch. Dermatol. Syph.*, 41, 912–18 (1940)
116. Sargent, F., Robinson, P., Johnson, R. E., *J. Biol. Chem.*, **153**, 285–94 (1944)
117. Hurley, H. J., Witkowski, J., *J. Invest. Dermatol.*, **36**, 259–72 (1961)
118. Thaysen, J. H., Schwartz, I. L., *J. Exptl. Med.*, **98**, 261–68 (1953)
119. Danton, R. A., Nyhan, W. L., *Proc. Soc. Exptl. Biol. Med.*, **121**, 270–71 (1966)
120. Garden, J. W., *J. Appl. Physiol.*, **21**, 631–35 (1966)
121. Consolazio, C., Matoush, L., Nelson, R., Hackler, L., Preston, E., *J. Nutr.*, **78**, 78–88 (1962)
122. Consolazio, C., Matoush, L., Nelson, R. A., Isaac, G. J., Canham, J. E., *Am. J. Clin. Nutr.*, **18**, 443–48 (1966)
123. Mitchell, H. H., Hamilton, T. S., *J. Biol. Chem.*, **178**, 345–61 (1949)
124. Coltman, C. A., Rowe, N. J., *Am. J. Clin. Nutr.*, **18**, 270–74 (1966)
125. Prasad, A., Schulert, A. R., Sandstead, H. H. Miale, A., Farid, Z., *J. Lab. Clin. Med.*, 62, 84–89 (1963)
126. Berenson, G. S., Burch, G. E., *J. Lab. Clin. Med.*, **49**, 401–9 (1957)
127. Apte, S. V., *Proc. Soc. Exptl. Biol. Med.*, **125**, 117–18 (1967)
128. Brusilow, S. W., Gordes, E. H., *J. Clin. Invest.*, **43**, 477–84 (1964)
129. Adachi, K., Yamasawa, S., *J. Invest. Dermatol.*, **46**, 510–11 (1966)
130. Gordon, R. S., Cage, G. W., *Lancet*, **1**, 1246–50 (1966)
131. Brusilow, S. W., Munger, B., *Proc. Soc. Exptl. Biol. Med.*, **110**, 317–19 (1962)
132. Foster, K. G., *J. Physiol. (London)*, **184**, 106–19 (1966)
133. Herrmann, F., Mandol. L., *J. Invest. Dermatol.*, **24**, 225–46 (1955)
134. Dill, D. B., Hall, F. G., Van Beaumont, W., *J. Appl. Physiol.*, **21**, 99–106 (1966)
135. Wyndham, C. H., Strydom, N. B., Morrison, J. F., Williams, C. G., Bredell, G. A. G., Peter, J., *J. Appl. Physiol.*, **21**, 107–10 (1966)
136. Harden, R., *J. Endocrinol.*, **28**, 153–57 (1964)
137. Collins, K. J., *Clin. Sci.*, **30**, 207–21 (1966)
138. Liebermann, J., *J. Am. Med. Assoc.*, **195**, 629–35 (1966)
139. Brusilow, S. W., Gordes, E. H., *Am. J. Diseases Children*, **112**, 328–33 (1966)
140. Brusilow, S. W., *Nature*, **214**, 506 (1967)
141. Komives, G. K., Robinson, S., Roberts, J., *J. Appl. Physiol.*, **21**, 1681–84 (1966)
142. Knowles, J. A., *J. Pediat.*, 66, 1068–82 (1965)
143. Rasmussen, F., *Studies on the Mam-*

mary Excretion and Absorption of Drugs (Carl F. Mortensen, Copenhagen, 87 pp., 1966)
144. Sisodia, C. S., Stowe, C. M., *Ann. N.Y. Acad. Sci.*, **111**, 650–61 (1964)
145. Sisodia, C. S. (Doctoral Thesis, Univ. Minnesota, Minneapolis, Minn., 1963)
146. Marth, E. H., Ellickson, B. E., *J. Milk Food Technol.*, **22**, 241–49 (1959)
147. Marth, E. H., Ellickson, B. E., *J. Milk Food Technol.*, **22**, 266–72 (1959)
148. Marth, E. H., *J. Milk Food Technol.*, **24**, 36–44 (1961)
149. Marth, E. H., *J. Milk Food Technol.*, **24**, 70–82 (1961)
150. Myers, R. P., *Residue Rev.*, **7**, 9–36 (1964)
151. Marth, E. H., *Residue Rev.*, **12**, 65–161 (1966)
152. Schanker, L., S., Shore, P. A., Brodie, B. B., Hogben, C. A. M., *J. Pharm. Exptl. Therap.*, **120**, 528–39 (1957)
153. Rasmussen, F., *Acta Pharmacol. Toxicol.*, **15**, 139–48 (1958)
154. Rasmussen, F., *Acta Pharmacol.*, **16**, 194–200 (1959)
155. Rasmussen, F., *Acta Vet. Scand.*, **2**, 151–56 (1961)
156. Rasmussen, F., *Acta Vet. Scand.*, **7**, 97–98 (1966)
157. Miller, G. E., Sisodia, C. S., Stowe, C. M., *J. Dairy Sci.*, **47**, 694 (1964)
158. Miller, G. E., Banerjee, N. C., Stowe, C. M., *J. Dairy Sci.*, **49**, 734 (1966)
159. Miller, G. E., Peters, R. D., Engebretsen, R. V., Stowe, C. M., *J. Dairy Sci.*, **50**, 769–72 (1967)
160. Banerjee, N. C., Miller, G. E., Stowe, C. M., *Toxicol. Appl. Pharmacol.*, **10**, 1604–12 1967)
161. Jacobs, M. H., *Cold Spring Harbor Symp. Quant. Biol.*, **8**, 30–39 (1940)
162. Tunnicliff, E. A., Swingle, K. F., *Am. J. Vet. Res.*, 26, 920–27 (1965)
163. Rasmussen, F., Linzell, J. L., *Biochem. Pharmacol.*, **16**, 918–19 (1967)
164. Høgh, P., Rasmussen, F., *Acta Vet. Scand.*, **6**, 178–92 (1965)
165. Langer, P. H., Burkhart, R. L., Schroeder, C. R., Welsh, M., *J. Dairy Sci.*, **31**, 103–9 (1948)
166. Henderson, J. L., *Residue Rev.*, **8**, 74–115 (1965)
167. Knipling, E. F., Westlake, W. E., *Residue Rev.*, **13**, 1–32 (1966)
168. Heineman, H. E. O., Jaynes, H. O., Heflin, J. L., *J. Dairy Sci.*, **49**, 509–16 (1966)
169. Loeffler, W. W., Trimberger, G. W., Fox, F. H., Ridgeway, R. L., Lisk, D. J., Gyrisco, G. G., *J. Agr. Food Chem.*, **14**, 46–47 (1966)
170. Bruce, W. N., Link, R. P., Decker, G. C., *J. Agr. Food Chem.*, **13**, 63–67 (1965)
171. Dorough, H. W., *J. Agr. Food Chem.*, **15**, 261–66 (1967)
172. Lynn, G. E., Shrader, S. A., Hammer, O. H., Lassiter, C. A., *J. Agr. Food Chem.*, **11**, 87–91 (1963)
173. Zweig, G., Pye, E. L., Peoples, S. A., *J. Agr. Food Chem.*, **11**, 72–74 (1963)
174. Zweig, G., Smith, L. M., Peoples, S. A., Cox, R., *J. Agr. Food Chem.*, **9**, 481–84 (1961)
175. Street, J. C., Chadwick, R. W., Wang, M., Phillips, R. L., *J. Agr. Food Chem.*, **14**, 545–49 (1966)
176. Bailey, G. W., White, J. L., *Residue Rev.*, **10**, 97–122 (1965)
177. St. John L. E., Jr., Wagner, D. G., Lisk, D. J., *J. Dairy Sci.*, **47**, 1267–70 (1964)
178. St. John, L. E., Jr., Ammering, J. W., Wagner, D. G., Warner, R. G., Lisk, D. J., *J. Dairy Sci.*, **48**, 502–3 (1965)
179. Fisher, D. E., St. John, L. E., Jr., Gutenmann, W. H., Wagner, D. G., Lisk, D. J., *J. Dairy Sci.*, **48**, 1711–15 (1965)
180. Stevens, M. A., Wolley, J. K., *J. Sci. Food Agr.*, **17**, 472–75 (1966)
181. Williams, K. I. H., Burstein, S. H., Layne, D. S., *Proc. Soc. Exptl. Biol. Med.*, **122**, 865–66 (1966)
182. Ruzicka, L., Goldberg, M. W., Meister, H., *Helv. Chim. Acta*, **23**, 559–61 (1940)
183. Patton, S., Forss, D. A., Day, E. A., *J. Dairy Sci.*, **39**, 1469–70 (1956)
184. Hartmann, A. F., Hartmann, A. F., Jr., Purkerson, M. L., Wesley, M. E., *J. Am. Med. Assoc.*, **185**, 706–9 (1963)
185. Kingsbury, J. M., *Poisonous Plants of the United States and Canada* (Prentice-Hall, Inc., Englewood Cliffs, New Jersey, 626 pp., 1964)
186. Allcroft, R., Carnaghan, R. B. A., *Vet. Rec.*, **75**, 259–63 (1963)
187. Allcroft, R., Rogers, H., Lewis, G., Nabney, J., Best, P. E., *Nature*, **209**, 154–55 (1966)
188. Park, R. J., *Nature*, **207**, 640 (1965)
189. Richter, H. E., *Wien. Tieraerztl. Monatsschr.*, **52**, 635–44 (1965)
190. McClanahan, B. J., McClellan, R. O., McKenney, J. R., Bustad, L. K., *Symp. Radioisotopes in Animal*

Nutrition & Physiology, 173–88 (I. A. E. A. Tech. Rept. Ser., Vienna, 1965)
191. Glenn, J. C., Hansard, S. L., *J. Animal Sci.*, **23**, 905–6 (1964)
192. Hind, H. W., Goyan, F. M., *J. Am. Pharm. Assoc.*, **38**, 477–79 (1949)
193. Bro-Rasmussen, F., Killmann, S. A., Thaysen, J. H., *Acta Physiol. Scand.*, **37**, 97–113 (1956)
194. Rexed, U., *Acta Ophthalmol.*, **36**, 711–18 (1958)
195. Thaysen, J. H., Thorn, N. A., *Am. J. Physiol.*, **178**, 160–64 (1954)
196. Giardini, A., Roberts, J. R. E., *Brit. J. Ophthalmol.*, **34**, 737–43 (1950)
197. Lewis, J. G., Stephens, P. J., *Brit. J. Ophthalmol.*, **42**, 754–58 (1958)
198. Balik, J., *Cesk. Oftal.*, **17**, 508–12 (1961); *Chem. Abstr.*, **59**, 13182c (1963)
199. Balik, J., *Cesk. Oftal.*, **18**, 8–12 (1962); *Excerpta Med., Sect. XII*, **16**, 1398 (1962)
200. Balik, J., *Acta Ophthalmol.*, **43**, 190–98 (1965); *Chem. Abstr.*, **64**, 6267; (1966)
201. Balik, J., Pavlova, D., Urbanova, S., *Cesk. Oftal.*, **22**, 263–67 (1966) *Chem. Abstr.*, **65**, 17577c (1966)
202. Balik, J., Urbanova, S., *Cesk Oftal.*, **22**, 268–72 (1966)
203. Razumovskii, M. I., *Fiziol. Zh. SSSR*, **49**, 1089–91 (1963); *Chem. Abstr.*, **60**, 7283g (1964)
204. Dundee, J. W., *Clin. Pharmacol. & Therap.*, **8**, 91–123 (1967)
205. VanDyke, R., Chenoweth, M. B., *Anesthesiology*, **26**, 348–57 (1965)
206. DiStefano, V., Borgstedt, H. H., *Science*, **144**, 1137–38 (1964)
207. Hucker, H. B., Ahmad, P. M., Miller, E. A., *J. Pharmacol. Exptl. Therap.*, **154**, 176–84 (1966)
208. McConnell, K. P., *J. Biol. Chem.*, **145**, 55–60 (1942)
209. McConnell, K. P., Portman, O. W., *J. Biol. Chem.*, **195**, 277–82 (1952)
210. Schultz, J., Lewis, H. B., *J. Biol. Chem.*, **133**, 199–207 (1940)
211. Heinrich, M., Jr., Kelsey, F. E., *J. Pharmacol. Exptl. Therap.*, **114**, 28–32 (1955)
212. Sandratskaya, S. E., *Toksikol. Redkiksh Metal.*, 117–35 (1963); *Chem. Abstr.*, **60**, 2247 (1964)
213. Ringler, I., *Endocrinology*, **68**, 281–91 (1961)
214. Vishwakarma, P., *Fertility Sterility*, **13**, 481–85 (1962)
215. Heap, R. B., *J. Endocrinol.*, **24**, 367–78 (1962)
216. Heap, R. B., Lamming, G. E., *J. Endocrinol.*, **25**, 57–68 (1962)
217. Sturgis, S. H., *Endocrinology*, **31**, 664–72 (1942)
218. *Bibliography of Reproduction* (Reproduction Res. Inf. Ser., Ltd., Cambridge, England)
219. Farrell, J. I., *J. Urol.*, **40**, 62–65 (1938)
220. Farrell, J. I., Lyman, Y., Youman, G., *J. Am. Med. Assoc.*, **110**, 1176–77 (1938)
221. Soanes, W. A., Gonder, M. J., Ricci, P., Shulman, S., *J. Urol.*, **90**, 72–74 (1963)
222. Aplington, J. P., Silver, S. B., *Invest. Urol.*, **4**, 303–6 (1967)
222b. Borski, A. A., Pulaski, E. J., Kimbrough, J. C., Fusillo, M. H., *Antibiot. Chemotherapy*, **4**, 905–10 (1954)
223. Darné, A., Doctoral Thesis, Royal Col. Vet. Surg., London, 1954. cited in Mann, T., *Biochemistry of Semen and of the Male Reproductive Tract* (Methuen, Co., Ltd., London, 493 pp., 1964)
224. Heath, H., Rimington, C., Glover, T., Mann, T., Leone, E., *Biochem. J.*, **54**, 606–11 (1953)
225. Smith, E. R., Ilievski, V., Hadidian, Z., *J. Pharmacol. & Exptl. Therap.*, **151**, 59–65 (1966)
226. Dziuk, P. J., Mann, T., *J. Reprod. Fertility*, **5**, 101–8 (1963)

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