Review

Spironolactone

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The isolation and identification of aldosterone was followed by attempts to synthesize spirolactone steroids capable of blocking its physiologic and pharmacologic effects.[1] The most important and effective aldosterone antagonists are spironolactone, canrenone, canrenoate and, more recently, prorenoate. The spironolactones were the first potassium-sparing diuretics and have been increasingly used for the clinical treatment of congestive heart failure, hepatic ascites, primary aldosteronism, and essential hypertension.[2-32]

Chemical properties and methods of quantitation

Spirolactones have a structure similar to that of other steroids, with a lactone ring as a substituent at C-17 (Fig. 1). Spironolactone and its metabolites are usually designated by Roman numerals in the chemical and pharmacologic literature. Spironolactone is the active constituent of Aldactone, whereas canrenoate is a water-soluble potassium salt used for intravenous injection (Fig. 1). When canrenoate is reconstituted from its lyophilized form prior to injection, the solution often becomes turbid after a short period of standing at room temperature. The turbidity appears to be due to precipitation of canrenone (aldadiene, SC-9376), a pharmacologically active derivative of canrenoate. Thus, canrenone can be formed from canrenoate both *in vitro* and *in vivo*. It is not established whether the turbid solutions are clinically effective when injected intravenously.

Several methods are available for quantitation of spironolactone and its metabolites in body fluids. These include radioactive tracer techniques, chromatography, fluorescence, mass spectrometry, and ultraviolet spectrometry.[33-39] A radioimmunoassay will soon be available.[40] One disadvantage of techniques based on quantitation of tritiated spironolactone is that relatively large amounts of tritiated water are formed by endogenous metabolism of the parent compound.[41]

Using spectrophotofluorometric technique for quantitation of canrenone, Karim and colleagues[42] were able to assay this compound in a 1 ml. plasma sample at levels as low as 15 ng./ml. The coefficient of variation for identical samples in the range of 75 to 1,200 ng./ml. was 8 per cent or less. Sadee and associates[36] modified the technique to allow separate quantitation of spironolactone, canrenoate, and the polar glucuronic ester conjugate of canrenoate. The method is sensitive and specific enough to allow reliable measurement of these compounds in plasma after therapeutic doses of spironolactone.

The presence of spironolactone and its metabolites in plasma appears to interfere with determination of plasma cortisol by fluorometric assay.[43-47] It is also suggested that spironolactone metabolites interfere with estimation of serum digoxin by radioimmunoassay.[48-51]

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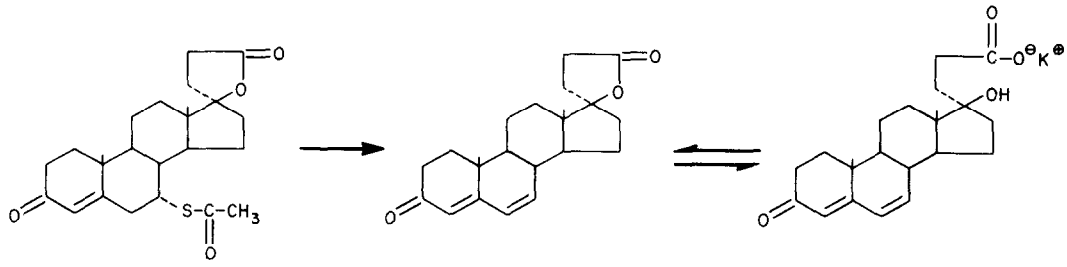

Fig. 1. Structural formula of spironolactone and its major metabolites, canrenone (aldadiene) and canrenoate (shown as the potassium salt).

Pharmacokinetics

Animal studies. Following intravenous administration of spironolactone to dogs or rats,[37, 52, 53] the apparent elimination half-life of the parent drug is approximately 10 minutes. Excretion of radioactive-labeled spironolactone and canrenoate occurs mostly via the biliary tract in the form of polar, conjugated metabolites (80 to 95 per cent within 12 hours in the rat; 35 per cent during 6 hours in the dog). Renal excretion of radioactivity reaches only 3 per cent over 12 hours in the rat and 1 per cent within 6 hours in the dog. Bioavailability studies in the dog indicate that absorption of spironolactone is about 80 per cent complete. A suitable pharmacokinetic model for spironolactone in these species has not yet been developed.

Clinical Studies.

Distribution, elimination, and accumulation. Spironolactone itself is very rapidly cleared by the human organism. The metabolites canrenone and/or canrenoate, having considerably longer half-life values than the parent drug, are usually measured in body fluids after administration of spironolactone to humans. The apparent elimination half-life of canrenoate plus canrenone was between 17 and 22 hours after a single intravenous injection of canrenoate to five patients.[54] Karim and co-workers[41] in a study of five healthy male subjects similarly observed a mean elimination half-life of 16.8 hours for these two compounds after single doses of spironolactone. After termination of chronic spironolactone therapy (200 mg. once daily), the apparent elimination half-life of canrenone averaged 19.7 hours; however, when the same total dose was divided into 50 mg. taken 4 times daily, the apparent elimination half-life was 12.5 hours.[55] With both dosage regimens, steady-state was achieved after about 4 days of therapy, although the amount of interdose fluctuation in plasma levels on the "q.i.d." regimen was less than on the once-daily schedule. The clinical significance of these fluctuations is not known.[55]

In another multiple dose study, 100 mg. of oral spironolactone was administered twice a day to six patients recovering from acute myocardial infarction.[56] Accumulation of canrenone and canrenoate was only 50 per cent complete after one to four days. The apparent elimination half-life values observed after both single doses and 10 days of chronic administration were not significantly different, being about 20 hours in both instances (range: 17 to 22 hours). The amount of time necessary for achievement of steady-state was longer than that predicted on the basis of single-dose studies. Thus elimination and accumulation half-lives are not consistent. The reasons for this are not established, although the authors suggest a change in macromolecular binding or tissue distribution due to cumulation of unknown metabolites.[56]

During three weeks of spironolactone therapy in 44 patients, steady-state plasma levels of canrenone were no different in patients with impaired renal or hepatic function than in individuals without such diseases.[56] Steady-state plasma levels differed fifteenfold among individuals receiving the same daily dose. Higher maintenance doses led to approximately proportional increases in steady-state plasma levels.

Biologic availability. Problems with bioavailability of spironolactone preparations have been observed since as early as 1962.[57, 58] A parenteral preparation of spironolactone for use in absolute bioavailability studies is not available.[59] Instead,

intravenous canrenoate in equimolar doses has been used as an absolute bioavailability standard.

After oral administration of a solution of canrenoate, the serum concentration curve was nearly superimposable upon that obtained after intravenous injection, suggesting that canrenoate is rapidly and completely absorbed from an oral solution and that a clinically important "first-pass effect" does not exist.[54] Bioavailability of spironolactone tablets reached 96 per cent in comparison to an oral solution, but only 60 per cent when compared with oral administration of canrenoate-K in one patient.[54] In a more extensive crossover study in 12 healthy volunteers,[60] bioavailability of conventional 25 mg. spironolactone tablets was compared to that of a new 100 mg. tablet formulation and to an oral solution. The mean (±S.D.) bioavailability of the two tablets relative to the oral solution, based upon the area under the 24-hour canrenone plasma concentration curve, were 99.6 ± 18.2 per cent and 92.1 ± 22.9 per cent. Differences in the peak plasma concentrations of metabolites among two tablet preparations (25 and 100 mg.) of spironolactone were unimportant.[60] Sponer and colleagues[61] investigated the absolute and relative bioavailability of two oral spironolactone preparations in 20 volunteers. Absorption of 100 mg. of spironolactone, given either as two tablets or one capsule, was complete. However, when 400 mg. were given orally as a single dose, absorption of the drug was reduced.

Metabolic pathways. As indicated previously, the metabolic degradation of spironolactone in humans proceeds very rapidly by enzymatic cleavage of the C-7 acetylthio substituent to yield canrenone. Serum concentrations of spironolactone fall to undetectable limits within a few minutes of a dose. The two major metabolites, canrenone and canrenoate, exist in equilibrium.[35, 41, 54]

Comparison of fluorescent compounds and metabolites in serum and urine with the findings from studies of radioactive-labeled spironolactone and canrenoate clearly demonstrate the formation of a variety of nonfluorescent radioactive metabolites, including tritiated water.[41] After administration of tritiated canrenoate, elimination of total radioactivity proceeds with a much slower half-life (43 to 70.5 hours) than does elimination of fluorescent substances due to the presence of nonspecific radioactivity. Karim and colleagues[41] suggest that the apparent elimination half-life of total radioactivity extractable into ethyl acetate (about 37 hours) probably represents that attributable to spirolactones. In any case, accumulation of these nonfluorescent and as yet unidentified metabolites may explain in part why maximal clinical effects of spironolactone are achieved only after several days of treatment, and that efficacy of the drug can still be demonstrated 2 to 3 days after the last dose. Since the activity of single doses of spironolactone persist for up to 24 hours,[62] once- or twice-daily dosage with spironolactone may be satisfactory.

Karim and co-workers[35] described the disappearance of serum radioactivity following intravenous tritiated canrenoate by a triexponential function. The terminal "elimination" portion of the curve was reached after 5 hours. Forty-seven per cent of radioactivity was excreted in the urine and 14 per cent in the feces within 5 days. Approximately 50 per cent of radioactive compounds were fluorescent metabolites. Only 1 per cent of the dose was excreted in the urine as unchanged drug. One of the major water-soluble metabolites was a glucuronide ester.[35] After oral administration of tritiated spironolactone in an alcoholic solution, no unchanged spironolactone was recovered in the urine. In 5 days, 32 per cent of radioactivity was excreted in urine and 23 per cent in feces. The major urinary metabolites were canrenone (5 per cent of the dose), the 6β-hydroxy-sulfoxide metabolite (5 per cent), and the glucuronide ester of canrenone (6 per cent). When potassium canrenoate was administered intravenously, 3.4 per cent of the dose was excreted in the urine as unchanged canrenone. Further study of human metabolites of spironolactone is needed, since metabolites other than canrenone and canrenoate may contribute to its clinical activity.[64, 65] Structure activity studies of spironolactone analogues suggest that beta-unsaturation at the C6/C7 position, gamma-lactone unsaturation, and gamma-lactone ring opening with formation of a water-soluble salt all result in decreased activity.[66]

Both spironolactone and canrenone are extensively bound to plasma proteins (89 per cent or more) at therapeutic concentrations.[67] Blood-to-

plasma concentration ratios are about 0.5, suggesting no selective uptake of the compounds by red cells.

Drug distribution and pharmacologic effects. In rats the maximal reduction of aldosterone-induced sodium retention occurs when renal elimination of spironolactone is maximal.[68] Thus, the extent of the tubular effects of the anti-aldosterones appears to depend on their concentration in the renal tubules. Clearance studies[68] indicate that spironolactone is secreted by the tubules. This secretion can be blocked with bromcresol green, with a parallel decline in renal effects. *In vitro,* 11-hydroxy-spironolactone inhibits the synthesis of aldosterone in rat adrenals.[69] *In vivo,* the drug stimulates the renin-angiotensin-aldosterone system to a great extent with hyperplasia of the zona glomerulosa of the adrenals.[30] Spironolactone induces hyperreninemia, hyponatremia, and hyperkalemia which again stimulates the secretion of aldosterone.[70] This effect of increased aldosterone secretion after high doses of 800 to 2,000 mg. per day of spironolactone has been applied clinically for treatment of the post-traumatic edema of the brain.[71]

Mechanisms of action

Spironolactone is a competitive antagonist of aldosterone and modifies electrolyte metabolism only in the presence of aldosterone-like compounds.[38, 72-77] It reverses all electrolyte-regulating effects of aldosterone, regardless of the tissue studied. The effects of spironolactone are surmountable by raising the level of aldosterone-like compounds.[78, 79] Spironolactone inhibits the formation of the aldosterone complex in the nuclei of kidney epithelial cells of adrenalectomized rats. This occurs at concentration ratios that inhibit the action of aldosterone in the rat *in vivo.*[80] Recent studies in humans suggest a direct inhibitory effect of canrenone on adrenal aldosterone production.[81]

In vitro studies with kidney tissue slices from rats demonstrate displacement of aldosterone from its specific intracellular receptors by spironolactone.[66]

Influence on myocardial contractility

Positive inotropic effects of the spirolactones have been demonstrated *in vitro,* and *in vivo* in humans during cardiac catheterization.[82-88] The injection of 200 to 400 mg. of canrenoate in 43 patients resulted in a long-lasting increase of stroke volume as well as an increase in the maximal slope of the pressure-time curve in both ventricles. These positive inotropic effects could also be demonstrated in digitalized patients, and therefore are additive to the effects of digitalis. Improvement in cardiac contractility has been observed during long-term spironolactone therapy as well.[75] The mechanism of this action is not well understood, but spironolactone does inhibit sodium-potassium ATPase in human erythrocytes, similar to that produced by cardiac glycosides.[89]

Effects on respiration

Respiratory improvement has been observed in patients with chronic respiratory insufficiency after administration of spironolactone.[90-95] Although progesterone, a structurally related steroid, produces direct respiratory stimulation, this has not been shown with spironolactone.[96-98] Canrenoate does not change the response to a carbon dioxide challenge.[99] Spironolactone lowers neither airway resistance nor pulmonary compliance.

Antiandrogenic effects

Erbler[100] demonstrated a clear decline in plasma testosterone levels over 9 hours after a single dose of 5 mg./Kg. of canrenone to healthy males. Stripp and associates[101] administered 400 mg. of spironolactone daily to five healthy male volunteers for 5 days. Plasma progesterone and 17α-hydroxy-progesterone increased significantly. Plasma follicle stimulating hormone and luteinizing hormone levels also increased, but the effect was only transient and was not significant by the third and fifth days of the study. Plasma testosterone, 17β-estradiol, and prolactin did not change significantly. However, the first plasma sample was not taken until 12 hours after the initial dose, at which time Erbler[100] found that testosterone levels were returning to normal.

Studies in rats suggest that spironolactone blocks testosterone receptors.[102, 103] Castro and co-workers[104] attempted to use spironolactone therapeutically for hypertrophy of the prostate, but obtained only temporary improvement of symptoms. Unwanted antiandrogenic effects

commonly accompany spironolactone therapy, and are discussed in the section on side effects.

Drug interactions

Antagonism by salicylates. In 1962 Elliott[105] suggested a possible antagonism of spironolactone's natriuretic effect when it was given with aspirin. This was later documented in laboratory animals and in man.[106-108] Sodium excretion during long-term treatment with spironolactone (100 mg. per day) was reduced by one-third when 600 mg. aspirin was coadministered.[108] In another study,[109] aspirin coadministration reduced urinary excretion of canrenone between 4 and 6 hours after ingestion of spironolactone. Such findings suggest that aspirin and spironolactone should not be coadministered if possible. A similar interaction was demonstrated for sodium salicylate, indomethacin and mefenamic acid, but not for the analgesic-antipyretic drug acetaminophen. In rats, however, indomethacin did not antagonize spironolactone's effect on the kidney.[110] Steiness[111] demonstrated reduction in the renal tubular secretion and clearance of digoxin by spironolactone, although the magnitude of the effect was small.

Enzyme induction and inhibition. The influence of spironolactone on microsomal enzyme activity and the pharmacokinetics of coadministered drugs has been investigated extensively in various animal species and in man[112-146] (Table I). In humans, simultaneous administration of 400 mg. of spironolactone shortens the half-life of digitoxin by 20 per cent. Urinary excretion of unchanged digitoxin decreases from 80 to 66 per cent with an increase of water-soluble metabolites from 12 to 26 per cent. The profound effects of spironolactone upon pharmacokinetics of methyldigoxin observed in rats are without any significance for human conditions.[147] Antipyrine half-life was shortened in nine volunteers from 12.4 to 7.6 hours after a 2 week period of spironolactone treatment. In animal studies the enhanced catabolism of many drugs by spironolactone has been successfully applied to prevent or reduce toxicity by these drugs (Table I). For other substances (such as mercury, furosemide, and digitalis), the exact mechanism by which spironolactone prevents toxicity in animals is not known.[138, 148-162] Some studies demonstrate inhibition of enzyme activity by spironolactone.[119, 122, 163, 164] Microsomal cytochrome P-450 activity in the guinea pig and the dog was reduced 50 to 80 per cent by spironolactone administration, with a simultaneous increase in 17α-hydroxylase activity. Spironolactone inhibits corticosterone production in quartered rat adrenals,

Table I. Effects of spironolactone on hepatic function

Species	*Effect*	*Reference*
Rat	Increased bile flow	112-115
	Increased liver weight	116
	Increased activity and/or quantity of liver enzymes:	
	bilirubin-UDP-glucuronyl transferase	112,114
	ethylmorphine N-demethylase	117-119
	aniline hydroxylase	118,120
	cytochrome-C reductase	116,117
	3,4-benzpyrene hydroxylase (in females)	117
	Accelerated biotransformation or elimination of:	
	aniline	121
	bilirubin	114
	benzo (a)pyrine	116
	pentobarbital	122,123
	hexobarbital*	117,121
	bromsulphthalein	113
	phenol-3,6-dibromophthalein disulfonate	113
	dimethylbenzanthracene	124
	bishydroxycoumarin	125
	3,4-benzpyrene	116
	diazepam	115
	spironolactone	117,126
	digitalis glycosides	119,127-137
Mouse	Increased liver weight	119,127
	Increased activity of liver enzymes:	
	ethylmorphine N-demethylase	119
	NADPH oxidase	119
	cytochrome P-450	119
	NADPH-cytochrome-C reductase	117
	NADPH-cytochrome P-450 reductase	119
	Accelerated hexobarbital metabolism	138
Man	Accelerated biotransformation of digitoxin	139
	Accelerated biotransformation of antipyrine	140-142

*Biotransformation stimulated in females; impaired in males.

although the effect of canrenone is considerably greater.[164]

Antihypertensive effects

Spironolactone produces very little fall in blood pressure in normotensive subjects. Until the early 1960's the blood pressure lowering effect of spironolactone in hypertensive patients was not considered to be attributable to a decrease of circulatory volume.[8-10] Recently, however, it has been shown that even in patients with primary hyperaldosteronism the antihypertensive action of spironolactone is nonspecific and largely dependent on depletion of salt and water.[165] Furthermore, maintenance of reduced plasma volume or extracellular fluid volume is essential for continued antihypertensive activity of spironolactone. This contrasts with earlier findings demonstrating that blood pressure is reduced either by spironolactone or thiazide diuretics in essential hypertensives, whereas patients with primary aldosteronism respond only to spironolactone.[11, 12] It now appears questionable whether high-dose spironolactone is the treatment of choice in primary aldosteronism. Brown and associates[13] compared the results of spironolactone therapy and ablative surgery in 67 patients with elevated aldosterone serum levels. They confirmed and extended earlier reports of the predictive value of spironolactone on the subsequent hypotensive effect of adrenal surgery in patients with adrenocortical adenoma.[166] On the other hand, occasional failure to respond to spironolactone and subsequently successful surgery have been reported.[3, 11, 13] The situation, however, might be different in cases with carcinoma or micronodular hyperplasia of the adrenal glands.[167] For the latter it has been stated that no fall in blood pressure can be expected after surgical intervention if a 4 week therapeutic trial with spironolactone is unsuccessful.[168] Thus spironolactone may be a reasonable therapeutic alternative for patients with adrenocortical adenoma who are not candidates for surgery.

Patients with essential hypertension can be divided into those with low, low normal, normal, and high plasma renin activity (PRA).[3, 168-171] Whereas spironolactone does not appear to be very effective in hypertensive patients with normal or elevated PRA, the drug reduces the blood pressure in about 75 per cent of patients with hyporesponsive PRA.[2, 3, 171] A better blood pressure response in this group of patients has also been demonstrated for hydrochlorothiazide; however, despite comparable diuretic response, the hypotensive response observed with spironolactone was significantly greater, suggesting that mineralocorticoid excess may be responsible for the hypertension and low PRA.[12] On the other hand, two reports suggest a similar antihypertensive effect for spironolactone and chlorthalidone, with both drugs having similar effects on PRA and plasma volume.[172, 173] A third study demonstrated that chlorthalidone, spironolactone, and propranolol had similarly effective antihypertensive properties in patients with essential hypertension and normal PRA.[174]

The value of classification of patients with essential hypertension according to PRA is not established. Spironolactone interferes with the PRA even up to 9 months after discontinuation of the drug.[175] Although aldosterone secretion rates are higher in secondary rather than in primary aldosteronism, spironolactone has little or no effect on the arterial pressure in secondary aldosteronism.

Clinical use as a diuretic

Spironolactone is an effective diuretic agent in patients with edema or ascites from heart failure, cirrhosis, or renal impairment and does not directly influence renal blood flow or glomerular filtration rate.[15-20] Whereas hepatic coma can be precipitated by treatment with thiazide diuretics, perhaps as a result of potassium depletion, this risk is lessened when spironolactone is used. Since aldosterone secretion is not raised in untreated congestive heart failure, the success of spironolactone treatment will be more evident when aldosterone secretion has been provoked by sodium depletion resulting from long-term therapy with other diuretics. Spironolactone is often useful as a diuretic in patients with edema due to the nephrotic syndrome who have not responded to thiazide treatment and bed rest alone.[23-28]

Electrolyte balance

Aldosterone antagonists block sodium reabsorption in the distal nephron, whereas most of the other diuretics prevent sodium reabsorption proximally. Thus, additional blockade of sodium reabsorption might be obtained by combining other diuretics with spironolactone. Ammonium and hydrogen ion excretion is decreased by

spironolactone.[10] Since the drug decreases sodium absorption in the distal tubule, the ability to excrete dilute urine is impaired and hyponatremia can be a consequence of therapy.

Spironolactone blocks aldosterone-dependent potassium excretion. This is therapeutically useful, since most patients with edema treated with other diuretics experience potassium depletion. It has been suggested that greater sodium diuresis will occur if potassium supplements are given during combined therapy with spironolactone and thiazide diuretics.[176-180] However, coadministration of potassium supplements and spironolactone should be undertaken only with great caution due to the risk of hyperkalemia. Spironolactone likewise impairs magnesium excretion. The clearance of magnesium is reduced by spironolactone, while the magnesium-to-potassium clearance ratio is unchanged.[181]

Wills and associates[182] have shown that spironolactone in a dose as low as 200 mg. daily increases urinary calcium excretion. However, Prati and colleagues[183] demonstrated that hypercalciuria after spironolactone administration is an artifact due to the calcium content (approximately 37 mg.) of commercially available spironolactone tablets.

Unwanted effects

A report from the Boston Collaborative Drug Surveillance Program[4] indicated that 788 (5.9 per cent) of 13,349 hospitalized medical patients received spironolactone during their hospital stay. Unwanted side effects were attributed to spironolactone in 164 (20.8 per cent) of these patients. These adverse effects included hyperkalemia (41.5 per cent of adverse reactions), dehydration (16.5 per cent), hyponatremia (11.5 per cent), gastrointestinal symptoms (11 percent), neurologic complaints (9.8 per cent), exanthema (2.4 per cent), and gynecomastia (1.2 per cent). Some of the unwanted effects, i.e., hyperkalemia, hyponatremia, hypovolemia, might have been avoided if the drug were administered more cautiously.[184, 185] Hyperkalemia clearly is the most important and serious potential complication of spironolactone therapy. The risk is greater in patients with renal insufficiency and those who receive potassium supplements.[3, 13, 184-189] In rare cases, hyperkalemia might contribute or lead to intermittent paralysis.

Because of its steroid configuration, spironolactone has endocrine effects which are not easily explained by a single mechanism.[100, 102-104, 190-196] In male patients, gynecomastia, impotence, and diminished libido have been reported with doses as low as 100 mg. per day. In women, reversible oligomenorrhea, amenorrhea, and breast soreness have been noticed. Loube and Quirk[197] observed five women in whom breast carcinoma developed during or after the prolonged administration of spironolactone. The number of cases, however, is too small to draw any conclusions and the findings may well be purely coincidental.

New spirolactones

Prorenoate is a water-soluble salt of a steroid acid structurally related to spironolactone.[198, 199] The potency of prorenoate in man with respect to spironolactone as measured by retention of potassium (3.8:1) is significantly higher than its relative potency in promoting natriuresis (1.6:1).[198] In a single dose study, the responses to prorenoate potassium 40 mg. were not different from those to spironolactone 100 mg.[200] The possible clinical role of prorenoate is now under evaluation.

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REFERENCES

1. Kagawa, C. M., Cella, J. A., and Van Arman, C. G.: Action of new steroids in blocking effects of aldosterone and desoxycorticosterone on salt, Science **126**:1015, 1957.
2. Adlin, V. E., Marks, D. A., and Channick, B. J.: Spironolactone and hydrochlorothiazide in essential hypertension, Arch. Intern. Med. **130**:855, 1972.
3. Crane, M. G., and Harris, J. J.: Effects of spironolactone in hypertensive patients, Am. J. Med. Sci. **260**:311, 1970.
4. Greenblatt, D. J., and Koch-Weser, J.: Adverse reactions to spironolactone: a report from the Boston Collaborative Drug Surveillance Program, J. A. M. A. **225**:40, 1973.
5. Gwinup, G., and Steinberg, T.: Differential response to thiazides and spironolactone in primary aldosteronism, Arch. Intern. Med. **120**:436, 1967.
6. Vaughan, E. D., Laragh, J. H., Gavras, I., Bühler, F. R., Gavras, H., Brunner, H. R., and Bear, L.: Volume factor in low and normal renin essential hypertension, Am. J. Cardiol. **32**:523, 1973.
7. Werning, C.: Kurzes Lehrbuch der Hochdruckkrankheiten, Stuttgart, 1975, Ferdinand Enke Verlag.
8. Hollander, W., and Chobanian, A. V.: Antihypertensive effect of spironolactone (SC-9420) steroidal antagonist, Circulation **20**:713, 1959.
9. Hollander, W., Chobanian, A. V., and Wilkins, R. W.: The antihypertensive actions of mercurial thiazide and spirolactone diuretics, *in*, Diuresis and diuretics, an International Symposium, edited by E. Buchborn and K. D. Bock, Berlin, 1959, Springer-Verlag, pp. 297-312.

10. Ross, E. J.: Aldosterone and its antagonists, Clin. Pharmacol. Ther. **6**:65, 1965.
11. Spark, R. F., and Melby, J. C.: Aldosteronism in hypertension: the spironolactone response test, Ann. Intern Med. **69**:685, 1968.
12. Spark, R. F., O'Hare, C. M., and Regan, R. M.: Low-renin hypertension: restoration of normotension and renin responsiveness, Arch. Intern. Med. **133**:205, 1974.
13. Brown, J. J., Davies, D. L., Ferriss, J. B., Fraser, R., Haywood, E., Lever, A. F., and Robertson, J. I. S.: Comparison of surgery and prolonged spironolactone therapy in patients with hypertension, aldosterone excess, and low plasma renin, Br. Med. J. **2**:729, 1972.
14. Winer, B. M., Lubbe, W. F., and Colton, T.: Antihypertensive actions of diuretics: comparative study of an aldosterone antagonist and a thiazide, alone and together, J. A. M. A. **204**:775, 1968.
15. Papadoyanakis, N., Darsinos, J., Alexandrou, K., and Karli, J.: High doses of spironolactone in the treatment of liver cirrhosis with ascites, Br. J. Clin. Pract. **26**:27, 1972.
16. Seller, R. H., Swartz, C. D., Ramirez-Muxo, O., Brest, A. H., and Moyer, J. H.: Aldosterone antagonists in diuretic therapy, Arch. Intern. Med. **113**:350, 1964.
17. Gold, H., Golfinos, A. F., Mehta, D., Messeloff, C. R., and Zahm, W.: Spironolactone in diuretic regimens with meralluride or thiazides for pseudointractable ascites of cirrhosis, J. Clin. Pharmacol. **12**:35, 1972.
18. Gold, H., Mehta, D., Golfinos, A., Messeloff, C., Kwit, N., and Zahm, W.: Spironolactone in regimens for pseudointractable edema of heart failure, J. Clin. Pharmacol. **11**:125, 1971.
19. Howard, M. M., and Leevy, C. M.: Management of ascites, Arch. Intern. Med. **112**:702, 1963.
20. Manning, R. T., and Behrle, F. C.: Use of spironolactone in renal edema, J. A. M. A. **176**:769, 1961.
21. McNay, J. L., MacCannell, K. L., and Oran, E.: Potassium-retaining diuretics: electrolyte changes induced in hypertensive patients, Pharmacologia Clinica **2**: 94, 1970.
22. McKenna, T. J., Donohoe, J. F., Brien, T. G., Healy, J. J., Canning, B. St. J., and Muldowney, F. P.: Potassium-sparing agents during diuretic therapy in hypertension, Br. Med. J. **2**:739, 1971.
23. Farrelly, R. O., Howie, R. N., and North, J. D. K.: Use of spironolactone and hydrochlorothiazide in treatment of oedema, Br. Med. J. **2**:339, 1960.
24. Genest, J., and Pigeon, G.: Use of diuretics in treatment of kidney disease, Ann. N. Y. Acad. Sci. **88**:890, 1960.
25. Reubi, F. C.: The action and use of diuretics in renal disease, Progr. Cardiovasc. Dis. **3**:563, 1961.
26. Ross, E. J., and Winternitz, W. W.: The effect of an aldosterone antagonist on the renal response to sodium restriction, Clin. Sci. **20**:143, 1961.
27. Slater, J. D. H., Moxham, A., Hurter, R., and Nabarro, J. D. N.: Clinical and metabolic effects of aldosterone antagonists, Lancet **2**:931, 1959.
28. Stewart, W. K., and Constable, L. W.: The diuretic response to hygroton, mersalyl and Aldactone, Lancet **1**:523, 1961.
29. Kert, M. J., Tarr, L. W., Franklin, S., Gold, E., Okun, R., and Maxwell, M.: Experience with the use of an aldosterone antagonist in selected hypertensive patients, Angiology **23**:617, 1972.
30. Werning, C.: Das Renin-Angiotensin-Aldosteron System, Stuttgart, 1972, Georg Thieme Verlag.
31. Ehrlich, U., and Klepzig, H.: Langzeittherapie bis über neun Jahre mit Spironolacton bei der hydropischen Herzinsuffizienz, Med. Klin. **71**:1546, 1976.
32. Hoffbrand, B. I., Edmonds, C. J., and Smith, T.: Spironolactone in essential hypertension: evidence against its effect through mineralocorticoid antagonism, Br. Med. J. **1**:682, 1976.
33. Gerhards, E., and Engelhardt, R.: Zum Stoffwechsel von 3-(3-oxo-7α-acetylthio-17β-hydroxy-4-androsten-17α-yl)-propionsäure γ-lacton, Arzneim. Forsch. **13**:972, 1963.
34. Gochmann, N., and Gantt, C. L.: A fluorometric method for the determination of the major spironolactone (Aldactone) metabolite in human plasma, J. Pharmacol. Exp. Ther. **135**:312, 1962.
35. Karim, A., Ranney, R. E., and Maibach, H. I.: Pharmacokinetic and metabolic fate of potassium canrenoate (SC-14266) in man, J. Pharm. Sci. **60**:708, 1971.
36. Sadée, W., Dagcioglu, M., and Riegelman, S.: Fluorimetric microassay for spironolactone and its metabolites in biological fluids, J. Pharm. Sci. **61**:1126, 1972.
37. Sadée, W., Abshagen, U., Finn, C., and Rietbrock, N.: Conversion of spironolactone to canrenone and disposition kinetics of spironolactone and canrenoate-potassium in rats, Naunyn Schmiedebergs Arch. Pharmacol. **283**:303, 1974.
38. Karim, A., Hribar, J., Aksamit, W., Doherty, M., and Chinn, L. J.: Spironolactone metabolism in man studied by gas chromatograph-mass spectrometry, Drug Metab. Disp. **3**:467, 1975.
39. Radó, J. P., Szende, L., Takó, J., Nagy, O., and Kozma, C.: Application of a simple fluorometric method on absorption of canrenone, Int. J. Clin. Pharmacol. **13**:123, 1976.
40. Hofmann, L. M.: A radioimmunoassay for aldadiene (canrenone), Chicago, Searle Laboratories (personal communication, 1975).
41. Karim, A., Zagarella, J., Hribar, J., and Dooley, M.: Spironolactone I. Disposition and metabolism, Clin. Pharmacol Ther. **19**:158, 1976.
42. Karim, A., Zagarella, J., Hutsell, T. C., Chao, A., and Baltes, B. J.: Spironolactone II. Bioavailability, Clin. Pharmacol. Ther. **19**:170, 1976.
43. Dumlao, J. S., Kannon, C., Krauss, T., and Brooks, M. H.: Spironolactone and plasma cortisol, Clin. Pharmacol. Ther. **14**:992, 1973.
44. Lurie, A. O.: Spironolactone and steroid assay, Lancet **2**:326, 1969.
45. Metcalf, M. G.: Spironolactone and plasma cortisol, Br. Med. J. **2**:1201, 1964.
46. Simon, N. M.: Coagulation nondisease, N. Engl. J. Med. **282**:1214, 1970.
47. Wood, L. C., Richards, R., and Ingbar, S. H.: Interference in the measurement of plasma 11-hydroxycorticosteroids caused by spironolactone administration, N. Engl. J. Med. **282**:650, 1970.
48. Jambroes, G., Kruyswijk, H. H., Boink, H. B. T. J., Maas, A. H. J., and Willebrands, A. F.: Clinical experiences with the determination of the plasma digoxin level, Ned. Tijdschr. Geneeskd. **117**:1802, 1973.
49. Huffman, D. H.: The effect of spironolactone and canrenone on the digoxin radioimmunoassay, Res. Commun. Chem. Pathol. Pharmacol. **9**:787, 1970.
50. Phillips, A. P.: The improvement of specificity in radioimmunoassays, Clin. Chim. Acta **44**:333, 1973.
51. Ravel, R.: Negligible interference by spironolactone and prednisone in digoxin radioimmunoassay, Clin. Chem. **21**:1801, 1975.
52. Sadée, W., Riegelman, S., and Jones, S. C.: Disposition

of tritium-labeled spirolactones in the dog, J. Pharm. Sci. **61**:1132, 1972.
53. Sadée, W., Riegelman, S., and Jones, S. C.: Plasma levels of spirolactone in the dog, J. Pharm. Sci. **61**:1129, 1972.
54. Sadée, W., Dagcioglu, M., and Schröder, R.: Pharmacokinetics of spironolactone, canrenone and canrenoate-K in humans, J. Pharmacol. Exp. Ther. **185**:686, 1973.
55. Karim, A., Zagarella, J., Hutsell, T. C., and Dooley, M.: Spironolactone III. Canrenone—maximum and minimum steady-state plasma levels, Clin. Pharmacol. Ther. **19**:177, 1976.
56. Sadée, W., Schröder, R., Leitner, V. E., and Dagcioglu, M.: Multiple dose kinetics of spironolactone and canrenoate-potassium in cardiac and hepatic failure, Eur. J. Clin. Pharmacol. **7**:195, 1974.
57. Levy, G.: Availability of spironolactone given by mouth, Lancet **2**:723, 1962.
58. Gantt, C. L., Gochmann, N., and Dyniewicz, J. M.: Gastrointestinal absorption of spironolactone, Lancet **1**:1130, 1962.
59. Tidd, M. J., Collins, W. T., and Chamberlain, J.: A comparison of the dissolution and bioavailability characteristics of three spironolactone tablet formulations, including preliminary data on two spironolactone metabolites, J. Int. Med. Res. **4**:86, 1976.
60. Hofmann, L. M., Dutt, J. E., Deysach, L. G., Loncin, H., and Tao, L.: Comparison of spironolactone tablet dosage forms in healthy humans, J. Pharm. Sci. **63**:1248, 1974.
61. Sponer, G., et al.: Pharmakokinetik von Aldosteron-Antagonisten, Der Krankenhausarzt (In press)
62. Edmonds, C. J., and Wilson, G. M.: The action of hydroflumethiazide in relation to adrenal steroids and potassium loss, Lancet **1**:505, 1960.
63. Hofmann, L. M., Polk, R. C., and Maibach, H. I.: Renal clearance of canrenoate in normal man, Clin. Pharmacol. Ther. **18**:748, 1975.
64. Ramsay, L. E., Shelton, J. R., Wilkinson, D., and Tidd, M. J.: Canrenone—the principal active metabolite of spironolactone? Br. J. Clin. Pharmacol. **3**:607, 1976.
65. Ramsay, L., Shelton, J., Harrison, I., Tidd, M., and Asbury, M.: Spironolactone and potassium canrenoate in normal man, Clin. Pharmacol. Ther. **20**:167, 1976.
66. Funder, J. W., Feldman, P., Highland, E., and Edelman, I. S.: Molecular modifications of antialdosterone compounds: effects on affinity of spironolactones for renal aldosterone receptors, Biochem. Pharmacol. **23**:1493, 1974.
67. Chien, Y. W., Hofmann, L. M., Lambert, H. J., and Tao, L. C.: Binding of spirolactones to human plasma proteins, J. Pharm. Sci. **65**:1337, 1976.
68. Hollmann, G., Senft, G., and Werner, C.: Tubuläre Wirkungen und renale Elimination von Spironolactonen, Naunyn Schmiedebergs Arch. Exp. Pathol. Pharmacol. **247**:419, 1964.
69. Erbler, H. C.: Selective inhibition of aldosterone synthesis by 11-hydroxylated spironolactone in rat adrenals, Naunyn Schmiedebergs Arch. Pharmacol. **280**:331, 1973.
70. Maebashi, M., and Yoshinaga, K.: Changes in plasma renin activity after administration of spironolactone, Jap. Circ. J. **31**:435, 1967.
71. Schmiedek, P., Baethmann, A., Schneider, E., Brendel, W., Enzenbach, R., and Marguth, F.: Use of spironolactone in the treatment of cerebral edema in neurosurgical patients, *in*, Extrarenal activity of aldosterone and its metabolites, edited by W. Brendel et al, Amsterdam, 1972, Excerpta Medica, pp. 234-237.
72. Kautzsch, G.: Beeinflussung der Schweisselektrolyte durch Spironolactone beim sekundären Hyperaldosteronismus, Dissertation Erfurt, 1964.
73. Liddle, G. W.: Aldosterone antagonists, Arch. Intern. Med. **102**:998, 1958.
74. Crabbe, J.: Decreased effectiveness of aldosterone on active sodium transport by the isolated toad bladder in the presence of other steroids, Acta Endocrinol. **47**:419, 1964.
75. Salassa, R. M., Mattox, V. R., and Power, M. H.: Effect of an aldosterone antagonist on sodium and potassium excretion in primary hyperaldosteronism, J. Clin. Endocrinol. Metab. **18**:787, 1958.
76. Uete, T., and Venning, E. H.: The effect of cortisone and spirolactone on potassium excreting action of aldosterone and desoxycorticosterone, Proc. Soc. Exp. Biol. Med. **109**:760, 1962.
77. Koczorek, K. R., Jahrmärker, H., Hofmann, H., Vogt, W., Schmieder, P., Simon, B., and Balde, E.: Kombinierte Anwendung antikaliuretischer Substanzen mit konventionellen Diuretika, *in*, Renaler Transport und Diuretika. Internationales Symposion Feldafing 1968, edited by K. Thurau and H. Jahrmärker, Berlin, 1969, Springer Verlag, pp. 269-271.
78. Kagawa, C. M., Sturtevant, F. M., and Van Arman, C. G.: Pharmacology of a new steroid that blocks salt activity of aldosterone and desoxycorticosterone, J. Pharmacol. Exp. Ther. **126**:123, 1959.
79. Liddle, G. W.: Specific and nonspecific inhibition of mineralocorticoid activity, Metabolism **10**:1021, 1961.
80. Herman, T. S., Fimognari, G. M., and Edelman, I. S.: Studies on renal aldosterone-binding proteins, J. Biol. Chem. **243**:3849, 1968.
81. Erbler, H. C., Wernze, H., and Hilfenhaus, M.: Effect of the aldosterone antagonist canrenone on plasma aldosterone concentration and plasma renin activity, and on the excretion of aldosterone and electrolytes by man, Eur. J. Clin. Pharmacol. **9**:253, 1976.
82. Grohmann, H. W., Theisen, K., Halbritter, R., Koczorek, K., and Jahrmärker, H.: Zum Verhalten der Refraktärzeit des menschlichen Herzens unter Aldadiene-Kalium, in, Extrarenal activity of aldosterone and its metabolites, edited by W. Bendel et al., Amsterdam, 1972, Excerpta Medica, pp. 119-121.
83. Strauer, B. E., Avenhaus, H., and Nose, M.: Evidence for a positive inotropic effect of aldadiene on the isolated ventricular myocardium, Klin. Wochenschr. **50**:387, 1972.
84. Tanz, R. D.: Studies on the inotropic action of aldosterone on isolated cardiac tissue preparations including the effects of pH, ouabain and SC-8109, J. Pharmacol. Exp. Ther. **135**:71, 1962.
85. Schröder, R., Ramdohr, B., Hüttemann, U., and Schuren, K. P.: Direkte positiv-inotrope Herzwirkung von Aldactone (Spironolacton, Canrenoat-Kalium), Dtsch. Med. Wochenschr. **97**:1535, 1972.
86. Schröder, R., Schüren, K. P., Biamino, G., Meyer, V., and Sadée, W.: Positiv-inotrope Herzwirkung von Aldadien-Kalium (Aldactone pro injectione), Klin. Wochenschr. **49**:1093, 1971.
87. Strauer, B. E.: The influence of the aldosterone-antagonist spironolactone on myocardial contractility, Arch. Int. Pharmacodyn. Ther. **201**:59, 1973.
88. Coraboeuf, E., and Deroubaix, E.: Effect of a spirolactone derivative, sodium canrenoate, on mechanical and

electrical activities of isolated rat myocardium, J. Pharmacol. Exp. Ther. **191**:128, 1974.
89. Kleeberg, U. R., and Belz, G. G.: Die Hemmung der Na^+-K^+-Membran-ATPase und der Rubidium-Aufnahme menschlicher Erythrozyten durch Spironolacton und seine Metaboliten, Verh. Dtsch. Ges. Inn. Med. **80**:1521, 1974.
90. Ferlinz, R. E., Schroers, E., and Stadeler, H. J.: Ergebnisse der Behandlung der chronischen generellen alveolären Hypoventilation mit Aldadiene-Kalium, Med. Welt **20**:1751, 1969.
91. Hänel, J.: Aldactone-Wirkung auf die fortgeschrittene respiratorische Insuffizienz (respiratorische Azidose) des chronischen Cor pulmonale, München. Med. Wochenschr. **105**:2179, 1963.
92. Hüttemann, U., and Schüren, K. P.: Zur Behandlung des chronischen Cor Pulmonale mit Aldactone (Spironolacton, Canrenoat-Kalium), Dtsch. Med. Wochenschr. **97**:1533, 1972.
93. Hüttemann, U., and Schüren, K. P.: Die Wirkung von Aldactone auf Atmung und Lungenkreislauf beim chronischen Cor pulmonale, Klin. Wochenschr. **50**:953, 1972.
94. Noble, M. I. M., Trenchard, D., and Guz, A.: The value of diuretics in respiratory failure, Lancet **2**:257, 1966.
95. Pocidalo, J. J., and Weber, J.: L'aldactone chez les insuffisants respiratoire chroniques avec coeur pulmonaire chroniques, *in,* Colloque sur la Spironolactone, edited by R. Cattan, Paris, 1962, Ballière, pp. 255-259.
96. Nolte, D., and Lueder-Luehr, J.: Untersuchungen an Gesunden zur Frage der atemstimulierenden Wirkung von Spirolactone, Klin. Wochenschr. **51**:200, 1973.
97. Landau, R. L., Bergenstal, D. M., Lugibihl, K. and Kascht, M. E.: The metabolic effects of progesterone in man, J. Clin. Endocrinol. Metab. **15**:1194, 1955.
98. Schäfer, J. H., Hüttemann, U., and Schüren, K. P.: Untersuchungen zur zentralen Atemwirksamkeit von Canrenoat-Kalium, Klin. Wochenschr. **51**:674, 1973.
99. Cochrane, G. M., and Clark, T. J. H.: Ventilatory response to spironolactone in respiratory failure, Br. J. Dis. Chest **66**:67, 1972.
100. Erbler, H. C.: Suppression by the spironolactone metabolite canrenone of plasma testosterone in man, Naunyn Schmiedebergs Arch. Pharmacol. **285**:403, 1974.
101. Stripp, B., Taylor, A. A., Bartter, F. C., Gillette, J. R., Loriaux D. L., Easley R., and Menard, R. H.: Effect of spironolactone on sex hormones in man, J. Clin. Endocrinol. Metab. **41**:777, 1975.
102. Basinger, G. T., and Gittes, R. F.: Antiandrogenic effects of spironolactone in rats, J. Urol. **111**:77, 1974.
103. Steelman, S. L., Brooks, J. R., Morgan, E. R., and Patanelli D. J.: Antiandrogenic activity of spironolactone, Steroids **14**:449, 1969.
104. Castro, J. E., Griffiths, H. J., and Edwards, E. D.: A double-blind, controlled clinical trial of spironolactone for benign prostatic hypertrophy, Br. J. Surg. **58**:485, 1971.
105. Elliot, H. C.: Reduced adrenocortical steroid excretion rates in man following aspirin administration, Metabolism **11**:1015, 1962.
106. Hofmann, L. M., Krupnick, M. I., and Garcia, H. A.: Interactions of spironolactone and hydrochlorothiazide with aspirin in the rat and dog, J. Pharmacol. Exp. Ther. **180**:1, 1972.
107. Tweeddale, M. G., and Ogilvie, R. I.: Antagonism of spironolactone-induced natriuresis by aspirin in man, N. Engl. J. Med. **289**:198, 1973.
108. Tweeddale, M. G.: Antagonism between antipyretic analgesic drugs and spironolactone in man, Clin. Res. **22**:727A, 1974.
109. Ramsay, L. E., Harrison, I. R., Shelton, J. R., and Vose, C. W.: Influence of acetylsalicylic acid on the renal handling of a spironolactone metabolite in healthy subjects, Eur. J. Clin. Pharmacol. **10**:43, 1976.
110. Hofmann, L. M., and Garcia, H. A.: Interaction of spironolactone and indomethacin at the renal level, Proc. Soc. Exp. Biol. Med. **141**:353, 1972.
111. Steiness, E.: Renal tubular secretion of digoxin, Circulation **50**:103, 1974.
112. Radzialowski, F. M.: Effect of spironolactone and pregnenolone-16α carbonitrile on bilirubin metabolism and plasma levels in male and female rats, Biochem. Pharmacol. **22**:1607, 1973.
113. Zsigmond, G., and Solymoss, B.: Effect of spironolactone, pregnenolone-16α-carbonitrile and cortisol on the metabolism and biliary excretion of sulfobromophthalein and phenol-3,6-dibromophthalein disulfonate in rats, J. Pharmacol. Exp. Ther. **183**:499, 1972.
114. Solymoss, B., and Zsigmond, G.: Effect of various steroids on the hepatic glucuronidation and biliary excretion of bilirubin, Can. J. Physiol. Pharmacol. **51**:319, 1972.
115. Haataja, M., Nieminen, L., Kangas, L., Möttönen, M., and Bjondahl, K.: Effect of spironolactone on pentobarbital anaesthesia, diazepam metabolism and toxicity of spironolactone and furosemide, Ann. Med. Exp. Biol. Fenn. **50**:57, 1972.
116. Solymoss, B., Toth, S., Varga, S., Werringloer, J., and Zsigmond, G.: Effect of spironolactone and ethylestrenol on benzo(a)pyrene hydroxylase (EC 1.14.1.1) and other chemical constituents of hepatic microsomes, Can. J. Physiol. Pharmacol. **49**:841, 1971.
117. Stripp, B., Hamrick, M. E., Zampaglione, N. G., and Gillette, J. R.: The effect of spironolactone on drug metabolism by hepatic microsomes, J. Pharmacol. Exp. Ther. **176**:766, 1971.
118. Gerald, M. C., and Feller, D. R.: Evidence for spironolactone as a possible inducer of liver microsomal enzymes in mice, Biochem. Pharmacol. **19**:2529, 1970.
119. Feller, D. R., and Gerald, M. C.: Interactions of spironolactone with hepatic microsomal drug-metabolizing enzyme systems, Biochem. Pharmacol. **20**:1991, 1971.
120. Talcott, R. E., and Stohs, S. J.: Metabolism of aniline and hexobarbital by liver homogenates of spironolactone-pretreated male rats, J. Pharm. Sci. **61**:296, 1972.
121. Talcott, R. E., and Stohs, S. J.: The effect of cyproterone acetate pretreatment on the *in vitro* metabolism of aniline, hexobarbital and ^{3}H-digitoxigenin, J. Pharmacol. Exp. Ther. **184**:419, 1973.
122. Solymoss, B., Classen, H. G., and Varga, S.: Increased hepatic microsomal activity induced by spironolactone and other steroids, Proc. Soc. Exp. Biol. Med. **132**:940, 1969.
123. Solymoss, B., Krajny, M., Varga, S., and Werringloer, J.: Suppression by nucleic acid- and protein-synthesis inhibitors of drug detoxication induced by spironolactone or ethylestrenol. J. Pharmacol. Exp. Ther. **174**:473, 1970.
124. Solymoss, B., Somogyi, Á., and Kovács, K.: Effect of spironolactone and proadifen on 7,12-dimethylbenz(a) anthracene-induced haematologic changes, Haematologia **5**:87, 1971.
125. Solymoss, B., Varga, S., Krajny, M., and Werringloer, J.: Influence of spironolactone and other steroids on the enzymatic decay and anticoagulant activity of bishydroxycoumarin, Thromb. Diath. Haemorrh. **23**:562, 1970.
126. Solymoss, B., Tóth, S., Varga, S., and Krajny, M.: The influence of spironolactone on its own biotransformation, Steroids **16**:263, 1970.

127. Feller, D. R., and Gerald, M. C.: Stimulation of liver microsomal drug metabolism in male and female mice by spironolactone and aldadiene, Proc. Soc. Exp. Biol. Med. **136**:1347, 1971.
128. Vöhringer, H-F., Weller, L., and Rietbrock, N.: Influence of spironolactone pretreatment on pharmacokinetics and metabolism of digitoxin in rats, Naunyn Schmiedebergs Arch. Pharmacol. **287**:129, 1975.
129. Klaassen, C. D.: Stimulation of the development of the hepatic excretory mechanism for ouabain in newborn rats with microsomal enzyme inducers, J. Pharmacol. Exp. Ther. **191**:212, 1974.
130. Wirth, K. E., and Frölich, J. C.: Effect of spironolactone on excretion of ^{3}H-digoxin and its metabolites in rats, Eur. J. Pharmacol. **29**:43, 1974.
131. Klaassen, C. D.: Effect of microsomal enzyme inducers on the biliary excretion of cardiac glycosides, J. Pharmacol. Exp. Ther. **191**:201, 1974.
132. Buck, S. H., and Lage, G. L.: Possible mechanism of the prevention of digitoxin toxicity by spironolactone in the mouse, Arch. Int. Pharmacodyn. Ther. **189**:192, 1971.
133. Castle, M. C., and Lage, G. L.: Effect of pretreatment with spironolactone, phenobarbital or β-diethylaminoethyl diphenylpropylacetate (SKF 525-A) on tritium levels in blood, heart and liver of rats at various times after administration of [3H]-digitoxin, Biochem. Pharmacol. **21**:1449, 1972.
134. Solymoss, B., Toth, S., Varga, S., and Krajny, M.: Influence of spironolactone and other steroids on the plasma level of digitoxin. *in*, Recent advances in studies on cardiac structure and metabolism, vol. 1, edited by E. Bajusz, and G. Rona, Baltimore, 1972, University Park Press, pp. 605-611.
135. Castle, M. C., and Lage, G. L.: Enhanced biliary excretion of digitoxin following spironolactone as it relates to the prevention of digitoxin toxicity, Res. Commun. Chem. Pathol. Pharmacol. **5**:99, 1973.
136. Abshagen, U.: Effects of pretreatment with spironolactone on pharmacokinetics of 4'''-methyldigoxin in rats, Naunyn Schmiedebergs Arch. Pharmacol. **278**:91, 1973.
137. Wirth, K. E., and Frölich, J. C.: The influence of spironolactone on the excretion and metabolism of ^{3}H-digoxin in the rat, Naunyn Schmiedebergs Arch. Pharmacol. **282**(Suppl.):R107, 1974.
138. Gerald, M. C., and Feller, D. R.: Stimulation of barbiturate metabolism by spironolactone in mice, Arch Int. Pharmacodyn. Ther. **187**:120, 1970.
139. Wirth, K. E., Frölich, C. J., Hollifield, J. W., Falkner, F. C., Sweetman, B. S., and Oates, J. A.: Metabolism of digitoxin in man and its modification by spironolactone, Eur. J. Clin. Pharmacol. **9**:345, 1975.
140. Taylor, S. A., Rawlins, M. D., and Smith, S. E.: Spironolactone—a weak enzyme inducer in man, J. Pharm. Pharmacol. **24**:578, 1972.
141. Huffman, D. H., Shoeman, D. W., Pentikäinen, P., and Azarnoff, D. L.: The effect of spironolactone on antipyrine metabolism in man, Pharmacology **10**:338, 1973.
142. Huffman, D. H., Pentikäinen, P., Shoeman, D. W., and Azarnoff, D. L.: The effect of spironolactone on antipyrine metabolism in man, Clin. Res. **21**:469, 1973.
143. von Bergmann, K., Schwarz, H. P., and Paumgartner, G.: Effect of phenobarbital, spironolactone and pregnenolone-16α-carbonitrile on bile formation in the rat, Naunyn Schmiedebergs Arch. Pharmacol. **287**:33, 1975.
144. Leber, H. W., Rawer, P., and Schütterle, G.: Beeinflussung mikrosomaler Enzyme der Rattenleber durch Spironolactone, Etacrynsäure und Furosemid, Klin. Wochenschr. **49**:116, 1971.
145. Horvath, E., Somogyi, Á., and Kovács, K.: Einfluss von Spironolacton auf das Regenerationvermögen der Leber bei Ratten, Klin. Wochenschr. **48**:385, 1970.
146. Selye, H., Mecs, J., and Savoie, L.: Inhibition of anesthetics and sedative actions by spironolactone, Anesthesiology **31**:261, 1969.
147. Abshagen, U., Rennekamp, H., and Kuhlmann, J.: Effects of pretreatment with spironolactone on pharmacokinetics of 4'''-methyldigoxin in man, Naunyn Schmiedebergs Arch. Pharmacol. **292**:87, 1976.
148. Selye, H.: Mercury poisoning: prevention by spironolactone, Science **169**:775, 1970.
149. deGuzman, N. T., and Yeh, B. K.: Potassium canrenoate in the treatment of long-term digoxin-induced arrhythmias in conscious dogs, Am. J. Cardiol. **35**:413, 1975.
150. Selye, H., Krajny, M., and Savoie, L.: Digitoxin poisoning: prevention by spironolactone, Science **164**:842, 1969.
151. Talcott, R. E., and Stohs, S. J.: Effect of phenobarbital and spironolactone pretreatment on digitoxin-induced mortality in male and female rats, Arch. Int. Pharmacodyn. Ther. **204**:86, 1973.
152. Selye, H., Mécs, I., and Tamura, T.: Effect of spironolactone and norbolethone on the toxicity of digitalis compounds in the rat, Br. J. Pharmacol. **37**:485, 1969.
153. Solymoss, B., Toth, S., Varga, S., and Selye, H.: Protection by spironolactone and oxandrolone against chronic digitoxin or indomethacin intoxication, Toxicol. Appl. Pharmacol. **18**:586, 1971.
154. Savoie, L., Krajny, M., and Selye, H.: Prophylactic action of spironolactone in digitoxin poisoning, Proc. Can. Fed. Biol. Soc. **12**:58, 1969.
155. Carlson, G. P., Fuller, G. C., and Fausto, N.: Effects of spironolactone on carbon tetrachloride hepatotoxicity, Proc. Soc. Exp. Biol. Med. **145**:182, 1974.
156. Selye, H., and Solymoss, B.: Protection by catatoxic steroids against meprobamate, Neuropharmacology **9**:327, 1970.
157. Selye, H.: Prevention of mephenesin intoxication by catatoxic steroids, Acta Pharmacol. Toxicol. **28**:145, 1970.
158. Selye, H.: Prevention of indomethacin-induced intestinal ulcers by various catatoxic steroids, Exp. Med. Surg. **28**:169, 1970.
159. Selye, H.: Prevention of indomethacin-induced intestinal ulcers by spironolactone and norbolethone, Can. J. Physiol. Pharmacol. **47**:981, 1969.
160. Selye, H.: Role of the liver in the prevention of indomethacin-induced intestinal ulcers by spironolactone, Acta Hepatosplenol. **17**:393, 1970.
161. Selye, H., Mandeville, R., and Yeghiayan, E.: On the catatoxic effect of antimineralocorticoids, Naunyn Schmiedebergs Arch. Pharmacol. **266**:34, 1970.
162. Selye, H.: Protection against methyprylon overdosage by catatoxic steroids, Can. Anaesth. Soc. J. **17**:107, 1970.
163. Menard, R. H., Martin, H. F., Stripp, B., Gillette, J. R., and Bartter, F. C.: Spironolactone and cytochrome P-450: impairment of steroid hydroxylation in the adrenal cortex, Life Sci. **15**:1639, 1974.
164. Erbler, H. C.: On the mechanism of the inhibitory action of the spironolactone SC 9376 (aldadiene) on the production of corticosteroids in rat adrenals in vitro, Naunyn Schmiedebergs Arch. Pharmacol. **277**:139, 1973.
165. Bravo, E. L., Dustan, H. P., and Tarazi, R. C.: Spironolactone as a nonspecific treatment for primary aldosteronism, Circulation **48**:491, 1973.
166. Beevers, D. G., Brown, J. J., Ferriss, J. B., Fraser, R.,

Lever, A. F., and Robertson, J. I. S.: The use of spironolactone in the diagnosis and the treatment of hypertension associated with mineralocorticoid excess, AM. HEART J. **86**:404, 1973.
167. Mantero, F., Armanini, D., and Urbani, S.: Antihypertensive effect of spironolactone in essential, renal and mineralocorticoid hypertension, Clin. Sci. Mol. Med. **45**:219s, 1973.
168. Peart, W. S.: Renin-angiotensin system, N. Engl. J. Med. **292**:302, 1975.
169. Distler, A., Keim, H. J., Philipp, T., et al.: Austauschbares Natrium, Gesamtkörperkalium, Plasmavolumen und blutdrucksenkende Wirkung verschiedener Diuretika bei Patienten mit essentieller Hypertonie und niedrigem Plasmarenin. Dtsch. Med. Wochenschr. **99**:864, 1974.
170. Klumpp, F., Braun, B., Klaus, D., Lemke, R., Zehner, J., and Zöfel, P.: Spironolacton und Thiabutazid bei der Behandlung der essentiellen Hypertonie, Dtsch. Med. Wochenschr. **100**:577, 1975.
171. Carey, R. M., Douglas, J. G., Schweikert, J. R., and Liddle, G. W.: The syndrome of essential hypertension and suppressed plasma renin activity, Arch. Intern. Med. **130**:849, 1972.
172. Hunyor, S. N., Zweifler, A. J., Hansson, L., Schork, M. A., and Ellis, C.: Effect of high dose spironolactone and chlorthalidone in essential hypertension: relation to plasma renin activity and plasma volume, Aust. N. Z. J. Med. **5**:17, 1975.
173. Acchiardo, S., Dustan, H. P., and Tarazi, R. C.: Similar effects of hydrochlorothiazide and spironolactone on plasma renin activity in esential hypertension, Cleve. Clin. Q. **39**:153, 1972.
174. Drayer, J. I. M., Kloppenborg, P. W. C., Festen, J., van 't Laar, A., and Benraad, T. J.: Intrapatient comparison of treatment with chlorthalidone, spironolactone and propranolol in normoreninemic essential hypertension, Am. J. Cardiol. **36**:716, 1975.
175. Lowder, S. C., and Liddle, G. W.: Prolonged alteration of renin responsiveness after spironolactone therapy, N. Engl. J. Med. **291**:1243, 1974.
176. Fáloon, W. W.: The effects of changing sodium and potassium intakes on the action of spironolactones, *in*, The clinical use of aldosterone antagonists, edited by F. C. Bartter, Springfield, Ill., 1960, Charles C Thomas, Publisher, pp. 115-126.
177. Ross, E. J.: Importance of potassium supplements during the use of spironolactone and thiazide diuretics, Br. Med. J. **1**:1508, 1961.
178. Taylor, F. F., and Faloon, W. W.: The role of potassium in the natriuretic response to a steroidal lactone (SC-9420), J. Clin. Endocrinol. Metab. **19**:1683, 1959.
179. Hood, W. G., Jr., Hill, S. R., Jr., Pittman, J. A., Jr., and Farmer, T. A., Jr.: Studies on the metabolic effects of spironolactone in man, Ann. N. Y. Acad. Sci. **88**:864, 1960.
180. Holten, C., and Peterson, V. P.: Malignant hypertension with increased secretion of aldosterone and depletion of potassium, Lancet **2**:918, 1956.
181. Mountokalakis, T., Merikas, G., Skopelitis, P., Vardakis, M., Sevastos, N., and Alivisatos, J.: Changes of fractional renal clearance of magnesium after sprionolactone administration in normal subjects, Klin. Wochenschr. **53**:633, 1975.
182. Wills, M. R., Gill, J. R., Jr, and Bartter, F. C.: The interrelationships of calcium and sodium excretions, Clin. Sci. **37**:621, 1969.
183. Prati, R. C., Alfrey, A. C., and Hull, A. R.: Spironolactone-induced hypercalciuria, J. Lab. Clin. Med. **80**:224, 1972.
184. Greenblatt, D. J., and Koch-Weser, J.: Adverse reactions to spironolactone, J. A. M. A. **225**:1387, 1973.
185. Winter, I. C.: Adverse reactions to spironolactone, J. A. M. A. **225**:1387, 1973.
186. Pongpaew, C., Songkhla, R. N., and Kozam, R. L.: Hyperkalemic cardiac arrhythmia secondary to spironolactone, Chest **63**:1023, 1973.
187. Sjoberg, W. E., Jr., and Kreisle, J. E.: Hyperkalemia and sudden death during spironolactone (Aldactone) therapy, Texas State J. Med. **58**:1022, 1962.
188. Herman, E., and Rado, J.: Fatal hyperkalemic paralysis associated with spironolactone, Arch. Neurol. **15**:74, 1966.
189. Radó, J. P., Marosi, J., Takó, J., Dévényi, I.: Hyperkalemic intermittent paralysis associated with spironolactone in a patient with cardiac cirrhosis, AM. HEART J. **76**:393, 1968.
190. Greenblatt, D. J., and Koch-Weser, J.: Gynecomastia and impotence complications of spironolactone therapy, J. A. M. A. **223**:82, 1973.
191. Clark, E.: Spironolactone therapy and gynecomastia, J. A. M. A. **193**:163, 1965.
192. Mann, N. M.: Gynecomastia during therapy with spironolactone, J. A. M. A. **184**:778, 1963.
193. Pentikainen, P. J., Pentikainen, L. A., Huffman, D. H., and Azarnoff, D. L.: The effect of spironolactone on sexual hormones in males, Clin. Res. **21**:472, 1973.
194. Levitt, J. I.: Spironolactone therapy and amenorrhoe, J. A. M. A. **211**:2014, 1970.
195. Mroczek, W. J., Davidov, M. E., Horoschak, A. A., and Finnerty, F. A., Jr.: Canrenoate in normal man, Clin. Pharmacol. Exp. Ther. **16**:336, 1974.
196. Erbler, H. C.: The effect of saluretics and spironolactone on aldosterone production and electrolyte excretion in man, Naunyn Schmiedebergs Arch. Pharmacol. **286**:145, 1974.
197. Loube, S. D., and Quirk, R. A.: Breast cancer associated with administration of spironolactone, Lancet **1**:1428, 1975.
198. Ramsay, L., Harrison, I., Shelton, J., and Tidd, M.: Relative potency of prorenoate and spironolactone in normal man, Clin. Pharmacol. Ther. **18**:391, 1975.
199. Ramsay, L. E., Hessian, P., and Tidd, M. J.: Bioassay of aldosterone antagonists in normal human subjects; a relationship between the level of plasma uric acid before treatment and apparent drug responses, Br. J. Clin. Pharmacol. **2**:271, 1975.
200. Ramsay, L. E., Shelton, J. R., and Tidd, M. J.: The pharmacodynamics of single doses of prorenoate potassium and spironolactone in fludrocortisone treated normal subjects, Br. J. Clin. Pharmacol. **3**:475, 1976.