Table II shows the activities of enzyme MAO and COMT in adrenal gland during 8 h of metopirone administration in dpm. At $^1/_2$, 4 and 8 h the activity of MAO rose to 111, 180 and 140% of its control values. The COMT activity also rose by 6, 30 and 100% during the above intervals. The urinary excretion of VMA/kg body wt./24 h in control, adrenalectomized and hypophysectomized rats injected with 4 IU of ACTH is also indicated in Table II. Hypophysectomy and adrenalectomy produced respective rises of 20 and 60% in VMA excretion. The treatment with ACTH only once declined the excretion of VMA to control level in hypophysectomized rats.

Discussion. Our results show that the decline in glucocorticoid concentration or their complete absence produces significant shifts in urinary and plasmatic catecholamines. These shifts in catecholamine excretion and release are immediately followed by their respective effects on hepatic glycogen and plasma glucose. Early studies[23] suggested that hormones of the adrenal cortex and catecholamines act as a single physiological unit. Many effects of catecholamines cannot be induced in the absence of corticosteroids[24]. HÖKFELT[25] reported that ACTH treatment influences the catecholamine levels in adrenals and heart. Studies performed during past few years provide sufficient evidence that the adrenal glucocorticoid hormones are of primary significance for the physiology of medullary chromaffin cells[26]. The decline in the concentration of glucocorticoids due to hypophysectomy severely effects adrenaline stores of adrenal gland[27,28]. The urinary excretion of adrenaline and noradrenaline in hypophysectomized humans during corticoid therapy provide supporting evidence that these hormones regulate excretion of catecholamines[29]. The studies on the role of glucocorticoids on adrenaline storage in adrenals or the maintenance of adrenal PNMT activity provide contrary evidence in catecholamine excretion, release and metabolism[2,27]. The inactivation of adrenal steroidogenesis by hypophysectomy declines the adrenal stores of adrenaline and PNMT activity significantly[2,4]. The administration of hydrocortisone or dexamethasone to hypophysectomized animals could maintain adrenal PNMT activity and adrenaline stores at control levels[2,4]. But the decline in glucocorticoids increases MAO and COMT activities. This suggests that these two enzymes, contrary to PNMT, have different hormonal specificities. PNMT is induced by glucocorticoids while MAO and COMT are inhibited by them. The higher urinary excretion of VMA in hypophysectomized and adrenalectomized rats provides good evidence for this observation. Recent studies[30,31] clearly indicate that adrenalectomy is followed by marked increase in cardiac MAO. Our experiments in progress show that adrenalectomy or hypophysectomy of the rat and rabbit foetuses or new-born results in significant rises in MAO and COMT activities in most of the body organs including the cerebral tissues.

Our preference for the use of Metopirone was based on the fact that it blocks the biosynthesis of corticoids immediately after its infusion and reduces cortisol to zero in just 4 h[8]. The rise in adrenaline urinary excretion after blocking glucocorticoid biosynthesis reflects that the presence of these hormones limits the excretion of adrenaline in blood which is the main source of urinary excretion of adrenaline[32]. The significant rise in urinary adrenaline of adrenalectomized rats after metopirone administration suggests that adrenaline from other sources of the body[33] was released by inhibition of extra-adrenal glucocorticoids. The rises in VMA excretion after hypophysectomy or adrenalectomy seem to be comparable with the concentrations of glucocorticoids in these two conditions. The corticoids are at the lowest level following adrenalectomy, while in hypophysectomized animals the adrenal cortex still functions and synthesizes these hormones at a lower intensity.

As the possible mechanisms by which glucocorticoids inhibit MAO and COMT activities, it could be suggested that the corticoids interfere with the synthesis of new enzyme protein. It appears that these hormones exert their effects at the level of RNA transcription from DNA[34].

These observations suggest that glucocorticoids which induce biosynthesis of adrenaline are equally important for the rate limiting control of catecholamine release, excretion and degradation.

Résumé. Nous avons étudié l'influence de l'inhibition de la biosynthèse des glucocorticoïdes par la Métopirone, sur la libération, la dégradation et l'excrétion des catécholamines chez le rat. Les résultats montrent qu'une diminution du taux de corticoïdes circulants chez des animaux normaux affecte profondément l'excrétion urinaire de l'adrénaline et de la noradrénaline. L'adrénalinémie est quadruplée quand le taux des corticoïdes est minimum. L'excrétion du VMA est augmentée de même que les activités monoamine-oxidase et catéchol-*o*-méthyl transférase.

H. PARVEZ and S. PARVEZ

Université de Paris XI, Centre d'Orsay, Laboratoire d'endocrinologie, Faculté des Sciences, F–91 Orsay (France),
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The Influence of Secretin on the Elimination of ^{14}C-Edrophonium in Bile

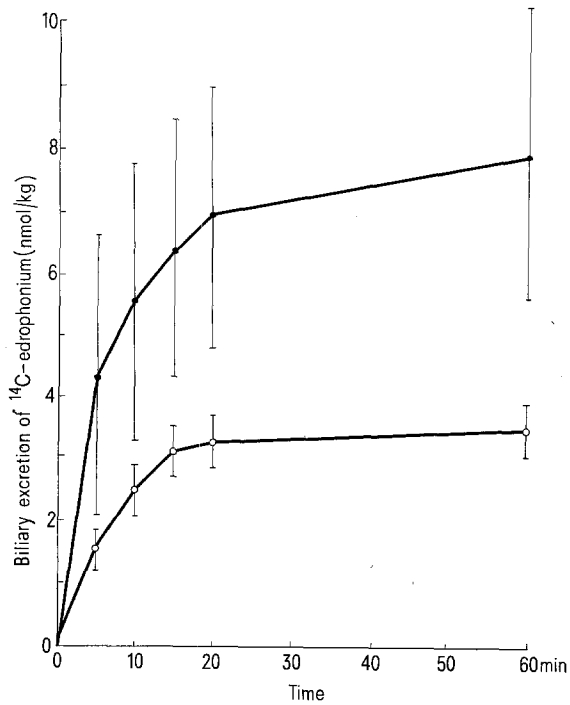
Although ^{14}C-edrophonium is mainly eliminated in bile as a glucuronide conjugate, small amounts of the unchanged drug can also be identified[1]. Biliary excretion of ^{14}C-edrophonium (but not of its metabolites) is influenced by the route of intravascular administration; after injection into the hepatic arterial tree, the proportion of the unchanged drug eliminated in bile is significantly greater than after i.v. injection[2]. The results of

these experiments are consistent with the direct transfer of ^{14}C-edrophonium from plasma to bile via the capillary plexus in the bile ductules, which is preferentially supplied by hepatic arterial blood[3]. (In contrast, the liver sinusoids are vascularized by both hepatic arterial and portal venous blood.) Since circumstantial evidence[4,5] suggests that secretin choleresis is dependent on the action of the hormone at a similar site in the distal biliary tree, the effects of secretin on the elimination of unchanged ^{14}C-edrophonium in bile were studied.

Materials and methods. Wistar rats of either sex (approximately 250 g body weight) were anaesthetized with urethane (1.4 g/kg, i.p.), the abdomen was opened, and the common bile duct and the left gastric artery were cannulated[2]. A fine polyethylene cannula was also placed in the left common carotid artery, and threaded down the aorta until its tip was at the level of the coeliac axis. At the start of each experiment, ^{14}C-edrophonium chloride (10.0 μCi/μmol; 2.0 μmol/kg) was injected into the hepatic arterial circulation by means of the cannulated left gastric artery, and samples of bile were collected and weighed at 5, 10, 15, 20 and 60 min; biliary volumes were estimated by dividing the weight of each sample by the specific gravity of bile. In some experiments, secretin (Boots Pure Drug Co. Ltd.; 1 U/kg/min) was infused intra-arterially at the level of the coeliac axis. Total radioactivity in samples of bile (usually 25 μl) was counted by liquid scintillation spectrometry at an efficiency of approximately 90%; ^{14}C-edrophonium was then separated from its metabolites by paper chromatography and counted in a similar manner.

Results. Infusion of secretin enhanced control rates of biliary secretion by approximately 70%. At 5, 10, 15, 20 and 60 min the incremental change in flow observed during secretin choleresis was similar, and at each time interval the concentration of unchanged ^{14}C-edrophonium in bile slightly increased or remained constant (Table). Values for the biliary excretion of ^{14}C-edrophonium were summated at 5, 10, 15, 20 and 60 min, and the results (see Figure) represent the mean ± standard deviation of 4–6 experiments. In the absence of exogenous secretin, total elimination of the unchanged drug in bile increased from 1.52 ± 0.32 nmol/kg at 5 min to 3.10 ± 0.40 nmol/kg at 15 min, although there was little or no further increase between 15 and 60 min. A similar pattern (associated with a marked increase in individual variability) was observed in experiments in which secretin was infused, although the quantitative excretion of the unchanged drug was invariably greater in the presence of the hormone (Figure). In these conditions, total elimination of unchanged ^{14}C-edrophonium increased from 4.29 ± 2.33 nmol/kg at 5 min to 7.93 ± 2.28 nmol/kg at 60 min. Differences between control and secretin-infused animals were invariably statistically significant ($P < 0.05$) at each time interval.

Discussion. In the guinea-pig, the clearance of inert solutes during secretin choleresis suggests that substances with a molecular weight above 100 (for instance, erythritol, mannitol and sucrose) do not readily cross epithelial cells in the bile duct and ductules[6]. In contrast, the permeability of the ductular system is apparently greater in the rat, since the clearance of both erythritol (MW = 122) and mannitol (MW = 182) is enhanced by secretin[7]. The results of the present experiments support this conclusion, since the biliary elimination of the phenolic quaternary amine ^{14}C-edrophonium was enhanced by secretin in the rat. Although intra-arterial infusion of the hormone increased bile flow rates by approximately 70%, the concentration of the unchanged drug slightly increased or remained constant. These experiments provide further evidence that low molecular weight drugs may be directly transferred from rat plasma to bile at distal ductular sites. If,



Biliary excretion of unchanged ^{14}C-edrophonium after injection into the hepatic arterial circulation of the rat. ○—○, control studies; ●—●, secretin infusion (1 U/kg/min). Each point and vertical bar represents the mean ± standard deviation of 4–6 experiments.

The effect of secretin on bile flow rates and the concentration of ^{14}C-edrophonium

Time (min)	Bile flow rate (μl/kg/min)		Concentration of ^{14}C-edrophonium (nmol/kg/ml)	
	Control rats	Secretin-infused rats	Control rats	Secretin-infused rats
5	29.1 ± 3.2	50.2 ± 4.8	43.8 ± 5.0	70.3 ± 12.0
10	30.6 ± 3.2	50.0 ± 4.1	25.4 ± 2.0	22.1 ± 3.0
15	30.4 ± 1.9	47.4 ± 5.9	18.5 ± 8.0	17.1 ± 5.6
20	29.6 ± 1.8	45.3 ± 7.1	5.1 ± 0.5	14.1 ± 6.1
60	26.9 ± 2.3	45.2 ± 6.8	1.2 ± 0.1	1.1 ± 0.2

Values represent the mean ± standard error of the mean of 4–6 experiments.

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for instance, ^{14}C-edrophonium was eliminated via the biliary canaliculus, its concentration in bile should be reduced (and its rate of excretion unaffected) during choleresis induced by agents acting on ductal or ductular mechanisms. In fact, circumstantial evidence[2] suggests that all the quaternary amine that gains access to parenchymal liver cells is rapidly metabolized to a 3-oxyglucuronide prior to excretion by the canaliculus.

In the present experiments, the influence of secretin on the elimination of ^{14}C-edrophonium in bile was most marked during the first 5 min. The initial increase in biliary elimination may be due to the transient high concentration of the drug in the periductal and periductular capillaries immediately after its injection into the hepatic arterial tree (i.e., before equilibration throughout extracellular fluid has occurred). In general, the biliary excretion pattern in both control and secretin-infused animals appears to accurately reflect the rapid removal of ^{14}C-edrophonium from the circulation, since the drug is almost completely cleared from extracellular fluid within 20 min of i.v. administration[8].

In previous experiments[2], it was shown that the biliary elimination of unchanged ^{14}C-edrophonium was significantly greater after injection into the hepatic artery than after infusion into the portal vein. Both these studies and the results of the present experiments support the hypothesis that unchanged ^{14}C-edrophonium is directly transferred from plasma to bile across the ductal or ductular epithelium.

Résumé. On a étudié l'effet de la sécrétine sur l'élimination biliare de ^{14}C-edrophonium et montré que cette excrétion est significativement plus élevée pendant l'injection de la sécrétine.

D. J. BACK and T. N. CALVEY[9]

Department of Pharmacology and General Therapeutics, University of Liverpool, Liverpool L69 3BX (England),
18 May 1972.

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Effect of Sodium Deoxycholate on Net Transintestinal Movement in the Uraemic Rat: Acute Experiments[1]

Bile salts were reported to increase intestinal absorption of various hydrophilic substances[2,3]. It has been suggested that the mechanism of action consists of an alteration of membrane structure[4,5]. If increased solute lumen-to-blood (l-b) transfer is the result of an altered membrane permeability, then increased solute transfer in the opposite direction should also be possible.

The purpose of the present investigation was to determine the effects of an unconjugated bile salt, sodium deoxycholate (NaDC), on net solute blood-to-lumen (b-l) transfer in the uraemic rat. Increased intestinal elimination of uraemic waste products could be helpful in the management of uraemia.

Materials and methods. Male WC albino rats (450 to 600 g body weight) were binephrectomized by bilateral lumbar incision 36 h prior to experiments and fasted (with water allowed ad libitum). The experiments were carried out using in situ single loop preparations under light ether anesthaesia. A midline incision was made to locate the small intestine. A segment of 35 cm of the proximal small intestine (approximately 3 cm from the ligament of Treitz) was carefully ligated at its two ends. No major blood vessels were occluded by these ties. 3 ml of a prewarmed mannitol-NaCl solution in the presence or

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Net transintestinal solute and water flow with control solution A (no NaDC) and with solution B containing 2 m*M* NaDC (mean ± S.D.)

Solution	A (control)	B (NaDC)	A (control)	B (NaDC)	A (control)	B (NaDC)
No. of segments	7	6	6	8	6	6
Time of exposition	10 min	10 min	15 min	15 min	30 min	30 min
Sodium (μEq/cm)	[a]1.41 ± 0.90 (p = NS)	[a]1.18 ± 0.61	[a]1.36 ± 0.30 ($p < 0.05$)	[a]2.45 ± 0.97	[a]3.77 ± 1.66 (p = NS)	[a]4.15 ± 2.16
Potassium (μEq/cm)	[a]0.31 ± 0.07 (p = NS)	[a]0.38 ± 0.06	[a]0.39 ± 0.04 ($p < 0.01$)	[a]0.52 ± 0.08	[a]0.48 ± 0.09 (p = NS)	[a]0.58 ± 0.09
Calcium (μg/cm)	[a]2.05 ± 0.87 (p = NS)	[a]2.74 ± 1.37	[a]2.26 ± 1.44 (p = NS)	[a]2.36 ± 1.04	[a]2.75 ± 0.91 (p = NS)	[a]3.41 ± 1.75
Water (μl/cm)	[b]8.5 ± 9.1 (p = NS)	[b]11.1 ± 6.8	[b]8.2 ± 2.6 (p = NS)	[b]8.9 ± 4.8	[a]8.8 ± 12.1 (p = NS)	[a]15.8 ± 10.3

[a] net b-l transfer. [b] net l-b transfer.