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Pharmacology of Cyclosporine (Sandimmune)

VII. Pathophysiology and Toxicology of Cyclosporine in Humans and Animals

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A. Renal Haemodynamics

WITHOUT any doubt, the most troublesome of the unwanted actions of cyclosporine (CS)† has been its action to depress renal function. This effect is most easily detected in humans by the increase in serum creatinine and serum or blood urea concentrations. However, numerous measurements of glomerular filtration rate in both humans and animals have clearly shown this to be depressed. The additional assessments of renal plasma flow or of renal blood flow in humans and animals have enabled the effect of CS on renal haemodynamics to be determined. Furthermore, micropuncture studies of single nephrons in rats and dextran-sieving studies in humans have enabled the effect of CS on glomerular dynamics to be defined with some precision. Thus, although the mediator of these changes remains elusive, the means by which they occur are fairly clear.

The reduction in renal plasma flow or renal blood flow indicates that the resistance to flow in the renal vasculature is increased. If the vessels are not blocked, this indicates vasoconstriction in the arterioles, the major resistance vessels of the kidney. There are two sets of arterioles in the kidney, those in front of the glomerular capillaries and those behind them. Whereas plasma flow reflects the *combined* resistance of both, glomerular filtration rate also reflects the *relative* resistance in both, because this determines the pressure in the glomerular capillaries between them. Hence, changes in glomerular filtration relative to changes in renal plasma flow, or changes in the filtration fraction, can indicate which of the arterioles is predominantly affected.

With only few exceptions, all studies in animals given CS during a period of days or weeks have shown both filtration rate and renal plasma or blood flow to be depressed. Only in one group has the decrease in filtration rate not been accompanied by a decrease in renal plasma flow (20, 142, 143). In all other studies, filtration rate and renal perfusion both decrease so that the filtration fraction remains unchanged (88, 129, 77, 167, 45, 87, 10) or decreases slightly at very high doses (77). In humans, also, filtration rate and plasma flow both decrease, and filtration fraction is generally unchanged (8, 183, 75, 71, 36, 171, 25, 188, 130) or slightly depressed (132, 131, 180). Thus, all of the studies indicate that the major increase in vascular resistance comes more from the afferent vessels in front of the glomerulus than from the efferent vessels behind it.

Micropuncture studies of the superficial nephrons in rats, in which filtration pressure can be assessed and glomerular filtration and blood flow can be measured, have confirmed that afferent vasoconstriction predominates. In general, filtration rate decreases when low perfusion limits the fluid available for filtration, when the net filtration pressure is low, or when either the surface area or the permeability of the filtering membrane decreases. Since neither the surface area nor the permeability of the filtering membrane can be determined individually, the permeability of the entire filter-

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†Abbreviations used are: CS, cyclosporine; PG, prostaglandin; Tx, thromboxane; C-peptide, connecting peptide.

ing surface, the filtration coefficient, is assessed from the ratio of filtration rate to net filtration pressure.

These major determinants of glomerular filtration and the influence that chronic application of CS has upon them is illustrated in table 1. After CS, glomerular capillary pressure decreases (178, 87, 10) so that filtration pressure and filtration rate decrease, indicating an increase in afferent resistance. Glomerular blood flow decreases because of this increase in afferent resistance, together with a smaller increase in efferent resistance (87, 178, 10). The filtration coefficient, which reflects the permeability of the filtering surface, is not reduced by chronic treatment with CS (10) and can even be raised (178).

In humans, it is clearly not possible to study glomerular dynamics directly. However, the clearance of dextran molecules of varying sizes relative to that of inulin allows the movement of dextran across the glomerular membrane to be calculated from a theoretical model. It is possible to derive the net pressure and filtration coefficient needed to account for the dextran movement using the measured values for filtration rate, plasma flow, and plasma oncotic pressure. Such analyses have indicated that the filtration coefficient is unchanged by CS (130), but the filtration pressure is reduced because of a greater increase in afferent than efferent resistance (133).

The reason for the increase in renovascular resistance that lowers renal perfusion and glomerular filtration is not clear. However, the type of renal dysfunction that results is similar to that occurring in prerenal azotaemia, in which vasoconstriction lowers renal blood flow and glomerular filtration, but tubular reabsorption remains intact. This leads to a reduction of flow in the tubular system that enables more urea than normal to diffuse out of the tubules and back into the blood stream where it accumulates. Typically, the decrease in renal function is characterised by a greater increase in serum urea concentration than in serum creatinine concentration, just as has been seen in humans (9, 132, 66, 96, 53) and in rats treated with CS experimentally (77, 154, 157, 51, 174, 59, 191, 196).

TABLE 1
Glomerular dynamics in humans and animals

	Animals (ref.)	Humans (ref.)
Filtration pressure	↓ (178, 87, 10)	↓ (130
Filtration coefficient	= (178, 10)	= (130)
Afferent resistance	↑ (87, 10)	↑ (133)
Efferent resistance	↑ (178, 87, 10)	↑ (133)

B. Renal Tubular Function

Generally speaking, drugs that affect renal function usually also affect both the reabsorptive and the secretory functions of the renal tubules. Particularly characteristic is a depression in the reabsorption of sodium and filtered fluid along the entire nephron. This causes the percentage of the filtered sodium that is excreted in the urine to increase, the volume of urine produced to increase, and the concentration of the final urine to decrease. However, none of this seems to be the case with CS, which induces only subtle changes in the function of the tubules, without a generalised loss of reabsorptive capacity.

That fraction of the sodium filtered by the glomerulus that is reabsorbed by the tubules or is excreted in the urine is seldom affected by CS. In humans, fractional sodium excretion was either not elevated during CS therapy (192, 122, 43, 183) or was only minimally elevated (33). In rats also, fractional sodium excretion was either not increased by prolonged treatment with CS (10, 45, 46, 51, 194, 145, 193) or increased only marginally (20). Correspondingly, fractional sodium reabsorption was not depressed (88, 112).

Estimates of the fraction of sodium that is reabsorbed in the more proximal part of the nephron are believed to be provided by measuring the clearance of lithium relative to that of inulin. These studies indicate that fractional sodium reabsorption in the earlier nephron segments is, if anything, enhanced in patients treated with CS (192, 43, 183) and in rats given it experimentally (46, 45, 193, 192, 47, 44). These findings taken together indicate that, far from being depressed, sodium reabsorption by the tubule is unaffected or even increased during CS therapy.

Correspondingly, there is little evidence to suggest that the output of urine is increased by CS or that the urinary concentrating mechanism is impaired to more than a trivial extent. Urine volume was generally unchanged or only marginally increased in rats given CS experimentally (20, 193, 192, 113, 47, 44) and unchanged in humans treated with CS (43). Urine osmolality was unaltered or only marginally depressed in rats treated with CS (168, 112) and urine concentrating or diluting ability was so minimally reduced in patients undergoing therapy (9, 11, 86) that this may be taken to be irrelevant.

Indirect information about the tubular handling of various solutes can be derived from their concentrations in serum or plasma. The concentration of magnesium is invariably reduced in humans during treatment with CS (140, 6, 176, 83, 82, 11, 4, 49, 71, 186) and in rats (194, 112, 54). Potassium concentration is marginally increased in humans (183, 164, 2, 49, 53, 70, 186) and rats (13, 62, 61), and bicarbonate concentration is mildly depressed in humans (9, 179, 11, 164, 2, 71, 58, 70) and rats (13). In addition, uric acid may be elevated in patients treated with CS (140, 36, 179, 76, 102, 172, 53, 35, 85, 31, 103).

These alterations suggest that magnesium reabsorption in the loop of Henle is impaired by CS, that potassium and acid secretion in the distal tubule are modestly depressed, and that net uric acid secretion in the proximal tubule is somewhat reduced. The decrease in fractional magnesium reabsorption or increase in fractional

magnesium excretion has been confirmed in rats (194, 112) and also in humans (140, 11, 4, 86). Also, a reduction in distal tubular acid secretion has been seen in rats (13). Finally, a reduction in the excretion of uric acid has been seen during CS therapy in humans (36, 76, 131) but has not been reported in animals.

Consequently, the alterations in tubular reabsorption and secretion seen with CS are not generalised but mostly specific, affecting predominately magnesium reabsorption but also potassium and acid secretion, as well as uric acid excretion. The preservation of a high level of sodium and fluid reabsorption and the maintenance of a high degree of urinary concentration suggests that impaired renal function is not associated with generalised tubular damage. As such, this type of renal dysfunction resembles prerenal azotemia, which is characterised by the preservation of tubular reabsorption but a lowering of renal perfusion.

C. Renal Morphology

Because of the clear action of CS to depress renal function and because of the danger of structural damage to the kidney, there is much information about renal morphology during CS therapy. In particular, following kidney transplantation, it has not been easy to distinguish the symptoms of graft rejection, with a depression in renal function, from drug toxicity, with a similar decrease in renal function. Hence, renal biopsy became a standard diagnostic tool following kidney transplantation to clarify the cause of sudden decreases in kidney performance. Additionally, the kidney has been extensively studied in experimental animals after treatment with CS.

The structural alterations seen in the kidney during treatment with CS are of two types. They are alterations to the tubular system, which are seen equally in humans and experimental animals, and changes to the vascular system, which have only ever been identified in humans. The changes to the tubular system are characteristic but not specific for CS and are reversible when the drug withdrawn. In contrast, the alterations to the vascular system are characteristic but not specific to CS and do not revert when the drug is discontinued.

The alteration seen in the renal tubular system that is most noticeable is tubular vacuolisation or ballooning, which is typical for the proximal straight tubule. This is seen in rats given CS experimentally (20, 51, 193, 56, 21, 174, 61, 117, 191, 113, 173, 111) and also in humans given CS after kidney or heart transplantation (131, 118, 119) or as a treatment for autoimmune diseases (116, 170), predominately when doses are and high. The vacuoles, which are similar in size, are generally empty and represent grossly dilated and extended portions of the endoplasmic reticulum.

Other alterations in the tubular system that are less noticeable include the development of cellular inclusion bodies, seen typically in the cells or the lumen of the proximal convoluted tubule. These are found both in rats treated with CS experimentally and in humans given CS for the treatment of many different conditions. However, in rats, the inclusion bodies are mostly giant lysosomes and only seldom giant mitochondria, whereas in humans they are invariably giant mitochondria and rarely giant lysosomes. A further morphological change common to humans and animals is the occasional occurrence of single cell necroses and the development of tubular microcalcifications.

The alterations that are seen in the vascular system are only found in humans and only seen in the arterioles and smallest arteries of the kidney. Here, individual smooth muscle cells and endothelial cells may develop vacuoles, and they may become necrotic. The necrotic endothelial cells are shed, leaving naked patches of basement membrane, but they may be replaced. This damage to the arteriolar wall is believed to cause the vessels to become occluded first with fibrin and platelets and then with proteinaceous material.

It is this occlusion of individual arterioles that seems to result in a localised degeneration of the tubules and development of an ischemia-induced interstitial fibrosis, which characteristically assumes a striped rather than a diffuse form. Such changes have been associated with CS therapy after kidney, heart, and bone marrow transplantation (132, 131, 118, 119, 137) or in patients with autoimmune diseases (116, 170, 139), particularly when initial doses or blood levels have been excessively high (118, 116).

Similar changes to the renal interstitium but not to the vasculature have been seen in rats treated with CS. This has been observed on several occasions (161, 20, 46, 78, 61) but has not always been found (56, 117). However, tubular microcalcification, which is a common cause of interstitial inflammation and fibrosis, is a frequent finding (161, 20, 61, 117, 173). Thus, in the rat, it is probable that interstitial fibrosis is the result of tubular damage, as reflected by calcium deposits within the cells but certainly not the result of vascular occlusion. In humans, however, the interstitial fibrosis associated with CS occurs only in conjunction with arteriolar occlusion.

D. Systemic Haemodynamics

It seems that the vasoconstriction caused by CS is not just confined to the kidney but is also found in the systemic circulation. CS often causes an increase in systemic arterial blood pressure. After discontinuation of CS, both renal vascular resistance and arterial blood pressure decreased, indicating that systemic vascular resistance had decreased (38). Also, during exercise, arterial blood pressure was seen to increase more in patients receiving CS than in those receiving alternative therapy (158). In normal rats, systemic arterial blood pressure is not increased by CS (175, 88, 77, 45, 61). However, the blood pressure response to vasoconstrictors

is blunted, suggesting that the vessels may be preconstricted (175).

It appears, in addition, that vasoconstriction is present in other internal organs during CS therapy. In humans, the use of CS seems to be associated with a decrease in both kidney and liver perfusion (101). In the rat, treatment with CS decreased perfusion to the kidney and pancreas and, at high doses, also to the spleen (145). A disturbance in vessel contraction and dilation has been seen in animals in single vascular beds or organs examined in isolation. Following treatment with CS, both endothelium-dependent and -independent vessel relaxation in the rabbit kidney were impaired (30), as was vessel constriction in the rabbit kidney (156, 121) and in the hindlimb vessels (156).

The implication of these observations that this may be a reaction of the smooth muscle cells themselves is supported by observations made on contractile cells grown in culture. Intracellular calcium concentrations were measured following stimulation with angiotensin II or arginine vasopressin after incubation with CS. The normal transitory increase in intracellular calcium that activates the contractile mechanism was found to be enhanced in both vascular smooth muscle cells (146, 114) and glomerular mesangial cells in the presence of CS (93, 115, 63). This suggests that contractile cells may be more responsive to any form of stimulation in the presence of CS.

Acute exposure of the isolated rat aorta to CS has been reported to cause vasoconstriction (195). This was not confirmed in the aorta, femoral, mesenteric, or renal arteries (126), the tail artery of normal rats (95), or small arteries from subcutaneous fat in humans (147). However, the response of the rat tail artery to vasoconstrictors was enhanced by acute exposure to CS (64, 95), whereas the response of the rat aorta was unchanged (126, 195). It is only after prolonged treatment with CS that the response of the isolated rat aorta to vasoconstrictor substances is enhanced (24, 23) or to vasodilators is diminished (108, 126), an effect also seen in the rat renal artery (199).

TABLE 2

Vascular responses of isolated vessels from normal rats

	Vessel	Response	Ref.
Acute exposure			
Alone	Aorta	Yes	195
	Aorta	No	126
	A. renalis*	No	126
	A. mesentericus	No	126
	A. caudalis	No	95
With vasoconstrictor	Aorta	Same	126, 195
	A. caudalis	Enhanced	64, 95
Chronic exposure			
With vasoconstrictor	Aorta	Enhanced	24, 23
With vasodilator	Aorta	Decreased	108, 126
	A. caudalis	Decreased	199

* A, artery.

The action of CS on isolated vessel segments is summarised in table 2. These results show that CS alone does not cause vasoconstriction but treatment with CS can enhance the response to vasoconstrictor substances and diminish the response to vasodilator substances in many vessels. This is compatible with the increase in vascular resistance seen in different organs and in the systemic circulation, which indicate that this action is not exclusive to the kidney. Whereas one possible mechanism for enhanced vasoconstriction and diminished vasodilation is the increased calcium response to stimulation, as seen in cultured cells even after acute exposure to CS, other mechanisms may also be involved.

E. The Renin-Angiotensin System

Because of the action of CS to decrease organ perfusion and increase arterial blood pressure in humans, the involvement of the renin-angiotensin system has been considered as a possible causal mechanism. Whereas there is unanimous agreement that in animals the activity of the renin-angiotensin system is increased during treatment with CS, in humans this is not so clear. Part of this uncertainty is caused by the influence of salt intake, diuretics, or antihypertensive agents on this system but part may arise because only one component of the system, renin activity, is generally measured.

In both dogs and rats, plasma renin activity was seen to be increased after treatment with CS (159, 160, 135, 16, 15, 129, 47, 44, 141, 110, 143, 113). In humans, in contrast, plasma renin activity is unchanged by CS therapy (39, 71, 132, 9, 19, 17, 40) or depressed (8, 41, 19, 131, 81). However, in the few cases in which total renin concentration has been measured, this was increased not only in rats (47, 44) but also in humans (132). Indeed, inactive renin seems to be increased by treatment with CS both in rats (110) and in humans (132), even though renin activity was not elevated.

The implication of these findings that the renin-angiotensin system may be stimulated by CS, even when renin activity is not increased, is supported by two observations: First, a dose-dependent increase in renin activity has been seen in humans early during treatment, but this was only transient and soon declined (156a). Second, the juxtaglomerular apparatus that produces and secretes renin is hyperplastic in humans (132) and also in rats treated with CS (182, 61). Thus, as summarised in tables 3 and 4, inactive renin is high and the juxtaglomerular apparatus is hypertrophic both in humans and animals, indicating stimulation, but in humans this is seldom reflected in an increase in renin activity.

One of the reasons for a high level of renin release with CS, be it active or inactive renin, seems to be its action to stimulate both renin release and synthesis. Renin content and renin release from slices of rat renal cortex were increased after chronic exposure to CS (16, 15). However, renin release from renal cortical slices from rats was also stimulated by acute exposure to CS

TABLE 3
Plasma renin activity in humans and animals

Chronic treatment	Humans (ref.)	Animals (ref.)
Active renin	↑ (156a)	↑ (159, 160, 135, 129, 15, 16, 47, 44, 141, 110, 143, 113)
	= (39, 71, 132, 19, 17, 40)	–
	↓ (8, 9, 41, 19, 131, 81)	–
Total renin	↑ (132)	↑ (47, 44)
Inactive renin	↑ (132)	↑ (110)

(14, 109). Also, the renin release and synthesis from isolated juxtaglomerular cells in culture was stimulated by acute exposure to CS (94). Thus, it seems that part of the increase in total renin seen in humans and animals may result from a direct action of CS on the renin-producing cells.

The significance of the increased activity of the renin-angiotensin system, however, remains unclear. Pharmacological blockade of this system cannot indicate whether or not circulating angiotensin causes hypertension or renal vasoconstriction for two reasons. First, a vasodilator can decrease blood pressure and improve renal vasoconstriction, whatever its cause. Second, decreasing blood pressure always leads to renal vasodilation because the kidney autoregulates its own blood supply. Thus, although blockade of the renin-angiotensin system with saralasin or captopril improves renal function (88), so do renal denervation or other vasodilators (178, 28, 128, 111, 190, 45). Furthermore, and renal autoregulation in response to hypotension accounted for most of the improvement seen (88).

Nevertheless, an involvement of the renin-angiotensin system in altering vascular reactivity does seem possible. In conscious dogs, local infusion of bradykinin causes a venoconstriction. Following a single oral dose or local infusion of CS, the effect of bradykinin on venoconstriction was reduced but could be restored by saralasin or a renin inhibitor (124, 125). This suggests that CS reduces the bradykinin response by activating vascular renin and stimulating angiotensin production. Also, in isolated pig renal arteries, acute exposure to CS enhances the contractile response to angiotensinogen but not to angiotensin I or II, suggesting that renin activation is occurring (127).

Consequently, it seems as though CS directly stimulates the synthesis and release of renin from the juxtaglomerular apparatus. This need not necessarily lead to an increase in renin activity, because in humans inactive renin is elevated and active renin unchanged or depressed, and only in animals are inactive and active renin both increased. Whether or not this increases circulating angiotensin and causes vasoconstriction is uncertain. However, this mechanism of renin activation may also operate in the blood vessels themselves, where angiotensin of local origin may sustain vasoconstriction.

TABLE 4
Tissue renin in humans and animals

	Humans (ref.)	Animals (ref.)
Chronic exposure		
Active renin release	–	↑ (15, 16)
Juxtaglomerular apparatus hyperplasia	↑ (132)	↑ (61, 182)
Acute exposure		
Active renin release	–	↑ (14, 94)
Inactive renin content	–	↑ (94)
Active renin content	–	= (94)

F. The Prostaglandin (PG)-Thromboxane (Tx) System

Once again, because of the action of CS to increase vascular resistance in the systemic circulation and in several of the internal organs, it has been proposed that an alteration in the profile of prostanoids may be involved. Whereas many of the prostanoids, such as PGE_2 or PGI_2 are vasodilators, others, such as $PGF_{2\alpha}$ or TxA_2, are vasoconstrictors. In particular, TxA_2 is a potent vasoconstrictor; therefore, very small increases in its concentration, coupled with small decreases in the levels of PGE_2 or PGI_2, could lead to a considerable degree of vasoconstriction.

This concept that the prostanoid profile may be altered by CS has derived some support from the urinary excretion pattern of prostanoid metabolites. In rats, the excretion of TxB_2 (the stable metabolite of TxA_2) is increased by CS (143, 89, 91, 174, 142, 32, 18, 144, 145), whereas in humans it is depressed (41, 92) or only modestly increased (37). In animals, the excretion of 6-keto-$PGF_{1\alpha}$ (the stable metabolite of PGI_2) was increased (129, 135, 174, 32) or unaltered (143, 91, 142), but in humans it was unchanged (8, 81) or depressed (41, 92). In animals, the excretion of PGE_2 was increased (174, 32), unaltered (129, 91, 135, 142), or depressed (143, 144), whereas in humans, it was unchanged (1, 8, 81) or possibly depressed (164).

Hence, as summarised in table 5, it is not clear that there is an alteration in the balance between dilatory and constrictory prostanoids. In animals, it seems that TxB_2 excretion is increased by CS, but the excretion of 6-keto-$PGF_{1\alpha}$ and PGE_2 is also increased. In humans, TxB_2 excretion is often depressed and the excretion of 6-keto-$PGF_{1\alpha}$ and PGE_2 may also be reduced. However, because PGI_2 is produced mainly by the vascular endothelium, TxA_2 by the platelets and glomerular mesangium, and PGE_2 in the renal medulla and cortex, urinary excretion may not accurately reflect local rates of production. In particular, the excretion of prostanoids is also affected by tubular reabsorption and secretion and also by urine flow rate and acidity. Hence, the prostanoid release from those tissues that produce them may provide more reliable information.

In renal tissue from chronically treated animals, TxB_2 release from isolated glomeruli or cortical slices was unchanged (143, 15, 29, 79) or increased (143, 18, 152,

TABLE 5
Urinary excretion of prostanoids in humans and animals

Chronic treatment	Humans (ref.)	Animals (ref.)
TxB_2	↑ (37)	↑ (143, 89, 91, 174, 142, 32, 18, 145, 144)
	↓ (41, 92)	–
6-keto-$PGF_{1\alpha}$	–	↑ (129, 135, 174, 32)
	= (8, 81)	= (143, 91, 142)
	↓ (41, 92)	↓ (143, 144)
PGE_2	–	↑ (174, 32)
	= (8, 1, 81)	= (129, 91, 135, 142)
	↓ (164)	↓ (143, 144)

50). The release of 6-keto-$PGF_{1\alpha}$ from isolated glomeruli was always depressed (29, 165, 152, 144, 79), and the release of PGE_2 from isolated glomeruli and cortical or medullary slices was reduced (202, 165, 152, 144, 79). In animal endothelial cells in culture, basal release of 6-keto-$PGF_{1\alpha}$ was increased when high doses and long exposure reduced cell replication or viability (29, 97), but in human cells with lower doses and shorter incubation, both basal and stimulated release were depressed (26, 27, 185, 65). Thus, as summarised in table 6, PGI_2 and PGE_2 production do seem to be reduced in the renal or vascular tissue of humans and animals at noncytotoxic doses, and renal or vascular TxA_2 generation may be increased.

Excessive TxA_2 production in the glomeruli, possibly from infiltrating inflammatory cells (18), whose TxB_2 release is increased by CS (152), has been suspected of causing renal vasoconstriction. Consequently, dietary fish oil supplements have been used to replace the synthesis of active TxA_2 by inactive TxA_3. In animals, this therapy has decreased tissue TxB_2 release (152, 50) and been found to improve renal function in some studies (152, 50) but not in all (80). In humans, also, fish oil improved renal function in one study (74) but not in another (189). However, fish oil supplementation in animals has been shown to depress CS blood levels (152) and even when blood levels seem unaffected (50, 80) may greatly depress plasma levels (80). Thus, it remains uncertain whether it is the reduction in TxA_2 or in CS concentrations that is beneficial when fish oil is administered.

TABLE 6
Release of prostanoids from renal and vascular tissue from humans and animals

	Humans (ref.)	Animals (ref.)
Renal tissue		
Chronic treatment		
TXB_2	–	↑ (129, 143, 152, 50) = (143, 164, 29, 79)
6-keto-$PGF_{1\alpha}$	–	↓ (29, 165, 152, 79, 144)
PGE_2	–	↓ (29, 165, 152, 144, 79)
Vascular tissue		
Acute treatment	–	↑ (202, 97)
6-keto-$PGF_{1\alpha}$	↓ (26, 27, 185, 65)	

G. Pancreatic Function

Several observations have been made that suggest that CS can impair the regulation of blood glucose both in humans and experimental animals. As a consequence, the function and the morphology of the pancreas has been examined in some detail in an attempt to identify the cause. The levels of blood glucose, serum insulin, or its connecting peptide (C-peptide) have been determined in the basal or resting state, as well as after stimulation by a glucose load or food intake. In addition, insulin release and synthesis from isolated human or animal islets kept in culture have been examined during incubation with CS.

In rats, CS treatment can cause degranulation and hydropic degeneration of the pancreatic β cells with cytoplasmic vacuolisation (72, 120, 174, 177, 67, 69, 52, 162, 196). These changes are not seen with low doses or short-term therapy (198, 123), and they reverse rapidly when the drug is withdrawn (120, 196, 69). However, the degranulation suggests that insulin synthesis can be depressed by CS . This is supported by a decrease in pancreatic insulin content in rats given CS (72, 198, 57, 68, 55, 67, 196, 69, 52, 60) that reverts when the drug is withdrawn (67, 69, 52, 60). Also, there is a decrease in stimulated insulin from isolated pancreatic tissue taken from rats and dogs treated with CS (123, 57, 68, 12, 34, 60). Reduced nucleic acid, protein, and proinsulin synthesis are found in the pancreatic tissue of rats treated with CS and of mice after culture with CS (5, 52).

Nevertheless, there are several reasons for believing that the impairment in glucose tolerance often seen in rats and humans treated with CS does not just reflect reduced insulin synthesis and inadequate insulin release. In animals, stimulated insulin release was increased in rats or pigs some weeks after treatment (197, 55, 54a), was unchanged in rats for 1 month (68, 197), and only depressed after longer periods of treatment (198, 197, 34, 3). Also, in rats treated with CS for some weeks, fasting serum insulin levels were not depressed with lower doses (197, 55), only with higher doses of CS (72, 120, 174, 57, 69, 52). Similarly, in patients treated with CS, stimulated C-peptide release was increased (134) or unchanged (149, 148) and fasting C-peptide levels were elevated (134, 138). Thus, it appears that CS may enhance insulin release both in humans and animals during short-term or low dose therapy.

Further evidence for this concept is provided by studies of isolated pancreatic tissue maintained in culture. Short-term incubation with CS was seen to increase stimulated insulin release in rat and mouse islets (200, 98), not to change it in rat islets (98), and to depress it in rat, hamster, or mouse tissue (150, 5, 48). In human tissue, long-term incubation with CS did not affect stimulated insulin release from foetal tissue (181) but did depress it in adult tissue (84, 136). However, depressed insulin release accompanied an increase in tissue insulin

TABLE 7
Fasting or stimulated serum insulin or C-peptide levels in humans and animals

	Humans (ref.)	Animals (ref.)
Fasting	↑ (134)	–
	–	= (174, 197, 55)
	–	↓ (72, 120, 69)
Stimulated	↑ (134)	↑ (68, 197, 55, 54a)
	= (149)	= (197)
	–	↓ (198, 197, 34, 3)

content (136), suggesting that insulin secretion may have been impaired. Hence, both enhanced and suppressed insulin release have been found with CS.

The findings that stimulated insulin release may be enhanced or suppressed by CS require careful interpretation if their significance is to be understood. As summarised in tables 7 and 8, CS is certainly able to depress stimulated insulin release from human and animal β cells. Furthermore, decreases in basal and stimulated insulin release in animals coincide with decreases in pancreatic insulin content and synthesis. Yet, these observations are invariably made in animals or in human or animal tissue exposed to doses greatly in excess of those used therapeutically in humans. In humans, treatment with CS has not been reported to decrease basal or stimulated serum insulin or C-peptide levels; it either increases them or leaves them unchanged.

Consequently, the glucose intolerance seen in humans following transplantation (138) does not seem to result from decreased insulin release. It may be influenced by concomitant therapy with steroids, because glucose intolerance has not been seen during monotherapy with CS (66a, 149, 148). Alternatively, it may reflect a true resistance to insulin, when normal or even enhanced insulin secretion and glucose intolerance go hand in hand. Such a condition has been seen in rats (197), and enhanced insulin secretion is seen in humans (134, 138) and animals (197, 55, 54a). Furthermore, insulin resistance has been identified in the fat cells of rats treated with CS (162). Thus, in humans, the cause of glucose intolerance during CS therapy is not clear, but there is no evidence for deficient insulin release.

TABLE 8
Resting or stimulated insulin release or content from isolated pancreatic tissue

	Humans (ref.)	Animals (ref.)
Chronic treatment		
Insulin content	–	↓ (72, 198, 57, 68, 60, 55, 67, 69, 52)
Stimulated release	–	↓ (123, 57, 68, 34, 60)
Acute exposure		
Insulin content	↑ (136)	–
		↓ (5)
Stimulated release	–	↑ (200, 98)
	= (181)	= (98)
	↓ (84, 136)	↓ (150, 5, 48)

H. Hepatic Function

Because the liver is one of the target organs involved in the toxic actions of drugs, many investigations have been directed toward determining whether CS exerts any action on liver function or structure. Alterations to the liver may range from cell destruction, with the release of intracellular enzymes and morphological signs of cell necrosis, to isolated disturbances in liver function. Because the functions of the liver include the production and secretion of bile and the synthesis of plasma proteins and blood-clotting factors, examination of the individual components in plasma or serum gives a broad assessment of overall liver function. In addition, the use of isolated preparations and cell culture systems enables changes in specific functions to be identified more clearly.

There is considerable evidence both in humans and animals that CS causes an accumulation of bilirubin and bile salts in blood. In rats, ultrastructural analysis reveals a picture of cholestasis in the bile capillaries, with bile salt deposits in the liver cells after treatment with CS (196). Bile flow and bile acid secretion are clearly suppressed by treatment with CS (100). An increase in bilirubin is not seen in rats with low dose CS treatment (166, 174) but is seen with higher doses (174, 196, 56, 191, 190, 67, 21). In humans, also, serum levels of bile salts are increased by CS therapy (155), and mild hyperbilirubinaemia is a constant finding (49, 73, 151, 155, 99, 105, 104, 53), seemingly related to the blood levels of CS (99, 105, 104).

Despite the clear evidence for bile retention, there is no good evidence for liver cell damage, as can be demonstrated by liver cell necrosis or an increase in circulating liver enzymes. In rats, morphological studies of the liver failed to show liver cell necrosis with high doses of CS (56, 21). Correspondingly, the transaminases, aspartate aminotransferase and alanine aminotransferase, were unchanged or even depressed by treatment with CS (166, 196, 56, 21, 191). Similarly, aspartate aminotransferase and alanine aminotransferase are generally unaltered during CS therapy in humans (49, 151, 155). In two clinical studies, a small increase in aspartate aminotransferase was seen, yet this did not affect the other trans-

TABLE 9
Liver function in humans and animals

	Animals (ref.)	Humans (ref.)
Serum bilirubin or bile salts	↑ (166, 196, 21 56, 191, 190, 67)	↑ (49, 73, 151, 155, 99, 105, 104, 53)
	= (166, 174)	–
Serum transaminases	–	↑? (104, 53, 85, 107, 90)
	= (166, 196, 56, 191, 21)	= (49, 151, 155)
	↓ (196, 191, 21)	–
Serum protein or clotting factors	= (166, 174)	= (53)
	↓ (56, 191, 190, 67, 21, 42)	– (49, 106, 101, 187, 11)

aminases in one study (53) and was caused by a decrease in the control values in the other (151). Similarly, the isolated instances of "hepatotoxicity" diagnosed during high dose therapy, early after transplantation (104, 85, 107, 90), reflected mostly increases in serum bilirubin, with the increase in serum transaminases being small or even absent (104, 90).

Consequently, the findings suggest that the accumulation of bile products in blood is not the result of liver cell damage but results from a disturbance in bile secretion by the liver. This view is completely supported by studies in isolated animal preparations. In the isolated, perfused rat liver, acute exposure to CS decreased both bile flow and bile secretion (153). In addition, in isolated hepatocytes, acute exposure to CS decreased the uptake and release of radiolabeled bile salts (22, 201, 163). Thus, it appears that CS interacts with the liver cell membrane to inhibit bile salt transport and, hence, bile production and bile flow.

In addition, it seems that CS at high concentrations may mildly depress protein synthesis by the liver. In rats, low doses of CS did not affect plasma albumin (166, 174) but did marginally depress total protein (42), whereas higher doses decreased both plasma albumin and total protein (56, 190, 191, 21) and lowered protein synthesis in isolated liver cell microsomes (7). Similarly, short-term exposure to CS need not influence protein synthesis in isolated hepatocytes (184) but can depress it (22, 7). In humans, also, serum albumin or protein concentrations may be unaffected by CS treatment (53) but can be mildly depressed (49, 11), as can the clotting factors V, VII, and XII (106, 187) and cholinesterase activity (101).

Thus, as summarised in table 9, bilirubin and bile salts are increased during CS treatment in humans and often in animals. Serum transaminases, in contrast, are seldom increased in humans and never increased in animals. This excludes liver cell destruction as a cause of hyperbilirubinaemia. All the evidence points to an isolated disturbance in bile secretion or cholestasis, caused by an interaction of CS with the bile salt transport proteins. There may, however, be a modest depression in protein synthesis by the liver, seen either as a decrease in serum albumin concentrations or as a reduction in clotting factors or cholinesterase activities. However, these effects are marginal and are not relevant at therapeutic concentrations of CS.

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