increase in flow averaged 2.62 ± SEM 0.21 and 1.50 ± 0.14 ml min⁻¹ ml⁻¹ respectively (P < 0.001). In the hypertensives, the response to nitroprusside was similar to that of the controls at 200 ng/min, but it was reduced at 800 ng and 3.2 μg/min. A significant reduction in the response of the hypertensives as compared with the controls was found for the increment in flow between 200 ng and 3.2 μg/min dose rates (5.14 ± 0.62 and 7.14 ± 0.61 ml min⁻¹ 100 ml⁻¹ respectively; P < 0.05) and for the increase in flow at the 3.2 μg/min dose rate when expressed as a percentage of the resting flow (166% and 285% respectively; P < 0.01).

Responses to the two drugs were related to each other by dividing the increase in blood flow induced by nitroprusside (3.2 μg/min) by the sum of the increases induced by verapamil (5 μg/min) during two separate infusions. The ratio averaged 2.27 in the controls and 1.07 in the hypertensives (P < 0.001).

The augmented response to verapamil might result from structural changes in the resistance vessels and need not imply any functional change in the smooth muscle (Folkow, 1978. Clinical Science and Molecular Medicine, 55, Suppl. 4) 38–22s). The impaired response to nitroprusside and the major alteration in the relative response to the two dilators cannot be accounted for in this way and suggest that there is a functional abnormality of vascular smooth muscle in primary hypertension.

26. CIRCULATING DOPAMINE AND RENIN RELEASE

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It has been suggested that dopamine is involved in the control of renin release (Davis & Freeman, 1976, Physiological Reviews, 56, 1–56). To investigate this further we have examined the relationship between the plasma levels of renin and dopamine in conscious dogs before and during the infusion of dopamine.

Six male beagle dogs with carotid artery loops were studied. The preparation and dose-response technique have been described elsewhere (Nicholls, Tree, Brown, Douglas, Fraser, Hay, Lever & Morton, 1978, Endocrinology, 102, 485–493). A 45 min intravenous infusion of saline was given as control followed by dopamine (Intropin, Armour-Stone Laboratories) infused consecutively at 0.15, 1, 15, 25 and 50 ng/min kg⁻¹, each rate being continued for 1 h. Arterial blood samples were drawn during the control period and at the end of each period of dopamine infusion. Plasma dopamine was measured by a modification of the radioenzymatic method of Da Prada & Zürcher (1976, Life Sciences, 19, 1161–1173) and renin concentration by radioimmunoassay (Millar, Leckie, Morton, Jordan & Tree, 1980, Clinica Chimica Acta, 101, 5–15).

The mean plasma dopamine concentration during the control period was 0.76 ± SEM 0.14 ng/ml. Infusion of dopamine increased the plasma concentration of the catecholamine from 4.43 ± 0.22 ng/ml at the lowest rate of infusion to 16.5 ± 10.6 ng/ml at the highest. Rate of infusion and plasma dopamine levels were closely correlated (r = 0.99, P < 0.001).

Increase of plasma dopamine concentration between 2 and 20 times the basal value produced no significant change in plasma renin concentration, but plasma dopamine 200 times the basal value caused a significant increase (P < 0.05) in renin concentration from a basal value of 15 ± 4 to 25 ± 4 μ-units/ml. At dopamine levels 2000 times basal, there was a further significant increase (P < 0.05) in renin concentration to 41 ± 9 μ-units/ml.

Thus although dopamine infusion at high levels can stimulate renin, a rise of endogenous circulating dopamine is unlikely to have any important effect.

27. CIRCUITRD VARIATION IN BLOOD PRESSURE AND HEART RATE IN PATIENTS WITH AUTONOMIC NEUROPATHY

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Long-term ambulatory monitoring of intra-arterial pressure and ECG was carried out on six patients with previously documented autonomic neuropathy and symptomatic postural hypertension. Two patients had associated Parkinsonism and two others additional signs of neurological multi-system atrophy, the remaining two having no other associated illness. All patients were monitored for 24 h undertaking usual activity during the daytime; all but one slept in hospital. Four patients were also studied during a subsequent day of complete bed rest. Recordings were analysed by computer to obtain hourly mean values of heart rate, systolic and diastolic blood pressures. The six subjects showed a highly consistent pattern of circadian variation in both heart rate and blood pressure. Five showed the normally expected trend in the heart rate with highest levels in the daytime falling during the night until the time of awakening. Four had a much reduced heart rate variability, shown both by a small day–night difference in heart rate (under 10 beats/min) and by a low mean hour-to-hour difference (less than 4 beats/min). Blood pressure trends, however, were completely reversed from normal with pressure falling after awakening, thereafter rising progressively throughout the day and reaching maximum levels in the early part of the night. The mean hour-to-hour difference was much higher than normal (in four
subjects greater than 25 mmHg). Bed rest appeared to produce little difference in the trends with a slightly lower daytime heart rate and higher night-time blood pressure. These observations correlate with circadian variability in the symptoms of postural hypotension and imply that therapy should be appropriately directed. They also suggest the relevance of some mechanisms in the normal circadian variation of blood pressure.

28. RENAL PROSTAGLANDINS DURING EXCRETION OF INTRAVENOUS INFUSION OF SODIUM CHLORIDE IN NORMAL HUMAN SUBJECTS

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In normal human subjects increased sodium and water excretion by the kidney has been associated with increased renal prostaglandin E (PGE) production. However, under certain circumstances inhibition of PGE synthesis by indomethacin has been reported to be natriuretic.

Ten normal subjects received an intravenous infusion of 3 litres of sodium chloride (9 g/l) over 1 h. Renal function was measured for the hour before saline infusion (I), for 1 h during and after the i.v. infusion (II) and for the next 1 h (III). Renal plasma flow (RPF) was significantly higher during period II than period III (921 ± 88 ml/min → 813 ± 72 ml/min, P < 0.01). There was great individual variability in the maximum rate of urine flow (V) (1:0 → 12-4 ml/min) and in the rate of sodium excretion (U_{Na}V) (240 → 1400 μmol/min). The rate of urinary excretion of PGE decreased significantly between the end of period I and the end of period III.

Seven of the subjects then repeated the study after taking 50 mg of indomethacin on the evening before the study and again 1 h before infusion of saline. As in the control experiments RPF was higher during period II than period III (741 ± 49 ml/min → 684 ± 39 ml/min, P < 0.02). By comparison with the control study lower values of RPF were found after indomethacin during period I (882 ± 82 ml/min → 700 ± 79 ml/min, P < 0.05), II (P < 0.05) and III (P < 0.025). The individual patterns of sodium and water excretion persisting after indomethacin but V and U_{Na}V were decreased by indomethacin during periods I and II (P < 0.05 in each case). The increment in sodium excretion between periods II and III was also decreased by indomethacin (P < 0.05).

Under these conditions increased sodium and water excretion by the kidney is associated with decreased urinary PGE excretion. The changes in RPF, V and U_{Na}V induced by indomethacin suggest that prostaglandins have an important role in maintaining renal blood flow and to a lesser extent in increasing sodium excretion.

29. ERYTHROCYTE METABOLISM IN PATIENTS ON HAEMODIALYSIS (HD) AND CONTINUOUS AMBULANT PERITONEAL DIALYSIS (CAPD)

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Although erythrocyte metabolism in chronic renal failure (CRF) has been extensively studied, there is still debate as to the factors affecting it in renal failure. We investigated two separate groups of nine patients with CRF treated with either HD or CAPD, in which such studies have not previously been reported. We measured: Hb, P_{H}, pH, P of blood P_{CO}, 35 mmHg (PH incubation), base excess (BE), P_{Na} in vivo, DPG, erythrocyte glucose consumption (GC) and lactate production (LP).

The complete data revealed significant correlations between GC and DPG (P < 0.05), LP and DPG (P < 0.001), illustrating the dependence of DPG on glycylate ratio.

The HD group were markedly acidotic (mean BE 11.6 ± 1.0 to 6.9 and anaemic (Hb 7.5 ± 1.5) with high P_{H} (2.19 ± 0.53) and low DPG (3.78 ± 2.2 μmol/ml packed erythrocytes; NR 4.55 ± 5.65). With HD, there was a significant fall in P_{H} (P < 0.01) and rise in pH in incubation (P < 0.02), BE (0.05 < P < 0.01), DPG (P < 0.05) and LP (P < 0.05). The rise in DPG, GC and LP occurred despite the fall in P_{H}. There were significant correlations between BE and GC (P < 0.01), LP and DPG (P < 0.01).

The CAPD group were much less acidotic (BE 3.3 ± 2.9), had similar Hb (7.8 ± 1.8) and P_{H} (2.05 ± 0.38) to the HD group, but raised DPG (6.84 ± 1.8). With CAPD, there was a significant rise in Hb (P < 0.01) and fall in P_{H} (P < 0.01), DPG (P < 0.01) and GC (P < 0.02). There were significant correlations between Hb and DPG (P < 0.01), P_{H} and DPG (P < 0.05), GC and DPG (P < 0.05), LP and DPG (P < 0.02).

We conclude that where acidosis is marked in CRF, it is the predominant factor influencing erythrocyte metabolism, whereas in less acidotic patients, P_{H} and Hb are more important. Despite the major metabolic changes in both groups, the erythrocyte adapted without significant change in P_{Na} in vivo. We confirm that CAPD increases Hb, thereby increasing oxygen-carrying capacity, apparently without affecting the oxygen affinity of Hb.

30. STUDIES ON URINE FREE Dopamine OUTPUT IN RATS WITH ACUTE RENAL FAILURE

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The syndrome of renal damage after glycerol injection is used as a model for acute renal failure in the rat. It does not depend solely on renin release (Flamenbaum et al., 1972, Kidney International, 1, 406). Prior oral loading with sodium chloride is protective (McDonald et al., 1969, Proceedings of the Society for Experimental Biology and Medicine, 131, 610). Our previous work has shown that oral salt increases both urinary and renal free dopamine in the rat (Ball et al., 1978, Clinical Science, 55, 167). We examined therefore the response of urine free dopamine output in the glycerol-injected rat, maintained on normal or high sodium chloride intakes.

Groups of rats were housed singly in metabolic cages. Body weight, sodium and fluid intake, urine volume and urine output of sodium, creatinine and dopamine were measured daily. The rats were fed on either a 5 or 20 mmol/day sodium diet for at least 14 days. Glycerol was then given subcutaneously (7 ml of 50% glycerol/kg body weight) and the rats were observed for a further 7 days.

The sodium-loaded rats’ urine volumes did not increase as much as those of the controls and the polyuric phase was reduced. Urinary creatinine fell after glycerol in the normal salt group, but not in the group on high salt. Urine dopamine increased transiently in the normal group, but then returned to control levels; in contrast, dopamine fell in the high salt group. Urinary creatinine fell after glycerol in the normal salt group, but not in the group on high salt. Urine dopamine increased transiently in the normal group, but then returned to control levels; in contrast, dopamine fell in the high salt group.

The pattern of dopamine excretion in the two groups was markedly different. The rebound increase in the salt-loaded rats, in the days after glycerol injection, suggests that dopamine could be an important intrarenal protective factor against acute renal failure.

31. DIFFERENTIAL PROSTACYCLIN PRODUCTION BY TISSUES FROM PREGNANT DIABETIC RATS

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Prostacyclin synthesis is markedly depressed in arterial tissue from both diabetic patients and experimental animals and this...