sympathetic drive raised cardiac output. A rise in cardiac output may increase blood pressure and overcome the attenuation produced by the rise in peripheral resistance. The net effect would be a rise in pressure in the region of the juxtaglomerular cells at the distal end of the afferent arteriole (*see* de Bono & Mills 1965).

When the blood pressure is raised by elevation of cerebrospinal fluid pressure (CSF) the progressive effect on the kidney is the reverse of that seen in carotid occlusion. Very small rises in CSF pressure may actually cause a sodium diuresis but any rise in blood pressure in excess of 10% causes a progressive fall in sodium output. With the highest rises in blood pressure the peripheral vasoconstriction is so intense that there is a profound fall in GFR adding to the sodium retention (James 1968). James also showed that denervation of one renal artery prevented the fall in sodium excretion when the blood pressure was raised by elevating CSF pressure. In this circumstance the rise in peripheral resistance is obviously the dominant factor in the elevation of blood pressure and thereby decreases the pressure in the vessels at the pressure-sensitive site in the kidney.

Profound changes in blood pressure are produced by stretching the right atrium after bilateral carotid ligation in the dog. The blood pressure may fall by 50 mmHg; this is prevented if the vagi are first sectioned. Despite the fall in blood pressure there is very little change in GFR, renal plasma flow or sodium output (Mills & Osbaldiston 1968). This is one of the few circumstances where such a fall in perfusion pressure can be brought about without causing sodium retention. Presumably the fall in pressure must be by vasodilatation so that the glomerular pressure and the pressure operating at the site affecting sodium excretion must be unchanged despite the fall in blood pressure.

Summary

Sodium diuresis by the kidney appears to be related to:

(1) Expansion of the blood volume.

(2) Release of a renal vasodilator of humoral origin as well as release of nervous tone.

(3) The relationship between the blood pressure and the tone on the renal afferent arteriole.

(4) Dilution of the blood by electrolyte solutions which decrease blood viscosity.

How the pressure-sensitive mechanism in the kidney operates to alter sodium excretion is unknown but since saline infusion decreases the capacity of the proximal tubule to reabsorb sodium (Dirks *et al.* 1965) it seems that either direct pressure or an intrarenal hormone must be operating to effect this change in proximal tubular function.

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Professor Klaus Thurau
(*Department of Physiology, University of Munich*)

The Dependency of Intrarenal Distribution of Single Nephron Filtration Rates on Dietary Salt Intake (Micropuncture Studies)

Our present understanding of the intrarenal mechanisms which adjust sodium excretion to sodium uptake or saline infusion is based on experimental results obtained primarily with two techniques: clearance and micropuncture studies.

The interpretation of both data assumes that all nephrons in the kidney function homogeneously. For example, if inulin clearance or the total kidney filtration rate remains constant but sodium excretion increases, it is generally assumed that this effect must be due to a decreased tubular reabsorption of sodium. On the other hand, the interpretation of micropuncture data is based on the assumption that the characteristics observed in the punctured nephron, mostly located at the surface of the kidney, are quantitatively representative of the whole nephron population.

I should like to discuss some recent observations in our laboratory, which indicate that both assumptions outlined are probably not correct and that the analysis of intrarenal regulating mechanisms is much more complex than previously anticipated.

Some years ago Dr Schnermann and I described micropuncture experiments which demonstrated that the juxtaglomerular apparatus in each nephron unit serves as a control system for the filtration rate of the single glomerulus which belongs to the same nephron unit (Thurau & Schnermann 1965). The data strongly suggested that an essential step in this control mechanism is the ability of the juxtaglomerular apparatus to secrete renin and thereby to form locally vasoactive angiotensin. Since the renin-secreting cells are located in the wall of the afferent arteriole, the angiotensin formed at that site will reduce the glomerular filtration rate by its vasoconstrictory action. It is obvious that, other things being equal, the vasoconstrictory potency of the juxtaglomerular apparatus will depend on its renin content.

Peart (1959) and Brown *et al.* (1965) published data which indicate that renin, however, is not distributed homogeneously within the cortex. They found the renin content of superficial juxtaglomerular apparatus considerably higher than in the deep layers of the kidney. In order to find out whether this uneven distribution of renin is associated with an uneven intrarenal distribution of single nephron filtration rates, we performed micropuncture experiments on the rat kidney in order to determine the filtration rate of single glomeruli in the superficial and deep layer of the cortex (Horster & Thurau 1968). The experimental technique is illustrated in Fig 1. Late proximal or distal segments of superficial nephrons were punctured and the intratubular fluid was collected quantitatively into a pipette. The filtration rate of the punctured nephron was calculated as TF/P inulin times intratubular flow rate. Simultaneously, GFR of the entire kidney was determined by conventional clearance technique. Then the papilla was exposed, and long loops of Henle were punctured. Since all long loops accessible at the papilla in the rat belong to nephrons which have their glomeruli in the deep juxtamedullary layer, the filtration rate of these glomeruli can be calculated from the micropuncture data according to the same formula as used for the superficial nephrons. In order to be sure that exposure of the papilla did not change filtration rates in cortical nephrons, these were rechecked after exposure of the papilla, while juxtamedullary nephrons were studied.

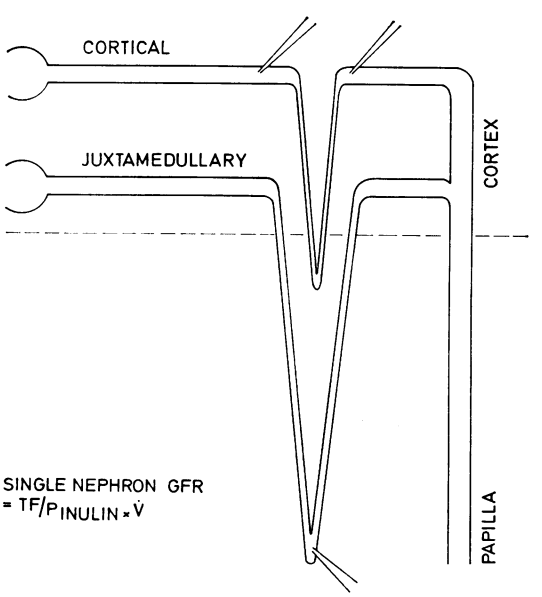

Fig 1 *Schematic representation of puncture sites for measurements of superficial and juxtamedullary single nephron filtration rates in the rat kidney*

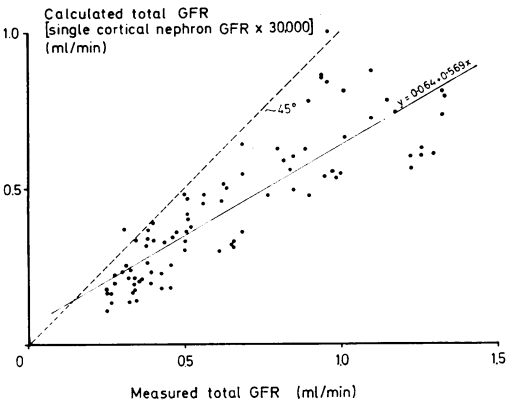

Fig 2 *Low sodium group. Correlation of total kidney GFR, measured by inulin clearance and total GFR, calculated from single nephron filtration rates assuming that single nephron filtration rate of all 30,000 nephrons is the same as that measured in superficial nephrons. The slope of the regression line is significantly different ($P<0.02$) from that of the line of identity. (Figs 2, 3, 4 and 5 are reproduced from Horster & Thurau 1968, by kind permission)*

Assuming that filtration rates in all glomeruli are the same, then multiplying the single nephron filtrate by the total number of glomeruli in one kidney, i.e. 30,000, should give the total kidney filtration rate. Fig 2 summarizes the results obtained using sodium-depleted rats. It is clear that the calculated values fall below the line of identity, indicating that nephrons with higher filtration rates than those found in the superficial nephrons contribute to total kidney GFR.

Fig 3 depicts filtration rates of juxtamedullary nephrons and filtration rates of superficial nephrons, both determined almost simultaneously

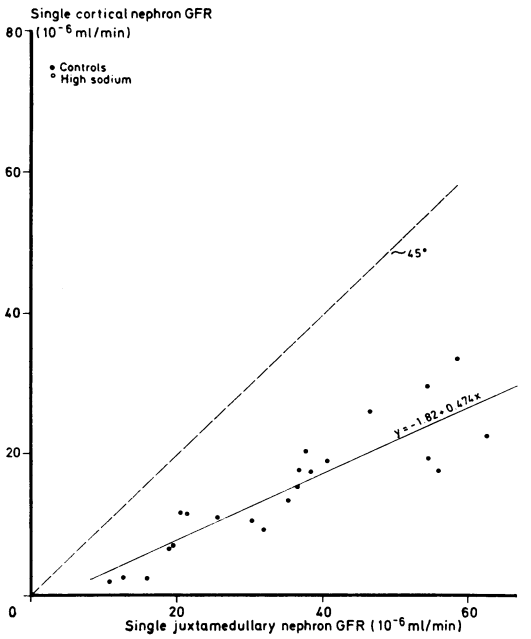

Fig 3 *Low sodium group. Correlation between simultaneously determined single superficial and single juxtamedullary nephron filtration rates. The slope of the regression line indicates a ratio between juxtamedullary and superficial filtration rate of 2·47*

in sodium-depleted rats. The regression line indicates that the filtration rate in the juxtamedullary nephrons under those conditions is approximately 2½ times that in superficial nephrons.

Using these values it can be calculated that 22% of all glomeruli belong to the juxtamedullary type with high filtration rates and 78% to the superficial type with low filtration rates, in order to account for total kidney filtration rate.

This numerical distribution, derived from functional data, is consistent with known anatomical observations. On the basis of glomerular size, structure of the vascular pole, and number of long loops of Henle, the percentage of glomeruli of the juxtamedullary type was found to be 20–28% (Sperber 1944, Lechène *et al.* 1966, Munkacsi & Palkovits 1966, Kriz 1967).

It is interesting to see how the intrarenal distribution of single nephron filtrate changes when the animals are kept on a high salt diet, since it is well known that high salt intake is followed by a depletion of renin in the juxtaglomerular apparatus. Indeed, when the rats were kept on high salt diet for 2–3 weeks, the intrarenal distribution of nephron filtration rates changed drastically (Fig 4). Here, juxtamedullary filtration rates are again plotted against superficial filtration rates. The black dots depict data from the low sodium group shown in Fig 3. In contrast, superficial filtration rates in the high sodium group exceed the deep nephron filtration rates.

In the sodium depleted group we calculated 78% of all glomeruli to be of the superficial type. Essentially the same numerical distribution is valid during high salt uptake (Fig 5). Accordingly, the calculated total kidney filtrate is identical with the measured inulin clearance.

Another conclusion should be mentioned: the intrarenal redistribution of filtration is not reflected in the total kidney filtration rate as measured by inulin clearance (*see* Table 1).

The major questions raised by these results are: (1) What causes this intrarenal redistribution of filtrates when salt intake is changed? (2) What is the physiological meaning of the uneven distribution of single nephron GFR?

As to the first question about the mechanisms: in accordance with our previous results about the regulation of each single nephron filtration rate by its own juxtaglomerular apparatus we would like again to suggest that these data support the existence of such an intrarenal regulatory mechanism. As already explained, it appears that approximately 80% of all glomeruli facultatively adjust their filtration rates to variations in salt load. Low salt rats have lower superficial filtrates, high salt rats have higher superficial filtrates.

It has been long appreciated that an increase in sodium uptake by some unknown mechanism

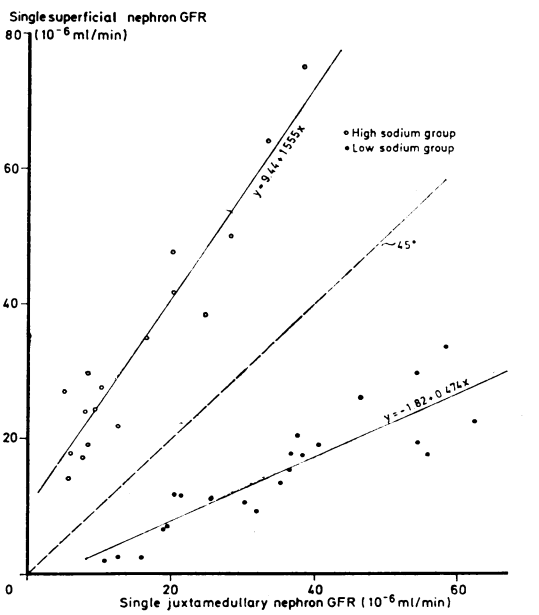

Fig 4 *Effect of high sodium diet on the correlation between single superficial and single juxtamedullary nephron filtration rates. Values for low sodium rats are identical with those in Fig 3*

reduces the renin content in the superficial juxtaglomerular apparatuses. Consistent with the reduced activity of this constrictory system is the increase in single nephron filtration rate in this part of the kidney. If we accept the general laws of enzyme kinetics we would have to postulate that the reduced renin activity should result in a decreased local formation of angiotensin during high salt intake.

In order to make renin activity a determinant of the local angiotensin activity one would have to postulate a high turnover rate of angiotensin at that site, or, in other words, a rapid local destruction of angiotensin. This would imply that an angiotensinase is also localized in the region of the juxtaglomerular apparatus. Recent studies by Dahlheim and his co-workers (unpublished) in our laboratory suggest such a localization of angiotensinase activity. Using Chandra's method of fractional centrifugation of renal homogenates (Chandra *et al.* 1964), they were able to demonstrate that the liquid pellet with the highest renin activity also contains the highest angiotensinase activity. If this finding can be independently corroborated by other biomethods, a high local turnover rate of angiotensin at the site of renin secretion would be almost certain.

Table 1

Mean values for single nephron filtration rates during low and high sodium diet (10^{-6} ml/min per g kidney weight) (Data from Horster & Thurau 1968)

	Low sodium	*High sodium*
Superficial	23·5±6·4 (n=59)	38·1±11·3 (n=28)
Juxtamedullary	58·2±13·6 (n=26)	16·5±6·6 (n=15)
Total kidney GFR (ml/min per g KW)	0·94±0·16 (n=26)	1·01±0·24 (n=15)

In order to cast these findings on intrarenal distribution of single nephron filtration rates in a physiological perspective I would like to consider another body of data which were recently obtained in our laboratory (Horster *et al.* 1968). When the deep single nephron GFR in rats with hereditary, hypothalamic diabetes insipidus (Valtin 1967) is determined in the presence and in the absence of exogenous ADH, remarkable differences are observed. In water diuresis the long loops are barely visible and their glomeruli have low filtration rates of $22{\cdot}8 \pm 12{\cdot}6 \times 10^{-6}$ ml/min per g/KW whereas after ADH administration the juxtamedullary single nephron filtrate is increased to 51·9±19·8. This effect may be the result of constriction of the efferent arteriole of the juxtamedullary glomeruli as suggested by several investigators (Fourman & Kennedy 1966, Moffat 1967, 1968). The superficial filtrates did not appear to be influenced by ADH (Schnermann *et al.* 1969). It is not difficult to accept that an

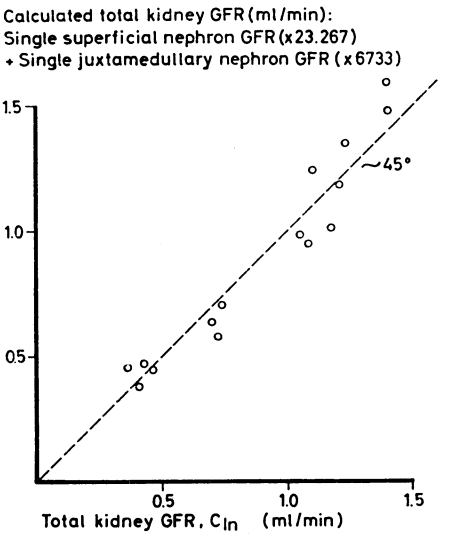

Fig 5 *High sodium group. Correlation between total kidney GFR, measured by inulin clearance and total GFR, calculated from single nephron filtration rates*

increased filtered solute load to the long loops in antidiuresis is followed by enhanced ascending limp sodium reabsorption and, therefore, an increase in TcH_2O.

These results demonstrate that the filtration rates of superficial and deep layers can vary independently in contrast to the apparent reciprocal function previously seen during high and low salt diet. That is, the former data suggest how the peptide angiotensin may regulate sodium excretion by acting at a cortical site, while the latter observations indicate how another peptide, ADH, determines the medullary conservation of water. Apart from this observation, it should be noted that ADH also enhances final urine concentration by increasing water permeability of the distal part of the nephron.

Accordingly, in view of the foregoing discussion we would like to suggest that the kidney as a whole represents two anatomical-functional units operating independently of each other. The cortical system with the short loops is primarily concerned with the regulation of salt excretion, and the deep medullary system with water excretion. However, both units appear to achieve their objectives in association with marked alterations of the filtrates of the nephrons involved.

Finally, the measurement of total kidney filtrate or micropuncture of only superficial nephrons would not be expected to cast any light on these remarkable discriminatory mechanisms occurring within different kidney regions.

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Dr D M Nutbourne
(Charing Cross Hospital Medical School, London)

Effect of Small Hydrostatic Pressure Gradients on the Rate of Active Sodium Transport across Isolated Living Frog-skin Membranes

The rate of active sodium transport across isolated living frog-skins from *Rana temporaria* was measured when the skins were bulged inwards and outwards by small constant hydrostatic pressure gradients and by pushing them mechanically in the absence of such gradients. The effect of pressure gradients in the absence of bulging was also studied.

It was found that bulging the skins in the absence of hydrostatic pressure gradients had no significant effect on the rate of sodium transport. However, when a sustained hydrostatic pressure gradient of 2–60 mm H_2O was applied, the rate of active transport changed. When the pressure was higher on the inside of the skin, i.e. the direction of the pressure gradient was opposite to that of the active sodium transport, then in all skins the rate of sodium transport fell. When the pressure was higher on the outside of the skin so that the direction of the pressure gradient was the same as that of the active sodium transport, then the rate of sodium transport rose and remained above control levels for at least an hour. In some skins the rate of transport remained high for many hours, in others after 1–2 hours the rate fell to below control values. Similar changes in sodium transport occurred when pressure gradients were applied to skins prevented from bulging by nylon or perspex grids.

It was concluded that when frog-skins are bulged by means of pressure gradients, the changes in sodium transport are not due to the coincidental increase in surface area of the skins but are due to the pressure gradients across them. It is possible that a pressure gradient changes the rate of flow of sodium and water along the intercellular channels from the actively transporting layer of cells on the outside of the skin to the inside of the skin. A full account of this work has already been published (Nutbourne 1968, *J. Physiol. (Lond.)* **195**, 1; Hutchings *et al.* 1969, *J. sci. Instrum.* **2**, 87).

Further work has shown that small pressure gradients of 0·5 to 3·0 mm H_2O also change the rate of sodium transport across frog-skins. When the pressure is higher inside the skin there is always a fall in sodium transport similar to that found at higher pressure gradients. When the pressure is higher outside the skin there is always a prolonged rise in sodium transport at very small pressure gradients. As the magnitude of the pressure gradient is increased, the rate of sodium transport ceases to rise and levels out at a value above control values. A further increase in pressure gradient then causes a prolonged fall in sodium transport. The critical pressure gradients at which the transport rate stops rising and at which it begins to fall seem to depend on the size of the piece of skin used and the tension at which it is mounted. The change of behaviour can occur at gradients of 1·0 mm H_2O, but when large pieces of frog-skin are used it may not occur until the gradient is several cm H_2O.

As such small pressure gradients change the rate of active sodium transport across the frog-skin, it is possible that pressure gradients may also cause similar changes in the rate of active sodium reabsorption in the proximal tubule of the kidney. This hypothesis is supported by the fact that electronmicroscopy of the proximal tubules shows intercellular channels similar to those in the frog-skin. The fact that these channels are shorter and straighter in the tubule might mean that the flow of sodium and water down them might be influenced by even smaller pressure gradients. If the results obtained with frog-skins can be applied to the proximal tubule of the kidney, it would mean that when the peritubular pressure is greater than the pressure inside the lumen of the tubule, the rate of sodium reabsorption would fall; and when the intratubular pressure rises slightly above the peritubular pressure, then the rate of sodium reabsorption would rise.

The following papers were also read:

Evidence for a Circulating Substance other than Aldosterone which Controls Sodium Excretion
Professor H E de Wardener (*London*)

Evidence on the Control of Sodium Excretion Obtained by Micropuncture
Professor Floyd C Rector jr (*Dallas*)