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DRUG INDUCED NEPHROPATHY

ESSAY

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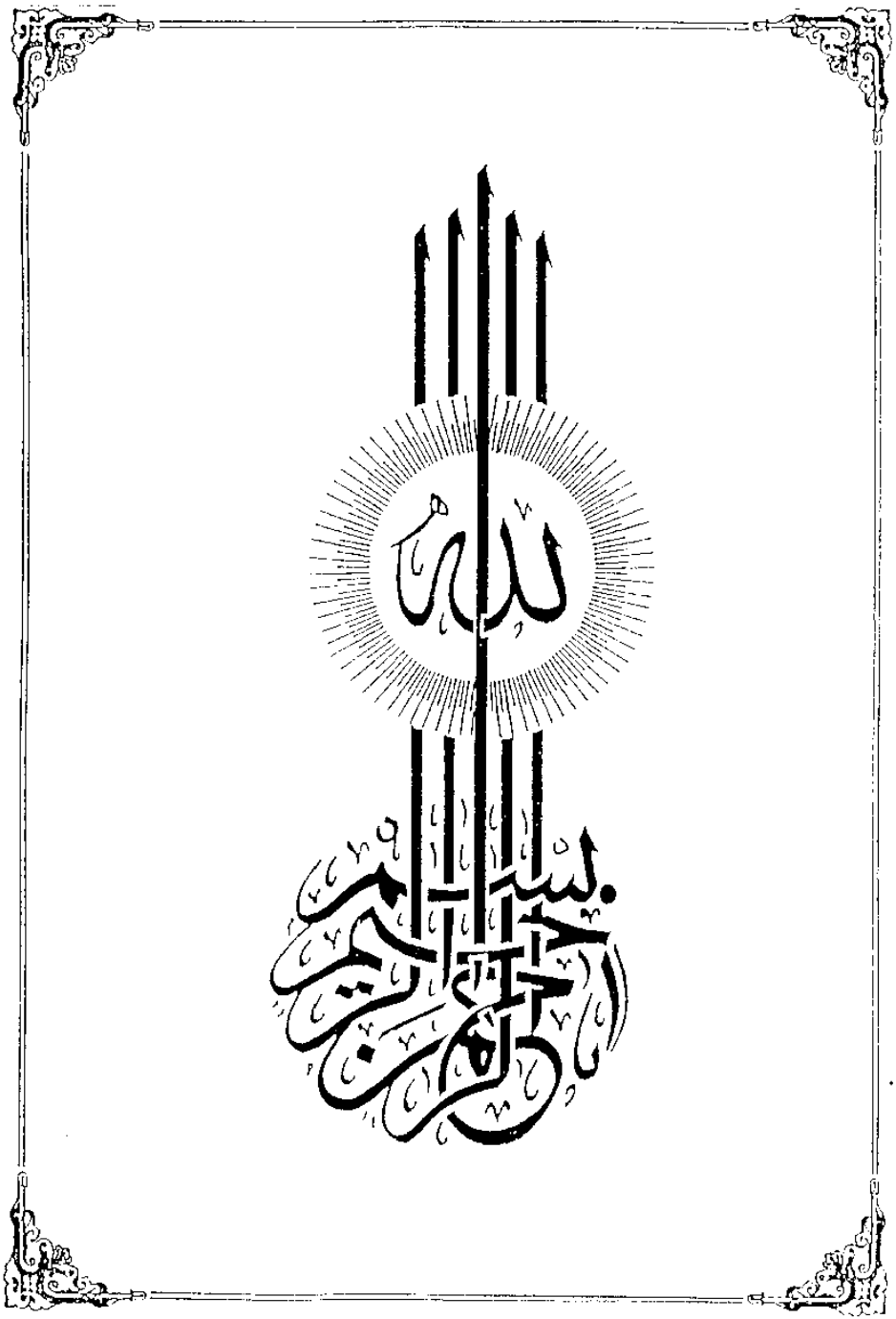

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INTRODUCTION

To look at the kidney simply as an organ of excretion would greatly underestimate both its importance and the far-reaching effects of renal intoxication. Instead, the kidneys should be viewed as major effector organs of haemostasis, preventing alterations primarily in volume, osmolarity, ionic composition, and pH of body fluids. This of course does not deny the role of the kidneys in the removal of waste products, their endocrine functions (e.g., production of erythropoietin, renin-angiotensin), and their contribution to general metabolism (e.g., gluconeogenesis). In any case we are dealing with a metabolically and functionally active organ system that is sensitive to a wide variety of physiologic, pharmacologic, and toxicologic stimuli (Jouis and John, 1975).

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REVIEW OF LITERATURE

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REASONS FOR THE UNUSUAL SUSCEPTIBILITY OF THE KIDNEY

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REVIEW OF LITERATURE

REASONS FOR THE UNUSUAL SUSCEPTIBILITY OF THE KIDNEY

Even though the kidneys may constitute less than 1 per cent of the body weight, they normally receive 20 to 25 per cent of the resting cardiac output . Indeed, the renal cortex has a much greater blood supply than many other organs, for instance, an average value in man may exceed 4 ml of blood per gram of cortex per minute. This extremely rich perfusion, from the point of view of the toxicologist, implies that large fractions of any circulating drug or poison will quickly reach the kidneys.

In addition to thevery large blood supply, a second functional property of the tissue helps to account for the frequency of renal toxic effects, namely, the ability of the organ to extract substances from the blood and to accumulate them within the renal parenchyma or in the tubular lumen. Renal secretion of organic acids is a well-documented example of this effect. In this case cellular trasport mechanisms lead to high intracellular concentrations of certain substrates such as para-aminohippurate (PAH) (Foulkes, 1963) or phenol red (Forster and Copenhanver, 1956). Pharmacologically active or toxic compounds may also be transported

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by this or similar tubular mechanisms. Thus, the effect of compounds such as organic mercurials on tubular reabsorption of Na^+ appears to be closely related to such transport (Kässler et al., 1959). However, not all preferential binding of metal compounds to the kidney can be attributed to metal transport. For example, the high cadmium content of kidneys is related to the presence of metallothionein (Pulido et al., 1966), a protein with high affinity for metals. It has also been suggested that the high concentration of lead in kidneys following severe exposure is due to the formation of lead-rich nuclear inclusion bodies (quoted by Jouis and John, 1975)

Another aspect of renal function also contributing to the frequency of toxic effects in the kidney is the fact that filtered substances may be concentrated in the tubular lumen as a result of salt and water reabsorption. In the case of a solute that, like inulin, is not reabsorbed from the glomerular filtrate, sodium and water reabsorption will lead to a relative concentration (the tubular fluid over plasma ratio or TF/P) of five at the end of proximal tubule, and final values of 100 or more in the collecting duct. This salt and water reabsorption process

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will also further increase the TF/P ratio of secreted solutes so that values as high as 500 are readily attained. In addition to high intratubular concentrations of certain solutes significant interstitial accumulation may also result from the countercurrent concentrating mechanisms in the renal medulla. The countercurrent exchange of small molecules such as Nacl and urea between ascending and descending vascular loops has been extensively reviewed (Kriz and Levetz , 1969). It clearly is responsible for the considerable osmolar gradients required to concentrate urine, and it could lead to higher levels of diffusible and potentially toxic molecules such as cyanide or fluoride in the renal medulla than in other tissues. Foreign compounds may thus become especially toxic to the kidneys by virtue of their high intraluminal, intracellular, or interstitial concentrations.

Finally, normal tubular functions other than simple fluid reabsorption permit toxic interactions in the kidneys that can not readily occur in other organs. An example of this phenomenon is the alteration in pH that occurs in the renal nephron. Maintenance of normal acid-base balance and correction of metabolic acidosis depend on secretion of

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hydrogen ions in both proximal and distal portions of the nephron. A substance whose solubility changes with pH may precipitate in the acidified tubular fluid and block the normal flow of urine. This is the case with sulfonamides, whose intratubular precipitation has often been observed (Jouis and John, 1975).

Alternatively, a toxic effect may be produced by a chemical species set free from a filtered precursor by the action of hydrogen ions. Such a mechanism has been invoked to explain the toxicity of uranyl ion circulating in plasma as a relatively inert but acid labile bicarbonate uranyl complex. Uranyl ion is thought to be liberated and concentrated in the tubular lumen as a result of normal tubular function. Although this is unlikely to account for all of the effects of uranyl ion on the kidney (Komiyama and Foulkes, 1968), it nevertheless provides a clear example of how the toxicity of chemical species may directly related to renal function.

In addition, the kidney, as is the case with any other metabolically active organ, is also sensitive to metabolic poisons. For example, cyamide injected into the renal artery of dogs causes saliuresis by inhibiting normal Nacl

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reabsorption (John and Jouis, 1975).

The special susceptibility of kidneys to toxic substances however, over and above that of other organs, stems in large part from some of the factors discussed above.

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RENAL EXCRETION OF THE DRUGS

Both the activity and the toxicity of a drug are strongly influenced by the rate at which it and its active metabolites are excreted.

In general, the more slowly they are excreted from the body, the higher the drug blood levels attained, the greater the amount of active chemical mode available for receptors, and the greater the activity and toxicity induced, and vice versa.

Since most remetabolized drugs and their active metabolites are excreted in the urine, the urinary route is of major importance in determining efficiency and safety of medications.

Over all, four aspects of excretion must be considered: 1) Glomerular filtration, 2) Tubular secretion, 3) Active tubular reabsorption, and 4) Passive tubular reabsorption. The first two act to remove drugs and their metabolites and eliminate them in the urine. The last two tend to counteract elimination by transporting some of the excreted substances back into the body. The actual rate and extent of excretion is the net effect of these factors.

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Glomerular Filtration :

Glomerular filtration is a physical function of the quarter billion nephrons in the kidney cortices. It transports large volumes of extracellular fluid (Total EcF of 12.5 liters every 10 minutes) containing electrolytes, nutrients, and other filtrable constituents including waste products from the blood into glomerular filtrate. The filtered substances cross the lipid-containing membrane that separates the fine vasculature from the glomerular filtrate. Most of the filtered substances are readily reabsorbed from the renal tubules by passive and active transport mechanism to maintain haemostasis of the EcF but about 1 ml. per minute of urine is not reabsorbed and is excreted.

The rate of glomerular filtration of a drug is altered by any changes in : 1) number of functioning glomeruli, 2) hydrostatic pressure within the glomerular vasculature, 3) osmotic pressure created by the non diffusible constituents of the vascular fluid, 4) renal blood flow, 5) extent of plasma binding, and 6) back pressure from the tubules, ureters, and bladder. Thus common causes of a reduced rate of glomerular filtration are pathologic changes in the renal vascular bed, and changes in renal plasma pressure

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