Mathematical model of the human renal system

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Abstract—*A mathematical model is presented which provides an overall description of the renal/body fluid system, comprising an interconnected set of physiologically based representations of the relevant subsystems of the human organism. The model is used to test a number of hypotheses relating to the dynamics and control of the human renal system, including dynamics of ADH clearance, glomerular tubular balance and the control of the rate of release of ADH. Results are presented establishing the validity of the model in a number of empirical tests.*

Keywords—*Fluid/electrolyte balance, Hormonal control, Kidney, Mathematical model, Model validation*

Med. & Biol. Eng. & Comput. 1985, **23**, 525–535

1 Introduction

THE IMPORTANCE of the renal system for maintaining a correct internal environment for the functioning of the human organism is well recognised. However, the complex mechanisms involved in this homeostatis are not fully understood. Mathematical modelling serves to highlight areas of weak knowledge and affords a means of testing candidate hypotheses regarding the mechanisms involved in this complex control system.

Many models of the renal/body fluid system have been developed to highlight specific features of the control system (e.g. REEVE and KULHANEK, 1967; GUYTON and COLEMAN, 1967; DEHAVEN and SHAPIRO, 1970; BLAINE *et al.*, 1972; GUYTON *et al.*, 1972; PACKER and PACKER, 1973; BIGELOW *et al.*, 1973; CAMERON, 1977; CAGE *et al.*, 1977; TOATES and OATLEY, 1977; CAGE *et al.*, 1981; LEANING *et al.*, 1982; 1985). Some of these provide detailed representations of portions of the renal system with few simplifying assumptions, whereas others are essentially empirical representations of the overall renal/body fluid system.

The model presented here provides a general overall representation (as opposed to one tuned to a specific individual) of the renal/body fluid system, made up of several interconnected physiologically based models of the relevant subsystems of the human organism. The overall model can thus be used effectively to test hypotheses regarding the control mechanisms of the human renal/body fluid system.

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First received 3rd July and in final form 29th December 1984

2 Model formulation

The conceptual form of the model, showing the subsystems incorporated and their interconnection, is depicted in Fig. 1. The detailed form of each subsystem and its mathematical realisation is given below. The subsystems are presented in an order which simplifies development of the mathematical model. A full list of model variables together with typical values is given in the Appendix.

2.1 *Cardiovascular system*

The cardiovascular system model is shown in block diagram form in Fig. 2. The equations and associated assumptions are presented below.

2.1.1 *Blood volume.* Block 1 represents an empirical relationship between extracellular fluid volume E and blood volume BV (GUYTON and COLEMAN, 1967). The nonlinear relationship is approximated mathematically by two linear equations:

$$\left.\begin{aligned} BV &= 0{\cdot}33E && (\text{if } E < 21{\cdot}0\ \text{l}) \\ BV &= 0{\cdot}015E + 6{\cdot}6 && (\text{if } E \geqslant 21{\cdot}0\ \text{l}) \end{aligned}\right\} \quad (1)$$

2.1.2 *Mean systemic pressure.* The experimental relationship between blood volume BV and mean systemic pressure MSP, established by RICHARDSON *et al.* (1961) is shown in block 2 and described by

$$MSP = 3{\cdot}5(BV - 3) \quad (2)$$

the validity of the model being restricted to cases in which the blood volume does not drop below 3 l.

2.1.3 *Total peripheral resistance.* Total peripheral resistance to blood flow in the model is under the control of the pressor substance angiotensin II in plasma (block 3 in Fig. 2). Short-term neural changes in vascular resistance are insignificant over the time resolution of the model. Other factors which may affect peripheral resistance are assumed to remain constant. The equations relating plasma angiotensin II concentration A and total peripheral resistance TPR were derived from the results of incremental infusions in humans (OELKERS *et al.*, 1974; DEHENEFFE *et al.*, 1976):

$$\left.\begin{aligned} TPR &= 19 + 0{\cdot}037A && (\text{if } A \leqslant 27\,\text{ng}\,\text{l}^{-1}) \\ TPR &= 12{\cdot}2 + 5{\cdot}44\log_{10} A && (\text{if } A > 27\,\text{ng}\,\text{l}^{-1}) \end{aligned}\right\} \quad (3)$$

2.1.4 *Cardiac output.* Cardiac output in the model is calculated from two families of curves (block 4 of Fig. 2). The first are the systemic function curves relating venous return VR to right atrial pressure RAP and mean systemic pressure MSP:

$$VR = f(RAP, MSP) \quad (4)$$

The second family comprises the cardiac function curves relating cardiac output CO to right atrial pressure RAP and a generalised index of cardiac effectiveness CE:

$$CO = g(RAP, CE) \quad (5)$$

According to the Frank-Starling law (e.g. GUYTON, 1971) heart performance balances venous return and cardiac output. The operating right atrial pressure, RAP_o is thus given by solution of

$$f(RAP_o, MSP) = g(RAP_o, CE) \quad (6)$$

Below expressions are given for f and g, and an algorithm for the iterative solution of eqn. 6. When RAP_o has been determined, CO may be calculated from eqn. 5.

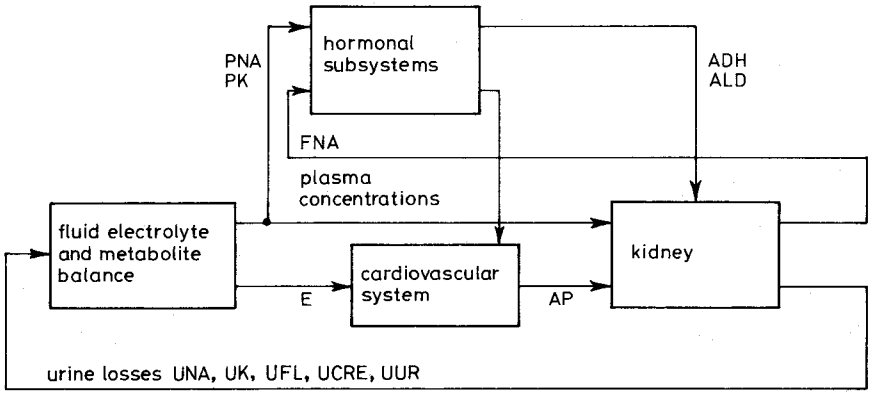

Fig. 1 *Model subsystems and interacting variables*

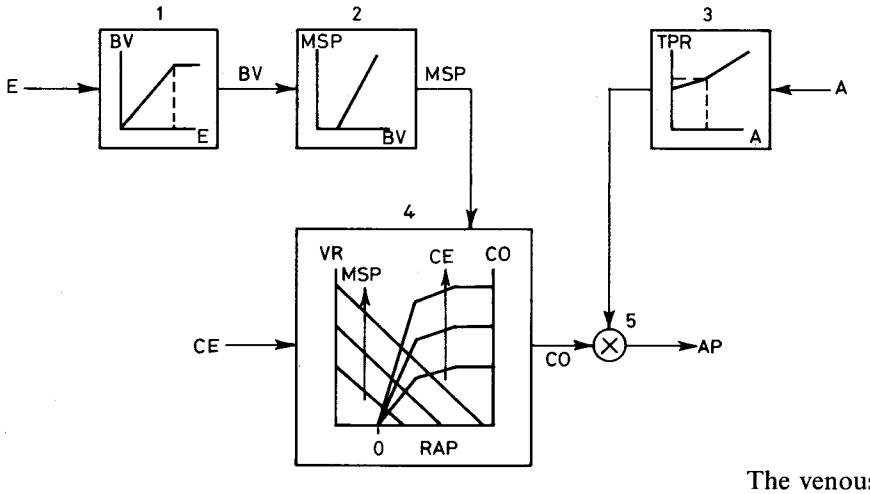

Fig. 2 *Block diagram of the cardiovascular system model*

1 *blood volume*
2 *mean systemic pressure*
3 *total peripheral resistance*
4 *cardiac output*
5 *arterial pressure*

The venous return VR is assumed to be proportional to the pressure drop across the systemic veins, hence eqn. 4 becomes

$$VR = \frac{(MSP - RAP)}{RVR} \quad (7)$$

where RVR is the return venous resistance, which is under humoral and neural control. Guyton's simplifying assumption (GUYTON, 1971) is adopted:

$$RVR = \alpha TPR \quad (8)$$

where α is a constant parameter (usually 0·07).

The relatively short-term effects of sympathetic and parasympathetic stimulation on the effectiveness of the heart as a pump are not taken into account in the model. However, the level of hypoeffectiveness of the heart is determined by relationships dependent on the state of the heart and on the levels of sodium and potassium in the extracellular fluid, PNA and PK, respectively.

Although evidence suggests a more complex form (HOFF *et al.*, 1939; FRIEDMAN *et al.*, 1959), as a first approximation, the relationship between the effectiveness of the heart as a pump CE and the excess cations in the extracellular fluid was assumed to be of the form:

$$\left.\begin{aligned} CENA &= 1{\cdot}0 && (\text{if } PNA < 148{\cdot}0) \\ CENA &= -0{\cdot}0125\ PNA + 2{\cdot}85 && (\text{if } PNA \geqslant 148{\cdot}0) \end{aligned}\right\} \quad (9)$$

$$\left.\begin{aligned} CEK &= 1{\cdot}0 && (\text{if } PK < 6{\cdot}5) \\ CEK &= -0{\cdot}065\ PK + 1{\cdot}43 && (\text{if } PK \geqslant 6{\cdot}5) \end{aligned}\right\} \quad (10)$$

$$CE = 0{\cdot}5(CENA + CEK) \quad (11)$$

The cardiac function curve g (eqn. 5) has significant non-linearity over the operating range and is approximated by four piecewise linear equations of the form

$$CO = a_i RAP + b_i \tag{12}$$

The values of a_i and b_i, which were derived from GUYTON (1971), are given in Table 1. Eqns. 7 and 12 may be solved to yield the operating right atrial pressure RAP_o

$$RAP_o = \frac{MSP - b_i RVR}{1 + a_i RVR} \tag{13}$$

The problem is that RAP_o is not known in advance and hence a_i and b_i are indeterminate. An iterative approach to determining the 'correct' RAP_o is thus adopted.

2.1.5 *Arterial pressure.* Block 5 of Fig. 2 represents the pressure/flow relationship between total peripheral resistance TPR, cardiac output CO and arterial pressure AP:

$$AP = CO \times TPR \tag{14}$$

To represent very-long-term effects on the circulation, a steady-state bias, calculated from initial condition information, was included in the above relationship, which becomes:

$$AP = CO \times TPR + DAP_o \tag{15}$$

2.2 *Kidney function*

Considering the kidneys as one large nephron, mathematical expressions are derived representing the effects of kidney functions on the tubular processing and eventual excretion of sodium, potassium and water in the urine. Data reported in the literature were used in the derivation of the relationships between variables wherever possible, but owing to the fact that renal physiology is still not fully understood certain assumptions concerning renal function had to be made. Detailed justifications for these assumptions can be found in UTTAMSINGH (1981).

2.2.1 *Glomerular function.* The rate of formation of glomerular filtrate GFR is dependent on the net pressure forcing fluid across the glomerular capillary membranes in the Bowman's capsules of the nephrons. The net filtration pressure is equal to the difference between the hydrostatic pressure in the capillaries, which is dependent on mean arterial pressure and the sum of the glomerular colloid osmotic pressure and the hydrostatic pressure of the fluid surrounding the capillaries. It is assumed that variations of these last two pressures within the physiological ranges have negligible effect on glomerular filtration. Using data of a form first obtained by SHIPLEY and STUDY (1951), the following relationship between GFR and AP is obtained:

$$\left.\begin{aligned} GFR &= 0{\cdot}0 && (\text{if } AP \leqslant 20{\cdot}0 \text{ torr}) \\ GFR &= 1{\cdot}92\,AP - 38{\cdot}4 && (\text{if } 20{\cdot}0 < AP \leqslant 75{\cdot}0 \text{ torr}) \\ GFR &= -0{\cdot}00808\,AP^2 + 2{\cdot}195\,AP - 13{\cdot}6 \\ & && (\text{if } 75{\cdot}0 < AP \leqslant 120{\cdot}0 \text{ torr}) \\ GFR &= 0{\cdot}035\,AP + 129{\cdot}2 && (\text{if } AP > 120{\cdot}0 \text{ torr}) \end{aligned}\right\} \tag{16}$$

The relative constancy of glomerular filtration rate as renal arterial pressure rises above and beyond the value of 90 mm Hg is known as the renal autoregulation of glomerular filtration rate, a phenomenon due to adaptive changes in the resistance of the afferent arterioles to renal blood flow. This is consistent with the macula densa sodium concentration theory of renin release (THURAU *et al.*, 1967) and with the theory of tubulo-glomerular feedback controlling GFR by the renin/angiotensin system.

Chemical analysis of the glomerular filtrate fluid, collected from the early portions of the proximal tubule, has shown that it is iso-osmotic and isotonic with protein-free plasma fluid obtained from the glomerulus (WINDHAGER, 1968). Therefore, ignoring the slight error due to the Gibbs-Donnan effect, the rate of filtration of sodium into the proximal tubule FNA is given by

$$FNA = GFR \times PNA/1000{\cdot}0 \tag{17}$$

2.2.2 *Proximal tubule segment.* The rates of reabsorption of sodium in the proximal tubule $SPTR$ and of flow of sodium into the loop of Henle $SFLH$ are given by:

$$SPTR = GTB \times FNA \tag{18}$$

$$SFLH = FNA - SPTR \tag{19}$$

where GTB is the 'glomerular-tubular balance'. This fraction—nearly three-quarters of the filtered sodium—is known to be a function of sodium concentration. Since the concentration of sodium in the proximal tubule is nearly equal to the concentration PNA in plasma (JOHNSTON *et al.*, 1967), the following linear relationship was assumed as a first-order approximation:

$$GTB = 5{\cdot}815 - 0{\cdot}0357\,PNA \tag{20}$$

In the absence of significant amounts of poorly reabsorbable solutes, the fraction of the water load passively reabsorbed in the proximal tubule is equal to the fraction of the sodium load reabsorbed (e.g. MALNIC *et al.*, 1966, for evidence from animal studies). Hence the rate of water reabsorption $EPTR$ and flow into the next segment (loop of Henle) $EFLH$ are given by:

$$EPTR = GTB \times GFR \tag{21}$$

$$EFLH = GFR - EPTR \tag{22}$$

2.2.3 *The loop of Henle.* The morphology and transport characteristics of the loop of Henle give rise to the countercurrent mechanism, the primary mechanism by which the kidneys control the osmolality of the final urine as required by the state of fluid balance in the body.

Examining the overall reabsorptive characteristics for sodium and water in the loop of Henle of the animal kidney, LANDWEHR *et al.* (1968) have demonstrated that the fraction of the water load reabsorbed is a function of the transit time, or an inverse function of the rate of flow, whereas the fraction of the sodium load reabsorbed remains fairly constant as the rate of flow of tubular fluid is varied. Extrapolation to the human kidney yields the following relationships for the rates of reabsorption of

Table 1 Parameters a_i and b_i of cardiac function (eqn. 12) as functions of RAP range and CE

Cardiac effectiveness	Range 1 $RAP \leqslant 0$		Range 2 $0 < RAP \leqslant 2$		Range 3 $2 < RAP \leqslant 4$		Range 4 $4 < RAP$	
	a_1	b_1	a_2	b_2	a_3	b_3	a_4	b_4
$CE > 0{\cdot}85$	0	0	3·0	5·25	0·875	9·5	0	13·0
$0{\cdot}85 \geqslant CE > 0{\cdot}62$	0	0	2·5	3·75	0·625	7·5	0	8·75
$0{\cdot}62 > CE$	0	0	1·7	2·125	0·375	4·75	0	6·25

water $ELHR$ and sodium $SLHR$ in this nephron segment:

$$\left.\begin{aligned} EBLH &= -0{\cdot}01\,EFLH + 0{\cdot}65 \\ ELHR &= EBLH \times EFLH \end{aligned}\right\} \quad (23)$$

$$SLHR = 0{\cdot}8\,SFLH \quad (24)$$

The rates of flow of water $EFDT$ and sodium $SFDT$ into the distal tubules are then given by:

$$EFDT = EFLH - ELHR \quad (25)$$

$$SFDT = SFLH - SLHR \quad (26)$$

2.2.4 *Distal and collecting segments.* The volume and osmolality of urine are controlled finally by the actions of the antidiuretic hormone (ADH) and aldosterone on the distal segments of the tubules. Using data from the literature, DEHAVEN and SHAPIRO (1970) have derived a quantitative relationship between the plasma level of ADH and the resulting rate of urine flow in man for use in their model. Assuming a normal value for the rate of delivery of tubular fluid to the distal tubule, this leads to the following approximate relationships for the effect of variations in the plasma concentration of ADH on the rate of reabsorption of fluid from the distal and collecting segments of the human nephron $EDTR$:

$$\left.\begin{aligned} EBDT &= 0{\cdot}0 \quad (\text{if } ADH \leqslant 0{\cdot}765 \text{ munits}\,l^{-1}) \\ EBDT &= 0{\cdot}383\,ADH - 0{\cdot}293 \\ &\quad (\text{if } 0{\cdot}765 < ADH \leqslant 3{\cdot}0 \text{ munits}\,l^{-1}) \\ EBDT &= -0{\cdot}0383\,ADH^2 + 0{\cdot}364\,ADH + 0{\cdot}109 \\ &\quad (\text{if } 3{\cdot}0 < ADH \leqslant 5{\cdot}0 \text{ munits}\,l^{-1}) \\ EBDT &= 0{\cdot}0012\,ADH + 0{\cdot}9653 \\ &\quad (\text{if } ADH > 5{\cdot}0 \text{ munits}\,l^{-1}) \end{aligned}\right\} \quad (27)$$

$$EDTR = EBDT \times EFDT \quad (28)$$

Urine flow UFL is then given by

$$UFL = EFDT - EDTR \quad (29)$$

ROEMMELT *et al.* (1949) have shown that the fraction of sodium reabsorbed under the influence of aldosterone is approximately 2 per cent of the filtered load of sodium. Hence, in the model:

$$\left.\begin{aligned} SDTR &= 0{\cdot}6\,SFDT \quad (\text{for } ALD \leqslant 0{\cdot}0\,\text{ng}\,l^{-1}) \\ SDTR &= (0{\cdot}003\,ALD + 0{\cdot}596)SFDT \\ &\quad (\text{for } 0{\cdot}0 < ALD \leqslant 85{\cdot}0\,\text{ng}\,l^{-1}) \\ SDTR &= (0{\cdot}00021\,ALD + 0{\cdot}833)SFDT \\ &\quad (\text{for } 85{\cdot}0 < ALD \leqslant 800{\cdot}0\,\text{ng}\,l^{-1}) \\ SDTR &= SFDT \quad (\text{for } ALD > 800{\cdot}0\,\text{ng}\,l^{-1}) \end{aligned}\right\} \quad (30)$$

The rate of excretion of sodium in the urine UNA is then given by

$$UNA = SFDT - SDTR \quad (31)$$

(Note that ADH can produce large percentage changes in fluid reabsorption whereas aldosterone has only a small modulating effect on sodium reabsorption. This suggests that ADH is the primary controller; however, a full analysis requires consideration of the overall dynamics.)

The results of MALNIC *et al.* (1966) suggest that the renal handling of potassium need not be modelled on a segmental basis. VALTIN (1973) proposed probable mechanisms for the secretion of potassium in the distal tubule.

In the light of these results, the excretion of potassium due to concentration dependence UKH and aldosterone $UKAL$, are represented in the model by the relationships:

$$UKH = 0{\cdot}107\,PK - 0{\cdot}505 \quad (32)$$

$$\left.\begin{aligned} UKAL &= 0{\cdot}00028\,ALD + 0{\cdot}0062 \\ &\quad (\text{if } ALD \leqslant 85{\cdot}0\,\text{ng}\,l^{-1}) \\ UKAL &= 0{\cdot}00009\,ALD + 0{\cdot}0224 \\ &\quad (\text{if } ALD > 85{\cdot}0\,\text{ng}\,l^{-1}) \end{aligned}\right\} \quad (33)$$

Combining eqns. 32 and 33 yields the net rate of excretion of potassium:

$$UK = UKH + UKAL \quad (34)$$

2.3 *Hormonal systems*

Having derived equations representing the effects of ADH and aldosterone on the distal and collecting segments of the nephron, the model representation of the control of the concentrations of these substances in plasma is developed.

2.3.1 *Control of ADH concentration.* Plasma ADH concentration is determined by three factors: the rate of release of ADH from the hypothalamus/pituitary system in response to signals from the osmoreceptors of the hypothalamus and from volume and pressure receptors in the vascular system, the rate of clearance of ADH from the body by the liver and kidneys, and the volume of distribution of ADH.

Adapting relationships derived by DEHAVEN and SHAPIRO (1970) and BIGELOW *et al.* (1973), the effect of differing osmolalities of plasma on the rate of release of ADH ($ADHSP$) was modelled as a dependency on PNA:

$$\left.\begin{aligned} ADHSP &= 0{\cdot}73\,PNA - 103{\cdot}43 \\ &\quad (\text{for } PNA \geqslant 141{\cdot}9\,\text{mosm}\,l^{-1}) \\ ADHSP &= 0{\cdot}06\,PNA - 8{\cdot}04 \\ &\quad (\text{for } PNA < 141{\cdot}9\,\text{mosm}\,l^{-1}) \end{aligned}\right\} \quad (35)$$

REEVE and KULHANEK (1967) derived a sigmoid shaped curve from physiological data for the relationship between the fractional change in the volume of body fluid and the rate of release of ADH. Modifying this relationship so that the variable causing the release of ADH was the deviation of the volume of the extracellular compartment DWV from the normal volume E_N:

$$DWV = E - E_N \quad (36)$$

The resulting relationship between the deviation of extracellular fluid volume from normal DWV and the rate of release of ADH $ADHSV$ is then approximated by:

$$\left.\begin{aligned} ADHSV &= 0{\cdot}0 \quad (\text{for } DWV \geqslant 1{\cdot}8) \\ ADHSV &= 0{\cdot}15 - 0{\cdot}083\,DWV \\ &\quad (\text{for } 1{\cdot}8 > DWV \geqslant 1{\cdot}0) \\ ADHSV &= 0{\cdot}813 - 0{\cdot}75\,DWV \\ &\quad (\text{for } 1{\cdot}0 > DWV \geqslant -1{\cdot}2) \\ ADHSV &= 1{\cdot}71 \quad (\text{for } -1{\cdot}2 > DWV) \end{aligned}\right\} \quad (37)$$

Data from JOHNSON *et al.* (1970) on sheep suggest that the signals for ADH release are additive. However, for the condition when both the osmolality and the volume of the extracellular fluid compartment are above normal, ARNDT

(1965) reported the optimal combined signal to be the sum of the weighted signals in favour of the signal from the volume receptors. The resulting signal for the release of ADH in the model *ADHS* is thus given by:

$$\left.\begin{aligned} ADHS &= \{(17{\cdot}0\,DWV \times ADHSV) + ADHSP\}/ \\ &\quad \{(17{\cdot}0\,DWV) + 1{\cdot}0)\} \\ &\quad (\text{for } POS > 299{\cdot}6\,\text{mosm}\,l^{-1} \\ &\quad \text{and } DWV > 2{\cdot}01) \\ ADHS &= [\{(33{\cdot}0\,DWV - 32{\cdot}0)ADHSV\} \\ &\quad + ADHSP]/ \\ &\quad \{(33{\cdot}0\,DWV - 32{\cdot}0) + 1{\cdot}0\} \\ &\quad (\text{for } POS > 299{\cdot}6\,\text{mosm}\,l^{-1} \\ &\quad \text{and } 1{\cdot}0 \leqslant DWV \leqslant 2{\cdot}0) \\ ADHS &= (ADHSV + ADHSP)/2{\cdot}0 \\ &\quad (\text{for all other conditions}) \end{aligned}\right\} \quad (38)$$

Czaczkes *et al.* (1964) have, however, provided evidence that the rate of ADH clearance varies with the ADH plasma level. Hence, the relationship between the concentration of ADH in plasma (*ADH*) and the rate of clearance in the model, *DADH* is of the same general form as that used by Bigelow *et al.* (1973) in their model of the renal system:

$$\left.\begin{aligned} DADH &= 0{\cdot}206 \quad (\text{for } ADH > 4{\cdot}0\,\text{munits}\,l^{-1}) \\ DADH &= 0{\cdot}374 - 0{\cdot}042\,ADH \\ &\quad (\text{for } ADH \leqslant 4{\cdot}0\,\text{munits}\,l^{-1}) \end{aligned}\right\} \quad (39)$$

The work of Reeve and Kulhanek (1967) suggests that ADH is mainly confined to the plasma compartment. The volume of the plasma compartment *PV* in the model is considered to be a constant fraction of the blood volume *BV*:

$$PV = 0{\cdot}6\,BV \quad (40)$$

Hence

$$\frac{d(ADH)}{dt} = (ADHS - ADH \times DADH)/PV \quad (41)$$

2.3.2 *Control of aldosterone concentration.* Aldosterone is the final component of the renin/angiotensin/aldosterone (R/A/A) system, the function of which is to effect feedback control on the rates of excretion of sodium and potassium, and thereby influence the volumes of the intracellular and extracellular fluid compartments.

In the absence of more explicit data, the linear relationship below was postulated as a representation of the control of the release of renin *RS* due to the load of sodium entering the distal tubule *SFDT*:

$$RS = 0{\cdot}0163 - 0{\cdot}0093\,SFDT \quad (42)$$

Although simple, this equation is consistent with two main theories for renin release: the macula densa sodium load theory for the release of renin (Vander and Miller, 1964) and the macula densa intraluminal sodium concentration theory of Thurau *et al.* (1967). The effects of other factors, such as posture (Gordon *et al.*, 1967), sympathetic stimulation (Taquini *et al.*, 1964), ADH and angiotensin II levels (Shade *et al.*, 1973), on the rate of release of renin are assumed to be negligible.

Renin is removed from the circulation on passage through the liver (Heacox *et al.*, 1967). Therefore the rate of clearance of renin from plasma can be assumed to be constant if the hepatic blood flow is assumed to be constant. From steady-state considerations a clearance rate of $0{\cdot}1351\,\text{min}^{-1}$ was found. Thus

$$\frac{dR}{dt} = (RS - 0{\cdot}135\,R)/PV \quad (43)$$

As an enzyme, renin acts on its substrate to release angiotensin I. This physiologically inactive substance is rapidly converted to angiotensin II by enzymes chiefly located in the lungs (Ng and Vane, 1968).

On the basis of work by Haas and Goldblatt (1967), the following equation was adopted for the rate of formation of angiotensin II *AS*.

$$AS = 583{\cdot}3\,R \times PV \quad (44)$$

Steady-state consideration gives a value for the rate of clearance of angiotensin II from plasma of $4{\cdot}04\,\text{l}\,\text{min}^{-1}$. Therefore, the balance equation regulating the concentration of angiotensin II in plasma *A* in the model is

$$\frac{dA}{dt} = (AS - 4{\cdot}04\,A)/PV \quad (45)$$

The factors known to increase the rate of release of aldosterone from the adrenal cortex are (Guyton, 1971) an increase in the concentration of angiotensin II in plasma, a decrease in sodium balance or concentration of sodium in plasma, an increase in potassium balance or concentration of potassium in plasma, and an increase in circulating adrenocorticotropic hormone (ACTH).

The effect of sodium balance is assumed to be mediated by the effect of the renin/angiotensin system on the release of aldosterone in the model. In addition, the role of ACTH in this control system is known to be relatively minor (Guyton, 1971). Therefore only angiotensin II and the concentration of potassium in plasma are considered in modelling the release of aldosterone.

The relationship between the concentration of angiotensin II in plasma and the rate of secretion of aldosterone in sheep was found experimentally to be of the form of the typical sigmoid shaped dose-response curve (Blair-West *et al.*, 1962). These results were extrapolated by Blaine *et al.* (1972) to represent the relationship between the concentration of angiotensin in plasma *A* and the rate of secretion of aldosterone:

$$\left.\begin{aligned} ALSA &= A \quad (\text{for } A < 18{\cdot}0\,\text{ng}\,l^{-1}) \\ ALSA &= 4{\cdot}43\,A - 61{\cdot}7 \\ &\quad (\text{for } 18{\cdot}0 \leqslant A < 34{\cdot}0\,\text{ng}\,l^{-1}) \\ ALSA &= 0{\cdot}78\,A + 62{\cdot}5 \\ &\quad (\text{for } A \geqslant 34{\cdot}0\,\text{ng}\,l^{-1}) \end{aligned}\right\} \quad (46)$$

The effect of the concentration of potassium *PK* on the rate of release of aldosterone *ALSK* has been investigated by Seif (1974), leading to the following relationship:

$$ALSK = 21{\cdot}64\,PK - 55{\cdot}5 \quad (47)$$

Since the manner in which the signals for the release of aldosterone are combined in the human organism is unknown, it was postulated that the net signal *ALS* is the weighted sum of the signals *ALSA* and *ALSK*:

$$ALS = (3{\cdot}0\,ALSA + ALSK)/4{\cdot}0 \quad (48)$$

On the basis of steady-state values a clearance rate of $0{\cdot}621\,\text{l}\,\text{min}^{-1}$ for aldosterone from plasma was found,

leading to the following equation:

$$\frac{dALD}{dt} = (ALS - 0{\cdot}62\,ALD)/PV \tag{49}$$

2.4 *Balance equations for fluid and electrolytes*

The body fluids and their constituents are modelled in terms of intracellular and extracellular compartments. The balance equations for the volumes of these compartments and for their sodium and potassium contents are derived below. It is assumed that within the timescale of the model water is transferred from the extracellular pool to the intracellular pool instantaneously to ensure osmotic equilibrium. Thus total body water is considered as a single pool, with an instantaneous partitioning into extracellular and intracellular spaces.

2.4.1 *Sodium and potassium balance.* Sodium and potassium enter the extracellular fluid pool through the gut as a result of ingestion, and leave by way of the kidneys. The time average of the daily ingestion rates of these electrolytes are *SODMIN* and *POTMIN*. The rate at which the electrolytes leave the body via the kidneys, *UNA* and *UK*, have been derived in eqns. 31 and 34. It is assumed that the active transport process balances the transcellular transfer of electrolytes by diffusion, so that there is negligible net transfer of electrolytes across the cellular barrier. Hence the rates of change of sodium and potassium in the extracellular (*TENA* and *TEK*) and intracellular (*TINA* and *TIK*) compartments are:

$$\frac{d(TENA)}{dt} = SODMIN - UNA \tag{50}$$

$$\frac{d(TEK)}{dt} = POTMIN - UK \tag{51}$$

$$\frac{d(TINA)}{dt} = 0 \tag{52}$$

$$\frac{d(TIK)}{dt} = 0 \tag{53}$$

The concentrations of sodium and potassium in the extracellular (*PNA* and *PK*) and intracellular (*INA* and *IK*) compartments are given by:

$$PNA = TENA/E \tag{54}$$

$$PK = TEK/E \tag{55}$$

$$INA = TINA/I \tag{56}$$

$$IK = TIK/I \tag{57}$$

where E and I are the extracellular and intracellular partitions of total body water.

2.4.2 *Fluid balance.* Ingested water is considered to pass into the total body water compartment from the gut at a constant rate *FLUMIN* and be removed in the form of urine by the kidneys at a rate *UFL* determined by eqn. 29. Thus the balance equation for this compartment is:

$$\frac{dW}{dt} = FLUMIN - UFL \tag{58}$$

As indicated above, the water compartment is partitioned into extracellular (E) and intracellular (I) spaces to ensure osmotic equilibrium. Thus, equating osmolities:

$$(TENA + TEK + TEC)/E = (TINA + TIK + TIK)/I \tag{59}$$

where *TEC* and *TIC* are constant terms representing the osmotic effects of the remaining body fluid components. Writing

$$TE = TENA + TEK + TEC \tag{60}$$

and

$$TI = TINA + TIK + TIC \tag{61}$$

it follows that

$$E = \frac{W}{1 + TI/TE} \tag{62}$$

and

$$I = \frac{W}{1 + TE/TI} \tag{63}$$

3 Representational validity of the model

The model equations were coded in Fortran IV. The differential equations, arranged in a separate subroutine, were integrated numerically by a fourth-order variable-step Runge-Kutta routine adopting a nominal step length of one minute. A full description of the program is given in UTTAMSINGH (1981).

The representational validity of the model was then examined by comparison of the model responses to a variety of stresses with the corresponding physiological responses reported in the literature.

Comparison of experimental results with those obtained from model simulation serves as an indication of the validity of the model of the renal/body fluid system of the healthy human. The experiments were chosen on the basis that the validity of all the subsystem models of the renal/body fluid system would be tested, but that the validity of

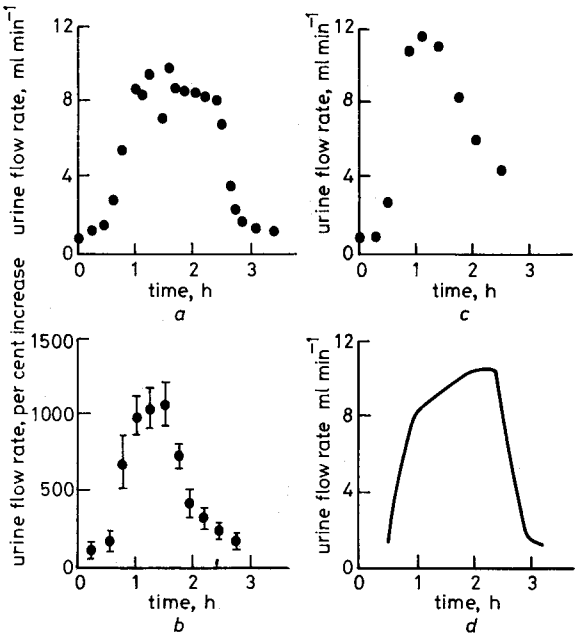

Fig. 3 *Urine flow following ingestion of 1 l of water; (a) data from BALDES and SMIRK (1934), (b) data for eight subjects (mean ± standard error of measurement), (c) data for one subject from (b). (d) model simulation*

the subsystem models with greatest uncertainty—the hormonal control systems—would be under greatest scrutiny.

3.1 *Effect of a water load*

The experiment consisted of monitoring the urine flow rate in a human subject following the rapid ingestion of 1 l of water. One frequently reported set of results (BALDES and SMIRK, 1934) is shown in Fig. 3*a*, with more recent unpublished data on eight subjects presented in Fig. 3*b*.

The major difference between these two sets of results, considering gross features, is the absence of the oscillations and plateau at the peak of the curve in the results shown in Fig. 3*b*. Consideration of the results of the eight individual experiments, an example of which is shown in Fig. 3*c*, suggests that this difference is not due to the process of averaging the results of the subjects. Rather, it appears that these features in the much publicised data reported by Baldes and Smirk are due to the peculiarities of the single subject on whom the experiment was conducted. However, apart from this difference, the features of the two sets of data are generally in agreement.

The ingestion of water was simulated by increasing the water content of the extracellular fluid compartment by 1 l at an instant in simulated time; and the effect of the transfer of fluid across the walls of the stomach into the fluid compartment on the response in the actual experiments was approximated by introducing a pure delay of 15 min in the simulated response immediately after the expansion of the extracellular compartment.

The simulation results are plotted in Fig. 3*d* for comparison. It is seen that the general features of the simulated urine flow rate response match those of the data presented by Baldes and Smirk. However, the features of the simulated response are seen to match those of the data shown in Fig. 3*b*.

This result indicates that the model is sufficiently valid to reproduce the features of response of the rate of flow of urine when a normal human is subjected to a water load stress. In particular, this test confirms the validity of the representation of the ADH control system in the model, since the variation in the rate of flow of urine is affected by the changes in fluid volume and the osmolality of plasma and subsequent changes in the concentration of ADH in plasma.

3.2 *Effect of a hypertonic saline load*

Experiments involving the infusion of hypertonic saline loads into adults and infants, and the subsequent monitoring of the rates of flow of urine, were reported by DEAN and MCCANCE in 1949. Each subject was deprived of fluid for 16 h before being infused with a solution of 10 per cent sodium chloride. DEAN and MCCANCE (1949) reported the urine flow rate response for one adult, who was infused with a dose of 0·91 g of sodium chloride per kg of body weight over a period of 65 min, and the average of the responses of all the adults, who were infused with various dosages over varying periods of time, as well as the responses of the infants. The features of the response of the single adult, plotted in Fig. 4, where the start of the experiment is considered to be the midpoint of the period of administration of the solution, are similar to those of the averaged response of the adults.

The experiment of loading the adult with a hypertonic saline load was simulated using the model of the renal/body fluid system of a normal human of 70 kg. This was achieved by appropriately programming values for the variables representing the rates of ingestion of sodium and water. Since representations of the stomach and intestines do not exist in the model, ingestion of the saline solution is equivalent to infusion in the real system.

The results of the simulation are plotted in Fig. 4 for comparison with the response data of the actual system. It is seen that there is close agreement between the response of the real system and that of the simulation.

This result indicates that the model is sufficiently valid to reproduce the real response to within acceptable limits. In particular, this test for the model confirms the validity of the kidney function model and the ADH control system model.

Furthermore, this test is of special interest, since the infusion of a hypertonic saline solution gives rise to conflicting signals for the release of ADH. Since the concentration of ADH in plasma is a major determinant of the rate of urine flow, the successful simulation of this experiment

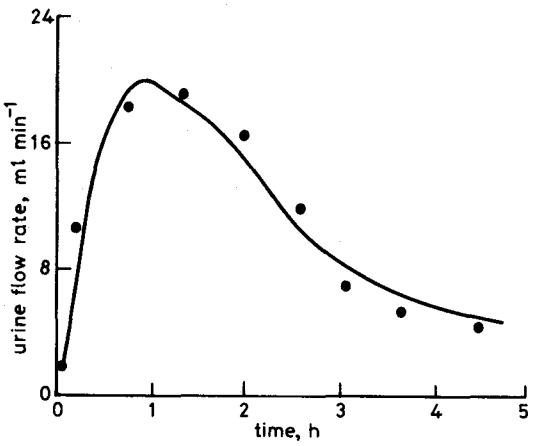

Fig. 4 *Urine flow following ingestion of hypertonic saline. Solid circles are experimental data from DEAN and MCCANCE (1949). The continuous line is the model simulation*

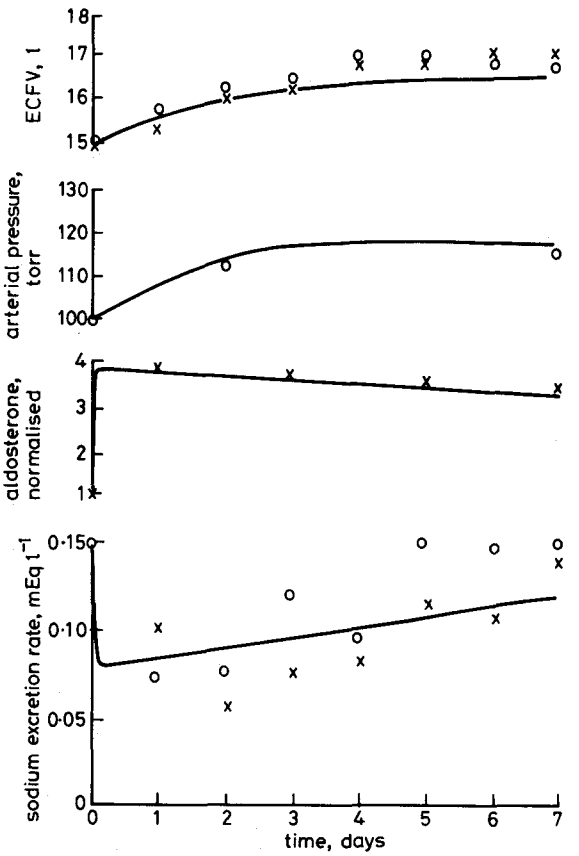

Fig. 5 *Aldosterone loading showing data (×) from RELMAN and SCHWARTZ (1952), data (○) from DAVIS and HOWELL (1953), and model simulation (—)*

indicates that the control action for combining the signals for the release of ADH in the real system is adequately represented in the model.

3.3 *Aldosterone loading*

RELMAN and SCHWARTZ (1952) conducted a fluid and electrolyte balance study during the course of daily intramuscular administration of 20 mg of deoxycorticosterone acetate (DOCA—a mineralocorticoid whose effects, apart from potency, are very similar to those of aldosterone) to three groups of healthy adult humans. Each group was on a high-, normal- or low-salt-intake regimen. DAVIS and HOWELL (1953) conducted a similar experiment on four dogs on a controlled normal-salt diet.

The results of the experiments, averaged for the humans on the normal diet, and for the four dogs, are shown in Fig. 5 as the time course of the following variables: extracellular fluid volume (extrapolated from weight gain data), arterial pressure, hormone level and sodium excretion rate. The most significant aspect of these results is the demonstration of the phenomenon of 'escape', where, after an initial fall due to the high level of sodium-retaining hormone, the rate of excretion of sodium rises to match the rate of intake.

The experiments were simulated, using the model, by multiplying the rate of secretion of aldosterone by a factor of four throughout the period of simulation. This approximately represents the administration of DOCA as described above (CAMERON, 1977).

The simulation results are shown in Fig. 5 for comparison with the experimental results. It is seen that the features of response of the variables of the simulation representing extracellular fluid volume, arterial pressure, hormone level and the rate of excretion of sodium are in agreement with those of the experimental data. In particular, the 'escape' phenomenon is clearly apparent in the simulation response. Examination of the other variables of the simulation indicate that the contributing factors to 'escape' are the elevation of glomerular filtration rate, due to the expanded extracellular fluid compartment and elevated arterial pressure, and the increase in the concentration of sodium in plasma, resulting in the increased rate of filtration, and hence excretion, of sodium.

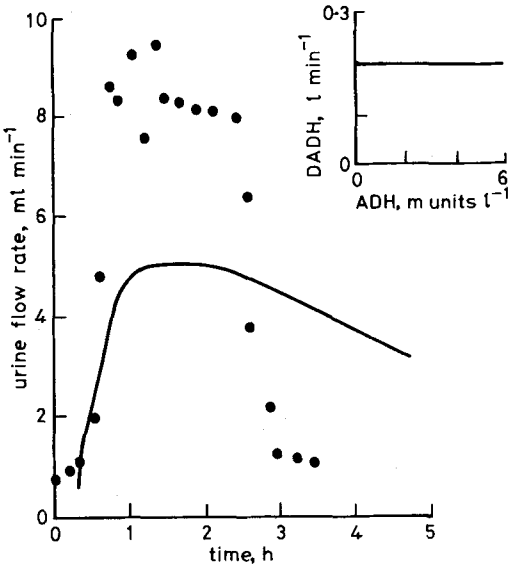

Fig. 6 *Urine flow following ingestion of 1 l of water with constant rate of clearance of ADH (panel insert) with data (●) from BALDES and SMIRK (1934) and model simulation (—)*

The simulation results presented in Fig. 5 thus contribute to the evidence of previous simulation tests, suggesting that the model is a sufficiently valid representation of the renal/body fluid system of a human to reproduce features of responses due to a variety of stresses. This test, in particular, serves to demonstrate the validity of the representation of the aldosterone system, the cardiovascular system, fluid balance and the renal handling of sodium.

4 Discussion

The mathematical model described in this paper has been developed for the primary purpose of aiding the testing of hypotheses relating to the dynamics and control of the human renal system. The results of the validation tests performed upon the model indicate its adequacy as a representation of the renal system and hence its appropriateness for hypothesis testing.

The hypothesis testing facility offered by the model has been used during the final stages of model development, with numerical expressions being postulated for relationships between system variables for which there were little or no available data. Adopting an iterative process of model development, candidate expressions for areas of the model with high uncertainty were tested. Those which produced implausible results were rejected and those giving acceptable responses on the basis of available data were retained. These new hypotheses must, of course, be subjected to further critical evaluation and testing as well as providing a guideline for experimental work.

This role of hypothesis testing is exemplified by considering ADH dynamics. Owing to the difficulty in measuring low plasma ADH concentrations, considerable uncertainty exists regarding the relationship between the rate of clearance of ADH and its level, particularly when low (LAUSON, 1960; CZACZKES *et al.*, 1964). It was first assumed that ADH clearance was independent of plasma concentration and so could be modelled by:

$$PV\frac{dADH}{dt} = ADHS - 0{\cdot}206\,ADH \tag{64}$$

Simulation results for the water load test, incorporating eqn. 64, are shown in Fig. 6. A second hypothesis was then examined for ADH clearance:

$$\left.\begin{aligned} DADH &= 0{\cdot}145\,ADH \\ &\quad (\text{if } ADH < 2{\cdot}0\,\text{munits}\,l^{-1}) \\ DADH &= -0{\cdot}042\,ADH + 0{\cdot}374 \\ &\quad (\text{if } 2{\cdot}0 \leqslant ADH \leqslant 4{\cdot}0\,\text{munits}\,l^{-1}) \\ DADH &= 0{\cdot}206 \quad (\text{if } ADH > 4{\cdot}0\,\text{munits}\,l^{-1}) \end{aligned}\right\} \tag{65}$$

Simulation of the water load test, incorporating eqn. 65 in the model, is depicted in Fig. 7. Given the inadequacies of these results, eqns. 64 and 65 were replaced by eqns. 39 and 41, leading to the more acceptable results already discussed as seen in Fig. 3.

The parameter values were obtained by manual fitting of the model to a specific set of data. Preliminary sensitivity studies indicated that the general patterns of model response are not substantially altered by parameter changes reflecting likely biological variability in the population under study.

This iterative procedure of hypothesis testing in the modelling process was also used in arriving at the expressions for glomerular tubular balance (eqn. 20) and the control of the rate of release of ADH (eqn. 38)

(UTTAMSINGH, 1981). Other areas of uncertainty, particularly concerning hormonal control, may also be analysed in a similar manner.

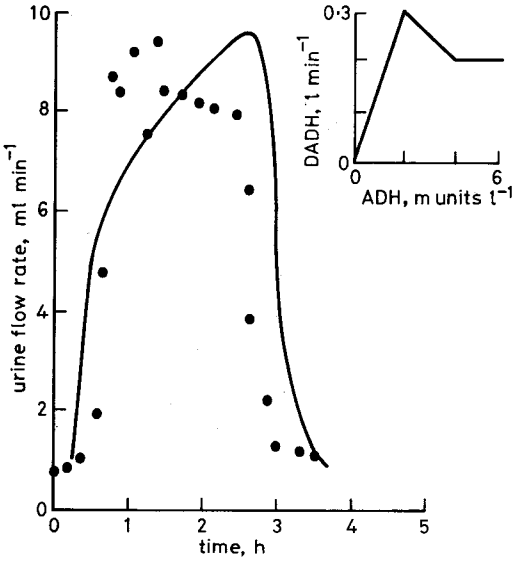

Fig. 7 *Urine flow following ingestion of 1 l of water with control of ADH clearance as shown in panel insert. Data (●) from BALDES and SMIRK (1934) and model simulation (—)*

Analysis by this method has the added benefit of affording deeper understanding of the workings of the system being modelled. This arises since, first, the simulations can yield dynamic responses of variables in the model which are difficult to measure in the real system and, secondly, the iterative procedure for hypothesis testing requires an 'educated guess' to be made for the form of the next hypothesis to be tested.

Although the formulation of a model for hypothesis testing has been the principal objective of this investigation, the model is capable of being developed further. By incorporating representations of renal failure and the artificial kidney machine, and tuning the parameters to the individual subject, the model can be used to predict the state of the patient with renal failure during and after dialysis—a predictive role of modelling to complement the explanatory, heuristic role described in this paper. This is reported in LEANING *et al.* (1982).

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Appendix

Model variables

Symbol	Definition	Typical value
A	concentration of angiotensin II in plasma ($ng\,l^{-1}$)	27·0
ADH	concentration of ADH in plasma ($munits\,l^{-1}$)	4·0
ADHS	net release rate of ADH ($munits\,min^{-1}$)	0·825
ADHSP	release rate of ADH due to plasma osmolality ($munits\,min^{-1}$)	0·84
ADHSV	release rate of ADH due to diminished fluid volume ($munits\,min^{-1}$)	0·81
ALD	concentration of aldosterone in plasma ($ng\,l^{-1}$)	85·0
ALS	net rate of secretion of aldosterone ($ng\,min^{-1}$)	52·7
ALSA	release rate of aldosterone due to angiotensin II ($ng\,min^{-1}$)	52·7
ALSK	release rate of aldosterone due to plasma potassium concentration ($ng\,min^{-1}$)	52·7
AP	arterial pressure (torr)	100·0
AS	rate of formation of angiotensin II ($ng\,min^{-1}$)	105·0
BV	blood volume (l)	5·0
CE	cardiac effectiveness	1·0
CEK	cardiac effectiveness due to abnormal potassium level	1·0
CENA	cardiac effectiveness due to abnormal sodium level	1·0
CO	cardiac output ($l\,min^{-1}$)	5·0
DADH	clearance rate of ADH ($l\,min^{-1}$)	0·206
DAP_o	steady-state bias on arterial pressure (torr)	*
DTPR	pressure effect of angiotensin II on circulation ($torr\,l^{-1}\,min^{-1}$)	0·0
DWV	excess fluid in extracellular compartment (l)	0·0
E	extracellular fluid volume (l)	15·0
E_N	normal extracellular fluid volume (l)	15·0
EBDT	fraction of water load reabsorbed in the distal nephron segments	0·952
EBLH	fraction of water load reabsorbed in the loop of Henle	0·33
EDTR	rate of reabsorption of water in the distal nephron segments ($ml\,min^{-1}$)	19·7
EFDT	rate of flow of water into the distal tubule ($ml\,min^{-1}$)	—
EFLH	rate of flow of water into the loop of Henle ($ml\,min^{-1}$)	31·25
ELHR	rate of reabsorption of water in the loop of Henle ($ml\,min^{-1}$)	10·55
EPTR	rate of reabsorption of water in proximal tubule ($ml\,min^{-1}$)	93·75
FLUMIN	rate of ingestion of water ($ml\,min^{-1}$)	*
FNA	filtered load of sodium ($mEq\,min^{-1}$)	17·75
GFR	glomerular filtration rate ($ml\,min^{-1}$)	125·0
GTB	fraction of filtered load of sodium reabsorbed in proximal tubule	0·75
I	intracellular fluid volume (l)	25·0
IK	intracellular concentration of potassium ($mEq\,l^{-1}$)	141·0
INA	intracellular concentration of sodium ($mEq\,l^{-1}$)	10·0
MSP	mean systemic pressure (torr)	7·0
PK	extracellular concentration of potassium ($mEq\,l^{-1}$)	5·0
PNA	extracellular concentration of sodium ($mEq\,l^{-1}$)	142·0
POTMIN	rate of ingestion of potassium ($mEq\,min^{-1}$)	*
PV	plasma volume (l)	3·0
R	concentration of renin in plasma ($GU\,l^{-1}$)	0·06
RAP	right atrial pressure (torr)	0·0
RS	rate of release of renin ($GU\,min^{-1}$)	0·008
RVR	resistance to venous return ($torr\,l^{-1}\,min^{-1}$)	1·4
SDTR	rate of reabsorption of sodium from the distal nephron segments ($mEq\,min^{-1}$)	0·757
SFDT	rate of flow of sodium into distal tubule ($mEq\,min^{-1}$)	0·89
SFLH	rate of flow of sodium into loop of Henle ($mEq\,min^{-1}$)	4·44
SLHR	rate of reabsorption of sodium from the loop of Henle ($mEq\,min^{-1}$)	3·55
SODMIN	rate of ingestion of sodium ($mEq\,min^{-1}$)	*

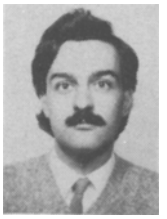
cont.

SPTR	rate of reabsorption of sodium in proximal tubule ($mEq\,min^{-1}$)	13·3
TE	total extracellular osmotic components (mEq)	4548·0
TEC	total extracellular osmotic components other than sodium and potassium (mEq)	2343·0
TEK	total extracellular potassium (mEq)	75·0
TENA	total extracellular sodium (mEq)	2130·0
TI	total intracellular osmotic components (mEq)	7805·0
TIC	total intracellular osmotic components other than sodium and potassium (mEq)	4030·0
TIK	total intracellular potassium (mEq)	3525·0
TINA	total intracellular sodium (mEq)	250·0
TPR	total peripheral resistance ($torr\,l^{-1}\,min^{-1}$)	20·0
UFL	urine flow rate ($ml\,min^{-1}$)	1·0
UK	net rate of excretion of potassium ($mEq\,l^{-1}$)	0·06
UKAL	rate of excretion of potassium due to aldosterone ($mEq\,min^{-1}$)	0·03
UKH	rate of excretion of potassium due to homeostasis ($mEq\,min^{-1}$)	0·03
UNA	rate of excretion of sodium ($mEq\,min^{-1}$)	0·128
VR	venous return ($l\,min^{-1}$)	5·0
W	total body water (l)	40·0

(* subject-dependent value)

Authors' biographies

Ranjeet J. Uttamsingh obtained a B.Sc. in Electrical Engineering from Imperial College, London in 1974 and an M.Sc. in Systems Engineering from the City University in 1975. He completed his Ph.D. in systems science also at the City University in 1981 with a thesis on 'A systems approach to renal dialysis'. He is currently with Combustion Engineering Simcon Inc. (New Jersey, USA) as a project manager, working on simulation and advanced computer control applications for the oil, gas and related process industries. He is also investigating potential artificial intelligence applications to the process industries.



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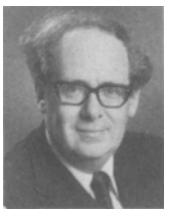

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