

# Contents

<b>1</b>	<b>Introduction: The scope of the analysis in this book</b>	1
<b>2</b>	<b>Sodium: The main cation of body fluids</b>	4
	Palaeochemistry of body fluids .....	4
	Evolutionary emergence of the renin-angiotensin system and aldosterone secretion .....	6
	Evolutionary emergence of salt appetite .....	8
<b>3</b>	<b>The natural history of sodium deficiency and salt appetite in wild animals</b>	10
	Introduction .....	11
	Salt appetite in the wild .....	11
	Herbivores .....	11
	Primates .....	18
	The metabolic basis of salt hunger in wild and range domestic animals .....	20
	Australia .....	20
	African game .....	34
	Central Asia .....	36
	North America .....	37
	Further observations on grazing cattle .....	41
	General consideration of ruminants and their adaptive capacities with change of diet .....	42
	Man .....	43
	Aggravation of low sodium status by superimposed natural causes .....	44
<b>4</b>	<b>Hominoid evolution and the influences on sodium homeostasis</b>	53
	Dietary sodium and salt appetite in herbivores, carnivores and omnivores .....	54
	Hominoid evolution .....	56
	Tool-making and the definition of man .....	56
	Man's earliest ancestors .....	57
	Jolly's hypothesis .....	58
	Some discoveries of the Leakeys .....	60
	Hunters and gatherers: Evidence on diet of early man .....	63
	Some more recent findings .....	64
	Chronology of divergence of Hominidae and apes and dietetic implications .....	66
	Diet of pongids .....	66
	Chronology of divergence .....	68
	Diet of hominids .....	70
	Discovery of fire .....	71
<b>5</b>	<b>Salt in history: Symbolic, social and physiological aspects</b>	76
	Symbolism .....	76
	History .....	76
	Mediterranean .....	76
	China .....	78
	Europe .....	79

Africa .....	80
France .....	83
India .....	84
Condiments, and some early views on salt in this context .....	85
Ethnographic data on use and non-use of salt .....	86
Eskimos .....	88
Bolivian Indians .....	88
Sahara nomads .....	89
Pattern and seeming paradox: A summary .....	89
<b>6 Cannibalism .....</b>	<b>91</b>
Introduction. Cannibalism—fact or largely fiction? .....	92
Animal data .....	93
Historical background .....	94
Fiji .....	95
Mexico .....	96
Africa .....	97
New Guinea .....	97
New Zealand .....	99
Australia .....	108
The Amazon Basin: The journals of Alfred Russell Wallace .....	109
Motivation, including nutritional status .....	111
<b>7 Physiological effects of sodium deficiency; the putative brain renin–angiotensin system .....</b>	<b>115</b>
Sodium status .....	116
Positive sodium status .....	118
Negative sodium status and its effects .....	118
Growth .....	118
Body weight and physical condition .....	119
Body fluid compartments and blood pressure .....	119
Organ blood flow .....	121
Plasma sodium concentration .....	122
Exchangeable sodium and bone sodium .....	122
Renal function .....	123
Plasma potassium .....	123
Pressor response .....	123
Sensitivity of tissue responses to hormones .....	124
Intestinal mobility .....	124
Tissue composition .....	125
Sodium deficiency in pregnancy .....	125
Brain electrolytes .....	126
Aldosterone secretion and action .....	127
Angiotensin and steroids in cerebrospinal fluid .....	128
The postulated brain renin–angiotensin system: Its possible role in sodium deficiency .....	130
<b>8 Techniques in study of salt appetite .....</b>	<b>137</b>
Introduction .....	138
Sodium depletion .....	138
Hormones .....	143
Permanent unilateral parotid fistula in the ruminant .....	144

<b>9 The sheep (a ruminant) as a felicitous creature for research in experimental endocrinology and body fluid regulation: Control of aldosterone secretion .....</b>	147
Introduction .....	148
Influence of digestive secretion on blood chemistry .....	149
Sheep as experimental animals in the study of body fluid homeostasis .....	149
Development of the permanent unilateral parotid fistula in the sheep .....	152
Appetite for rock salt in sheep with a parotid fistula .....	153
The discovery of aldosterone .....	154
Desiderata for valid experimental investigation of the causation and manner of secretion of a hormone .....	154
Mode of control of aldosterone secretion .....	159
<b>10 Salt taste and the response to sodium deficiency .....</b>	168
Introduction .....	168
Some species differences in anatomy of taste reception .....	170
Innervation .....	170
Discrimination and psychophysics .....	172
Taste electrophysiology .....	176
The effect of salt deprivation on taste sensitivity .....	175
Insects and salt appetite .....	178
Behavioural thresholds and preferences in salt deficiency .....	179
Specific effects of adrenal insufficiency on taste .....	180
Species differences in taste behaviour, including birds .....	182
Salt intake of sodium-replete rats .....	184
<b>11 The evidence that salt appetite induced by sodium deficiency is instinctive .....</b>	188
Introduction .....	189
Wild animals .....	189
Laboratory rats .....	190
Adrenalectomy .....	190
Behaviour study of naive rats upon initial experience of sodium deficiency .....	193
The drinking of lithium solutions in sodium deficiency .....	196
The Krieckhaus experiments .....	196
Investigation of sheep .....	197
Group A: No access to electrolyte solutions before parotid fistula operation	198
Group B: Access to electrolyte solutions for 1 h per day for 11–14 days before parotid fistula operation .....	203
Group C: Long-term access to solutions before parotid fistula operation .....	208
Summary of sheep experiments .....	209
Discussion and further analysis .....	210
Taste .....	210
Innate and learned behaviour .....	210
Salt appetite in the general context of ingestive behaviour .....	217
<b>12 Physiological analysis of salt appetite behaviour .....</b>	221
Time delay of onset of appetite .....	222
Specificity of sodium appetite with body sodium deficit .....	227
The behaviour of sodium-deficient sheep .....	228
Behaviour changes evoked during experiments on voluntary sodium intake	229
Visceral conditioned reflexes evoked by distance receptor stimuli .....	230
Study of sampling behaviour as an index of salt appetite drive .....	232
The relation between voluntary sodium intake and body sodium balance in normal and adrenalectomized animals .....	234

Sheep .....	234
Rats .....	238
Rabbits .....	240
<b>13 The study of salt appetite in sodium deficiency by operant behaviour .....</b>	<b>242</b>
Introduction .....	243
Bar-press experiments with sheep .....	243
Reaction to small deviation of body sodium content .....	244
Comparison with reaction to water deficit: Body error detected .....	248
The influence of learning in bar-press behaviour .....	249
Bar-pressing during slow fluctuation of sodium status .....	250
Bar-pressing for water on a regime of continuous access to sodium bicarbonate for days .....	250
Physiological mechanisms in ad libitum drinking in the dog .....	253
<b>14 The consummatory act of satiation of salt appetite in sodium deficiency .....</b>	<b>255</b>
Introduction .....	256
Time characteristics of satiation of salt appetite .....	257
Sheep .....	257
Rats .....	257
Rabbits .....	258
Effect of variation of concentration of sodium solution on intake .....	260
Sodium-deficient sheep: Voluntary drinking .....	260
Sodium-deficient sheep: Sodium bicarbonate access by bar-pressing .....	263
Sodium-deficient rats: Access to sodium solution by bar-pressing .....	264
Sodium-deficient rats: Voluntary drinking .....	264
Influence of prior introduction of sodium solution into stomach or rumen .....	265
Water and sodium drinking in sheep with an oesophageal fistula .....	267
Effect of placing water in the rumen on water intake after 48 h of water deprivation .....	267
Water drinking after 48 h of water deprivation when the oesophageal fistula was open .....	269
The effect of placing water in the rumen on water intake after 48 h of water deprivation when the oesophageal fistula was open .....	270
Mechanisms of satiation of thirst .....	272
Voluntary drinking of sodium bicarbonate solution by sodium-deficient sheep with an open oesophageal fistula .....	274
<b>15 Plasma volume change and the influence on salt appetite .....</b>	<b>280</b>
Plasma volume change and thirst in rats .....	280
Plasma volume and salt appetite .....	281
Effect of rapid infusion of 500 or 750 ml of 6% dextran in isotonic saline on sodium appetite of sodium-deficient sheep .....	283
<b>16 Influence of concurrent water depletion on salt appetite during sodium deficiency .....</b>	<b>286</b>
Physiological influences on acceptability of salt solutions .....	286
Studies on concurrent water and sodium deficiency in sheep .....	287
Sodium deficiency: Experimental conditions .....	287
Water depletion: Experimental conditions .....	287
Concurrent depletion of sodium and water: Experimental conditions .....	287
Sodium deficiency .....	287
Water deficiency .....	287
Concurrent water and sodium deficiency .....	289

Bar-press experiments on sheep with concurrent water and sodium deficiency .....	291
Concurrent water and sodium deficiency in the rat .....	292
<b>17 Hepatic sodium receptors and their possible influence on salt appetite .....</b>	<b>295</b>
Hepatic influence on sodium excretion .....	295
Receptors in the portal vein .....	296
Hepatic receptors and thirst .....	297
Influence of hepatic portal infusion on saline and water intake .....	297
<b>18 The stimulating effect on salt appetite of desoxycorticosterone, aldosterone and other adrenal steroids.....</b>	<b>301</b>
The effect of desoxycorticosterone acetate .....	301
Anti-thyroid drugs .....	303
Investigations by George Wolf on DOCA- and aldosterone-induced salt appetite .....	303
Physiological levels of desoxycorticosterone secretion .....	304
Studies on wild rabbits .....	304
The question of a physiological role of mineralocorticoids in salt appetite .....	305
The question of learning .....	306
ACTH and salt appetite .....	306
Mechanism of salt appetite induction by mineralocorticoids .....	308
<b>19 The effect of electrical stimulation and lesions of the central nervous system on salt appetite.....</b>	<b>310</b>
Introductory considerations on electrical stimulation .....	311
Brain stimulation and access to the stream of consciousness: The question of consciousness in animals .....	312
The phenomenon of psychogenic sudden death .....	316
Components of awareness .....	318
Deep-seated brain stimulation in the human and other species .....	320
Salt ingestion responses to diencephalic electrical stimulation in the unrestrained conscious sheep .....	324
Methods .....	324
Results .....	324
Appetitive significance of induced ingestion .....	327
Anatomical distribution of effective stimulation sites .....	328
Significance of results with electrical stimulation .....	329
The influence of brain lesions on salt appetite in sodium deficiency, and also saline preference of normal animals .....	330
South American studies .....	330
The amygdala .....	331
The zona incerta .....	331
The studies of George Wolf and colleagues .....	332
Studies in Stockholm on goats .....	333
Review of lesion work by George Wolf and colleagues .....	334
<b>20 The effect of rapid systemic correction of sodium deficiency on salt appetite .....</b>	<b>338</b>
Introduction .....	339
The experimental model: The sodium-deficient sheep .....	339
Intracarotid infusion in sheep .....	340
Discussion of intracarotid infusion data .....	342
Intravenous infusions in sheep .....	343

Intracarotid infusion in goats .....	345
Further analysis of effect of intravenous infusion in sheep .....	346
Rapid intravenous infusion of Ringer saline: Appetite tested 10 min later .....	347
Rapid infusion of Ringer saline: Appetite tested 120 min later .....	348
Infusion of 4 M sodium chloride: Appetite tested 120 min later .....	350
Summary .....	350
Bar-press experiments on sodium-deficient sheep: Effect of concurrent automatic intravenous infusion of sodium chloride on sodium bicarbonate intake .....	352
Detail of the experimental design .....	353
Results .....	353
Discussion .....	356
Influence of self-determined intravenous infusion of osmotically active substances on operant behaviour of sodium-deficient sheep .....	357
No water available during experimental period .....	357
Water available during experimental period .....	358
<b>21 The endocrine effects of rapid satiation of salt appetite in sodium deficiency</b> .....	363
Introduction .....	363
Hormonal changes following fluid ingestion .....	364
Rapid inhibition of aldosterone secretion produced by satiation of salt appetite in sodium-deplete sheep with adrenal autotransplants .....	367
Behaviour .....	368
Initial individual experiments .....	368
Experiments to examine the mechanism of rapid evanescent inhibition of aldosterone secretion .....	372
Angiotensin II concentration in arterial blood .....	372
Plasma sodium concentration and neural effects on the adrenal gland .....	373
The effect of dexamethasone suppression of ACTH secretion on aldosterone secretion in the sodium-deplete animal .....	374
Implications of gustatory-alimentary inhibition of aldosterone hypersecretion in relation to current ideas of control of aldosterone secretion .....	375
<b>22 The influence of the renin-angiotensin system and experimental hypertension on salt appetite</b> .....	382
The renin-angiotensin system .....	384
Actions of angiotensin .....	384
Angiotensin in the brain .....	385
Angiotensin II in the genesis of thirst and water intake .....	386
Systemic infusion of angiotensin .....	387
Intracranial injection of angiotensin II .....	389
Mode of action of angiotensin II in the brain .....	391
Summary of evidence on role of angiotensin II in thirst .....	392
Angiotensin in the genesis of salt appetite .....	393
Effect of intravenous angiotensin II infusion on the sodium appetite of sodium-deficient sheep .....	393
The effect of bilateral nephrectomy on the sodium appetite of sodium-deficient sheep .....	393
Studies on the renin-angiotensin system and salt appetite in the rat .....	395
Nerve growth factor .....	400
Significance of results with intracranial infusion of renin and angiotensin .....	402
The effect of hypertension on the salt appetite of sodium-replete and sodium-deficient animals .....	404
Salt appetite in hypertensive rats .....	404

The effect of experimental renal hypertension on the sodium appetite of sodium-deficient sheep .....	405
The influence of genetic susceptibility to hypertension on salt appetite.....	406
Salt appetite in the spontaneously hypertensive rat .....	407
Endocrine pharmacology.....	408
<b>23 Salt appetite during reproduction, including discussion of learned appetites and aversions, and pica .....</b>	<b>417</b>
Pica .....	418
History .....	418
Current literature .....	420
Anaemia as cause.....	421
Vitamin-specific hunger and learned appetites.....	422
Long-delay learning .....	425
Human pregnancy and salt appetite .....	427
Pseudocyesis .....	428
Infantiphagia and placentiphagia .....	428
Salt appetite in pregnancy and during lactation in experimental animals .....	429
Study of wild rabbits .....	430
Pregnancy .....	431
Lactation .....	432
Sodium balance .....	432
Analysis of hormonal factors influencing salt appetite in pregnancy and lactation .....	434
Pseudopregnancy .....	434
$17\beta$ -Oestradiol .....	435
Progesterone .....	435
$17\beta$ -Oestradiol plus progesterone .....	435
The role of ACTH and adrenal glucocorticoids in salt appetite .....	436
ACTH .....	436
Cortisol .....	436
Corticosterone .....	436
Cortisol plus corticosterone .....	436
Bilateral adrenalectomy .....	437
Hormones influencing salt appetite in lactation: Prolactin, oxytocin and growth hormone .....	440
Synergism of hormones .....	441
<b>24 Theories on genesis and satiation of salt appetite .....</b>	<b>451</b>
Introduction .....	454
The different behavioural elements constituting salt appetite .....	454
Innate behaviour .....	454
Motivation and drive .....	455
Action-specific energy and the reticular activating system.....	456
The genesis of salt appetite drive in the brain: The time delay of onset .....	458
Different theories of the genesis of salt appetite .....	459
Change in the taste receptor.....	460
Hypothalamic receptor reacting to changed sodium concentration in cerebral blood .....	460
Increase in blood aldosterone concentration .....	460
Change in the concentration of sodium and potassium or Na/K ratio of the saliva .....	462
The sodium reservoir hypothesis.....	462
Reduction of sodium concentration in the neurones subserving sodium appetite .....	463

Experimental procedures aimed at altering sodium concentration in neurones in sodium-deficient and sodium-replete sheep .....	469
Intracarotid ouabain infusion in sodium-deplete sheep .....	470
The effect of similar intracarotid ouabain infusion on water or food intake in the same sheep when water-deprived or starved .....	471
The effect of ouabain on instrumental conditioning related to salt appetite....	471
Discussion of the effect of ouabain on sodium appetite .....	472
Changes within the physiological range in the sodium concentration of cerebrospinal fluid .....	473
A brief consideration of the physiology of cerebrospinal fluid and the blood-brain barrier.....	473
Intraventricular infusion experiments on sodium-deficient sheep .....	478
Intraventricular infusion experiments on sodium-replete sheep .....	483
Summary and discussion of physiological implications of these findings on altered sodium concentration of cerebrospinal fluid .....	488
The effect of steroid and peptide hormones on salt appetite .....	492
Steroid hormones: Mode of action.....	493
Oestrogen induction of prolactin receptors and relevance to salt appetite .....	495
Rapid non-genomic effects of steroid hormones in the central nervous system .....	496
The action of peptide hormones.....	497
<b>25 The appetite for phosphate, calcium, magnesium and potassium, and the question of learning .....</b>	<b>515</b>
Phosphate appetite in pastoral and wild animals .....	517
Experiments on phosphate-deficient cattle in the field .....	519
Laboratory experiments on mineral appetite in rats .....	521
Phosphate appetite .....	521
Calcium appetite .....	521
Magnesium appetite .....	523
Potassium appetite .....	523
Experimental analysis of phosphate appetite in cattle .....	524
The effect of pregnancy and lactation .....	527
Conclusions from experiments on cattle .....	529
The basis of recognition of a needed substance .....	529
Neophilia .....	531
The laboratory rat: The species most studied, and the influence of domestication .....	531
<b>26 Clinical studies of salt appetite .....</b>	<b>535</b>
The patient of Wilkins and Richter .....	536
Observations of salt appetite in patients with Addison's disease and other conditions .....	536
Experimental study of salt appetite in man.....	537
Other evidence of dietetic wisdom in man or lack of it .....	538
Possible regression of salt appetite in contemporary man.....	539
<b>27 Salt intake and high blood pressure in man .....</b>	<b>542</b>
Introduction .....	548
Preamble on hedonic behaviour and individual variation.....	549
Epidemiology of hypertension .....	551
Incidence.....	551
Some postulated aetiological factors .....	553
Primitive peoples, unacculturated societies: With some comparisons .....	556
New Guinea .....	556

Salt trade in New Guinea .....	562
Other Pacific areas .....	563
The study by Lot Page .....	565
Africa .....	569
Asia .....	570
South and Central America .....	571
Caribbean region .....	577
North America .....	578
Japan .....	580
<b>Sodium intake and blood pressure within Western populations .....</b>	<b>584</b>
<b>Hypertension and taste .....</b>	<b>587</b>
Animal studies .....	587
Human studies .....	588
Amelioration of hypertension by low salt intake .....	590
Animal studies of induction of hypertension by high salt intake .....	594
Salt intake of infants and adolescents .....	598
The mechanism of hypertension induced by high salt intake .....	601
An overview, with some additional physiological considerations .....	603
Diet, sodium status and salt taste .....	603
Intra-uterine and neonatal influences .....	606
The impact of technology and commerce .....	607
Genetic susceptibility and environmental influences .....	607
Animal experiments on genetic susceptibility .....	610
Markers of genetic susceptibility .....	612
Expression of genetic influence in the population .....	616
Conclusion .....	620
<b>Subject Index .....</b>	<b>631</b>