ASPECTS OF RENAL FUNCTION IN INFANTS BETWEEN 25-34 WEEKS GESTATION

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I hereby declare and affirm that
this Thesis is entirely my own work
and composition.

This Thesis is dedicated to my husband, without whom many things would not have been possible.

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ABSTRACT

This thesis describes an observational study of renal function in preterm babies. During the course of the study no attempt was made to manipulate clinical conditions. The study was performed in three parts.

The principal portion of the work was an observation of renal function during the first week of life, in a group of infants between 25-34 weeks gestation, who required intensive care; the influence of gestational age, postnatal age, birth weight and respiratory adaptation were explored. Comparison is made with published parameters of renal function derived from healthy preterm neonates.

Glomerular filtration rate was assessed as endogenous creatinine clearance during prolonged urine collection. No increase in glomerular filtration rate was shown between days 2-7 of life. The population of infants studied here, who required intensive care, showed little difference from published parameters of glomerular filtration rate measured in healthy preterms.

Creatinine excretion rate was used to derive a regression equation predicting muscle mass from weight and gestational age. Muscle mass was found to increase from 12% of birth weight at 25 weeks gestation to 19% at 34 weeks

and 24% at 40 weeks. This is in agreement with classic dissection studies which have shown muscle mass to be 25% of body weight at term.

Changes in urine flow rate, urine osmolality and sodium balance were studied. The influence of respiratory adaptation on various parameters of renal function and particularly on sodium handling was investigated. Positive sodium retention was seen in babies with respiratory disease; sodium retention changed to sodium loss at a point coinciding with improvement in respiratory function. The diuresis that accompanied the improvement in respiratory function, in infants with hyaline membrane disease, was characterised as a natriuresis, with increased creatinine clearance and osmolar clearance but unchanged free water clearance.

Renal function was compared during periods of hyperglycaemia and normoglycaemia. The degree of hyperglycaemia observed did not result in an osmotic diuresis but was associated with a significant decrease in fractional sodium excretion and urinary sodium loss.

The second part of the study determined the incidence, aetiology, diagnostic indices and outcome of acute renal failure in a series of 388 consecutive admissions. The incidence in this tertiary referral centre was found to be

6.2%. The difficulties involved in making an accurate diagnosis of acute renal failure are examined.

In the third part of this work serum beta-2-microglobulin was studied in a group of 'well' preterm babies and its value as an index of glomerular filtration rate assessed.

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INTRODUCTION

Neonatal Intensive Care

The care of the immature infant now constitutes the major workload of neonatal intensive care units. Although only approximately 0.9% of all live born babies in this country are below 1500 g birth weight, these infants take up about 50% of the total cot days required for intensive care [Royal College of Physicians of London 1988]. In addition to increasing complexity of intensive care practice, the number of babies requiring intensive care is also rising. The number of livebirths of less than 1500 g birthweight has risen by 29% between 1981 and 1986 [Royal College of Physicians of London 1988]. The technological and medical skills necessary have largely developed over the last decade, during which time the survival of such infants has improved dramatically. In England and Wales the neonatal survival rate of babies less than 1000 g birth weight has increased from 21.4% in 1975 to 47.6% in 1985 and that of babies between 1000-1499 g from 62.6% to 86.4% [Royal College of Physicians of London 1988]. However as the limits of viability are pushed further back the neonatal paediatrician is faced with the problems of both greater organ immaturity and of superimposed pathology.

Neonatal intensive care in the United Kingdom is generally held to have begun in the late 1970s. In the

development of neonatal intensive care the initial thrust was concerned primarily with the problems of ventilation. Assisted ventilation as routine management for babies with respiratory failure evolved from a research basis in the 1960s. Subsequently the advent of real time ultrasound revealed the extent of intracranial sequelae and research centred in this area; this was the herald for snowballing advances in other brain imaging and neurological investigatory techniques which have led to a better understanding of neurodevelopmental morbidity in preterm and asphyxiated neonates. In relative terms, little attention was afforded other systems.

The tiny, immature infant

A typical infant, of extreme immaturity, to be found in today's neonatal intensive care units is likely to be receiving ventilatory support, total or partial parenteral nutrition and to have continuous monitoring of a number of physiological variables including paO2, paCO2, blood pressure, skin temperature and ECG. Intravenous and intraarterial access will be available and the infant will be nursed beneath a radiant warmer or in an incubator.

Disturbances of fluid and electrolyte balance are common in such infants; physiological data are difficult to obtain. Simple measurements are made difficult by the

small size and frailty of the infants. The blood volume of approximately 75 ml kg^{-1} requires the development of microassay techniques. Blood specimens are obtained from indwelling lines or from heelprick; in the former there is the risk of contamination by infusate, in the latter of obtaining a haemolysed specimen.

Urine collection poses a particular problem. Standard self adhesive urine collection bags are often too large for the smallest infants and, in the moist environment of their use, leakages frequently occur. Preterm infants have extremely thin, friable skin and breakdown of the skin of the perineum, thighs and groins is a real problem. Neonates do not empty their bladders completely on voiding, rendering external urine collections of short duration, inaccurate. Bladder catheterisation is both difficult to carry out in the tiniest infants and ethically inacceptable as a routine, given the risks of trauma to delicate tissues and of introducing infection.

Accurate weighing is essential in the assessment of fluid balance. A sick infant, possibly paralysed for ventilation, must be weighed rapidly. Beam and spring balances are both insufficiently accurate and slow to equilibrate. An electronic balance accurate to 2-4 g is necessary, making meticulous allowance for the weights of a variety of monitoring electrodes, infusion cannulae,

endotracheal tube stabilisers and possibly chest drains.

An extrauterine existence prior to term is an abnormal event and 'normality' in terms of physiological parameters is therefore difficult to define.

Most very low birth weight infants require intensive care during the first days of life and there has been a reluctance to collect data during this period because of the complex clinical setting. Confining data collection to physiologically stable infants has had three consequences; early literature has a preponderance of small for gestational age babies of low birth weight but relative maturity because the distinction between low birth weight and preterm and low birth weight and small for gestational age was not appreciated until the 1960s [Butler & Bonham 1963]; subsequently studies of 'preterm' infants included disproportionate numbers of infants of moderate immaturity, i.e. of greater than 30 weeks gestation as opposed to those of extreme immaturity or less than 30 weeks gestation [Aperia & Zetterstrom 1982]; more recently workers have tended to study preterm infants of greater postnatal age, thus introducing the confounding variable of extrauterine maturation. The neonatal paediatrician has therefore been obliged to base management of fluid and electrolyte balance on data

extrapolated from infants of greater maturity or postnatal age or from animal studies.

The primary aim of this study was to provide data relating to renal function and the clinical management of sodium and water balance in a typical group of infants requiring admission to a neonatal intensive care unit. No attempt was made to manipulate clinical conditions; rather, the form of the study was entirely observational.

Three groups of infants were studied: firstly several parameters of renal function were evaluated during the first week of life in a group of infants between 25-34 weeks gestation who were receiving intensive care; secondly the incidence, aetiology, diagnostic indices and outcome of acute renal failure in a series of 388 consecutive admissions to a neonatal intensive care unit were evaluated; thirdly serum beta-2-microglobulin was studied in a group of 'well' preterm babies and its value as an index of glomerular filtration rate assessed.

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THE DEVELOPMENT OF RENAL FUNCTION

Present knowledge of renal function in the extremely immature infant has on the whole arisen from extrapolation from studies on immature animals and older human infants. There has been very little direct study of extremely immature infants in the first days of life and less of the human fetus *in utero*. This chapter will review the information available relating to the development of renal function in the extremely immature infant. Although investigations on animal models will be touched on, it is intended to concentrate here on features relating directly to the human fetus and neonate.

Anatomical development

The development of human renal function and the definitive kidney is believed to proceed with the formation of the three excretory organs, the pronephros, mesonephros and metanephros. The pronephros has no excretory role, merely giving rise to the mesonephric duct; it arises at around the third week of gestation and involutes over the following fortnight. O'Rahilly and Muecke [1972] have shown that although nephrotomes become differentiated from the intermediate mesoderm at three weeks and are formed rostrally, they do not appear to be nephric tubules. These authors have therefore argued that "the concept of the pronephros does not apply to the human embryo". The functional significance of the mesonephric kidney varies greatly between different mammalian species. The mesonephros comprises primitive tubules and glomeruli and in the human fetus, degenerates by the twelfth week [McCrory 1972]. There is overlap betwen the development of the mesonephros and the metanephros, with the first definitive nephrons arising from the metanephros in the fifth week and becoming functional by eight weeks. During the fifth week the blastema of the metanephros is penetrated by the ureteric bud, which will form the collecting system.

Nephrons are formed in a centrifugal manner with the first in the innermost region of the cortex. At 22 weeks all nephrons are juxtamedullary [Potter 1965]. By 35 weeks gestation each kidney contains the full complement of one million nephrons [MacDonald & Emery 1959]. Birth does not accelerate nephrogenesis [Potter & Thierstein 1943].

The renal blood supply is established by the ninth week and arises from the aorta at the level T12 - L2, a relationship that is constant between 24 and 44 weeks [Phelps et al 1972]. The renal artery divides into segmental arteries. These are end arteries, with no anastomoses between their branches at any level of division, rendering renal tissue in the region of their distribution vulnerable to ischemia following obstruction to flow. Further division gives rise in turn to interlobar, arcuate and interlobular arteries, from the last of which afferent arterioles lead to glomeruli. The glomerular capillary supply is connected to the peritubular capillaries by efferent arterioles. The venous drainage, unlike the arterial system, has anastomoses at several levels. The blood supply of the juxtamedullary nephrons differs from that of the outer cortical nephrons; the former have a network of vessels accompanying the loop of Henle to the tip of the medulla and then returning to the corticomedullary region, thereby allowing it to function as a countercurrent multiplier.

The morphological development of the kidney is accompanied by a changing distribution of intrarenal blood flow. In the immature puppy kidney, relative perfusion is highest in the juxtamedullary nephrons [Olbing et al 1973]. In the lamb, the intrauterine environment is also characterised by a relatively low renal blood flow and high renal vascular resistance [Aperia et al 1977; Robillard et al 1981 (i)]. The kidneys of fetal rhesus monkeys receive approximately 2.7% of the combined ventricular output [Behrman et al 1970]. Rudolf et al [1971], studying the circulation of the previable human fetus demonstrated a decrease in cardiac output to the kidneys, from a mean of 6% in fetuses of under 50 g to around 3% in fetuses of over 151 g. With the completion of nephrogenesis, there is a centrifugal redistribution of renal blood flow with decreased renal vascular resistance [Gruskin et al 1970].

Tubular function has begun by the ninth week and by the fourteenth week the loops of Henle are functioning. However even at term there is still an anatomical underdevelopment of the proximal tubules [Fetterman et al 1965]. The largest, most mature juxtamedullary glomeruli possess the longest proximal tubules. During postnatal life the tubules lengthen, increasing absorptive and secretory capacity.

Kidney length increases from a mean of 31 mm at 24 weeks gestation to 36 mm at 32 weeks and 41 mm at term [Jeanty et al 1982].

Little is known of the development of fetal renal sympathetic innervation. Although studies of the fetal lamb suggest that sympathetic function is not established till late in gestation [Assali et al 1962], Zimmerman [1972] describes innervation of the distal convoluted tubules in 13-16 week gestation human fetuses.

Intrauterine renal function

Though the placenta is the major regulatory organ of the fetus and intact renal function is not necessary for fetal development, fetal renal function may influence fetal outcome. The most obvious example is the effect of reduced urine production on amniotic fluid volume and resultant fetal malformation; it is also probable that derangements in fetal regulation of extracellular fluid volume are responsible for some instances of poly and oligohydramnios.

Urine production

The human fetus begins urine production at around five weeks gestation. Kurjak et al [1981], using the

method devised by Campbell et al [1973], observed an increase in urine production from about 2 ml h^{-1} (4.5 ml kg^{-1} h^{-1}) at 20 weeks gestation to about 12 ml hr^{-1} (6 ml $kg-^{-1}$ hr^{-1}) at 32 weeks and 26 ml h^{-1} at 39 weeks (8 ml kg^{-1} h^{-1}). Urine production then declines abruptly [Wladimiroff & Campbell 1974].

The factors regulating fetal urinary output in the human are poorly understood. The maternal administration of frusemide normally results in fetal diuresis. However the stressed fetus of an abnormal pregnancy may show no response to maternal frusemide and is more likely to have a lower urine production rate [Wladimiroff & Campbell 1974] even when renal function is normal [Harman 1984] . This may be due to the increased level of antidiuretic hormone shown to occur in the stressed human infant at birth [De Vane & Porter 1980] and in the fetal lamb subjected to hypovolaemic [Kelly et al 1983] or asphyxial [De Vane et al 1982] stress. Vasopressin is present in the human fetal pituitary by 11-15 weeks gestation [Levina 1968;Schubert et al 1981].

There may be other hormonal influences on fetal urine production. Aldosterone affects electrolyte handling in the fetal lamb in a manner similar to the adult response [Siegel et al 1981]. However cortisol, while having little renal effect on the adult sheep kidney except at high

levels, results in increased fetal urinary flow and the increased excretion of sodium, potassium and chloride [Wintour et al 1985].

Between 34 - 40 weeks, the human fetus swallows between 200 and 600 ml of amniotic fluid daily [Gitlin et al 1972]. However there is no clear relationship between fetal urinary output, swallowing and amniotic fluid volume. Van Otterlo et al [1977], studying 67 normal pregnancies from 36 - 41 weeks gestation and 16 diabetic pregnancies between 28 - 40 weeks, found no relationship between the rate of fetal urine production and amniotic fluid volume. However a low urine flow rate was found with oligohydramnios with growth retardation of the fetus. Similarly, congenital malformations that prevent the ingestion of amniotic fluid are not invariably associated with polyhydramnios [Abramovitch et al 1979]. Wladimiroff and Campbell [1974] found no correlation between fetal weight and voiding rate.

Though unecessary for intact development, the fetal kidney does respond appropriately to regulate water and electrolyte imbalance. Maternal polyhydramnios and neonatal hyponatraemia have been described in association with prolonged maternal ingestion of chlorothiazide [McCrory 1972]. It is likely that the fetal kidney responded to salt depletion by increasing urine output in

an attempt to correct the fetal sodium and water imbalance. In the chronically catheterised fetal sheep preparation, the maternal infusion of hypertonic saline has been shown to produce peaks in fetal vasopressin before and at peak fetal sodium concentration. This suggests that there was a rapid fetal to mother flow of water following maternal hypertonic saline administration and a combined volume-osmolar stimulus to the fetus [Leake et al 1977].

A strong correlation has been shown between maternal plasma volume and amniotic fluid volume when fetal malformations and diabetic pregnancies are excluded. The same authors [Goodlin et al 1983] also present evidence to suggest that fetal endocrine responses influence maternal plasma volume.

Tubular function

Gersh [1937] has studied the morphological differention of the thick and thin limbs of the loops of Henle in several animal species and correlated this with evidence of tubular function. On the basis of morphological criteria thus determined, he concluded that function was possible in human loops of Henle in the metanephros at thirteen weeks.

Fetal urine is an ultrafiltrate of fetal serum and is

hypotonic throughout gestation, made so by selective reabsorption of sodium and chloride. A concentration of sodium in fetal urine exceeding 100 $mmol^{-1}$ and osmolality exceeding 210 mosm kg^{-1} has been shown to be predictive of impaired renal function and poor fetal outcome [Golbus et al 1985]. The healthy fetus is thus capable of considerable retention of sodium, an obvious corollary to the demands of growth.

The fetus at term also excretes a large amount of sodium, approximately 8 mmol kg^{-1} day^{-1}; this is of course in the face of an ad libitum intake via the placenta and is more than twice the amount such an infant is likely to receive from breast milk. The fetus must therefore have the capacity to increase tubular reabsorption of sodium still further, a response that comes into play following birth and the removal of transplacental supplies.

The infant in utero is in a state of relative water diuresis, excreting around 20% of filtered water and forming urine with a low urea and creatinine urine to plasma ratio (approximately 5). There is virtually no phosphate or glucose in fetal urine, despite the fact that fetal serum has a higher concentration of inorganic phosphate than maternal serum [McCance & Widdowson 1953] demonstrating that these two discrete transport mechanisms are functional in the fetal kidney.

Glomerular filtration

Glomerular filtration depends upon ultrafiltration pressure (the balance between hydrostatic pressure across the glomerular membrane and the osmotic pressure of non filtered colloids), renal plasma flow and the ultrafiltration coefficient (a function of total capillary surface area and permeability per unit area). The development of these factors during gestation has not been studied to any great extent in the human fetus.

A mean glomerular filtration rate (GFR) of 2.66 ml min^{-1} (SD 1.47) has been estimated in term infants in utero in the six hours prior to delivery [Kurjak et al 1981] using ultrasound measurement of fetal urine production rate, cord blood creatinine and creatinine concentration in first voided urine. Other measurements of GFR have not been made in the human fetus in utero though attempts are being made to develop appropriate techniques [Glick et al 1985; Adzick et al 1985].

The results of animal studies cannot be extrapolated directly to the human fetus in view of variations in differentiation in relation to gestational age and the duration of intrauterine existence. An abrupt increase in GFR at the time of completion of nephrogenesis has been shown to occur in several mammalian species. The reasons

for this are not known. Until this point, although there is a steady increase in absolute GFR, GFR factored by weight remains relatively stable [Robillard et al 1975]. In chronically catheterised fetal lambs GFR increases at the same rate as body weight [Robillard et al 1975]. In the dog nephrogenesis is not completed until three weeks after birth; in the human nephrogenesis is completed at 34 weeks gestation and GFR has been said to increase at this conceptional age [Arant 1978, Al-Dahhan et al 1983, Engle & Arant 1983] (see chapter 5 for further discussion).

Hormonal regulation

There are several hormonal systems influencing renal function during development; these include the renin-angiotensin-aldosterone system, kallikrein-kinin, the prostaglandins, vasopressin, vasotocin, the adrenergic system, corticosteroids and atrial natriuretic peptide.

The human fetal kidney is able to produce renin from an early age. Juxtaglomerular cell granulation has been demonstrated at 15 weeks gestation [Molteni et al 1974]. Though renin does not cross the placenta [Symonds et al 1968], either a low salt or a high potassium intake by the mother will induce hypersecretion of renin in the fetal lamb [Moore et al 1974]. Plasma renin activity and plasma

angiotensin II concentrations are higher in the fetus than in the mother [Broughton-Pipkin et al 1974]. Levels of these hormones increase following hypotension and hypoxia; in the fetal lamb model it has been shown that the renin-angiotensin-aldosterone has a greater role in modulating blood pressure and renal haemodynamics near term than early in gestation [Robillard & Nakamura 1988]. Exposure of the human fetus to angiotensin-converting-enzyme (ACE) inhibitors has been reported to cause oligohydramnios, neonatal renal failure and severe hypotension in addition to teratogenicity [Mehta & Modi 1989].

The renal prostaglandins are modulators of renal vascular tone. Inhibition of prostaglandin synthesis by indomethacin causes an increase in renal vascular resistance [Matson et al 1981].

Vasopressin, or antidiuretic hormone, is present in the human fetal posterior pituitary by the 11th week of gestation [Levina 1968]. Vasopressin is believed to contribute to water homeostasis during fetal life. Both volume and osmoreceptor controls of vasopressin secretion are functional in the last trimester of gestation in the lamb fetus [Weitzman et al 1978]. Although the fetal nephron is believed to be less sensitive to vasopressin than the adult [Daniel et al 1982], the syndrome of

inappropriate antidiuretic hormone secretion does occur in extremely immature infants [Rees et al 1984].

Vasotocin is a neuropeptide that differs from vasopressin by a single amino acid substitution. Its role in the human fetus is not clear but in the lamb it is believed to be more important in the regulation of fetal sodium than fetal water [Ervin 1988].

The role of the sympathetic nervous system is largely unstudied in the human fetus. In the fetal lamb renal denervation does not affect renal haemodynamics [Robillard et al 1986] but stimulation of the renal nerves produces a fall in renal blood flow and rise in renal vascular resistance [Robillard et al 1987]. It is suggested that maturation of the renal adrenergic system is associated with a down regulation of beta adrenoceptors in renal vessels [Robillard et al 1988].

Atrial natriuretic peptide is produced in myocytes and has potent natriuretic and diuretic properties. Atrial natriuretic peptide may prove to be an important regulator of sodium homeostasis during perinatal life. Fetal levels are consistently higher than maternal [Yamaji et al 1986]. The fetus increases the cardiac content of atrial natriuretic peptide in response to intravascular volume expansion [Ross et al 1987].

Cortisol has been shown to be natriuretic in the lamb fetus [Wintour et al 1985].

Perinatal homeostasis

At birth the newborn kidney must abruptly assume control of fluid and electrolyte homeostasis. Total renal blood flow has been shown to increase during this period in the sheep [Nakamura et al 1987] and in canine puppies, the regional distribution of intrarenal blood flow changes; blood flow to the outer cortex increases while juxtamedullary blood flow remains unchanged [Jose et al 1971].

The fetus <u>in utero</u> excretes a large volume of hypotonic urine of low sodium content. Following birth the infant enters a phase of relative oliguria. There is no evidence that GFR falls acutely in the first day following birth. GFR, when measured in the first day of life, correlates with gestational age when expressed in absolute terms (ml min^{-1}) but shows if anything a tendency to fall when expressed factored for body weight (ml min^{-1} kg^{-1} [Leake & Trygstad 1977]. This is similar to the pattern of development seen in the chronically catheterised sheep fetus [Robillard et al 1975], but is in marked contrast to the postnatal change in GFR when a rise occurs which is

disproportionately higher than the rise in body weight.

The first urine formed postnatally is hypertonic to plasma with an increased concentration of urea, potassium and phosphate but not of sodium and chloride [McCance & Widdowson 1953].The change in urine volume thus appears to be brought about by a decrease in free water clearance. This may be mediated by the increased levels of arginine vasopressin (AVP) present in the neonate around delivery [Alexander et al 1980; Leung et al 1980].

The phase of relative oliguria is followed, after a variable period of hours to days, by a diuretic phase during which the extracellular space undergoes contraction. Sodium is the principal electrolyte of extracellular fluid and is of necessity lost during this contraction. In infants with respiratory disease the time of onset of diuresis is determined primarily by the onset of improvement in respiratory function. Though this association has been the subject of several investigations the underlying mechanisms have not been explained. Earlier suggestions that the diuresis represented an improvement in renal function consequent on improved oxygenation [Cort 1962, Guignard et al 1976] were refuted when it was shown that the diuresis was not initiated subsequent to the improvement in respiratory function [Engle et al 1983, Heaf et al 1982, Langman et al 1981]. Certain authors [Engle et

al 1983, Heaf et al 1982, Langman et al 1981, Costarino et al 1985] have concluded that the diuresis precedes the improvement in respiratory function. However careful examination of their data reveals that they equally show that the onset of the diuretic phase in fact follows the onset of improvement in respiratory function and that continuing diuresis then accompanies continuing respiratory improvement. This subject is further discussed in chapter 8.

There are maternal influences on neonatal fluid and electrolyte balance: an expanded extracellular volume has been described in preterm neonates whose mothers had received intravenous fluids prior to delivery [Rojas et al 1984]; these infants, who were hyponatraemic, had an increased risk of developing pulmonary air leak, i.e. interstitial emphysema, pneumothorax, pneumomediastinum and pneumopericardium [Mohan et al 1984].

Despite certain functional limitations, the kidney <u>in utero</u> shows a sophisticated degree of maturation by the third trimester. Though the fetus is now known to play a role in modulating fluid flux between maternal, fetal and amniotic fluid compartments, these functions have neither been stressed nor have they been necessary for survival. Immediately following birth however, a remarkable series of pulmonary, cardiovascular and renal adaptations

are required to enable independent extrauterine survival. Neonatal renal function will be further discussed in the specific chapters that follow.

3

METHODS

In this chapter, the basic methods utilised in this study as a whole, are described. Methodological details of specific relevance to individual aspects of the study are detailed in the appropriate chapters.

The Regional Neonatal Intensive Care Unit, Liverpool Maternity Hospital.

The neonatal unit where this study was carried out is a tertiary referral centre admitting approximately 450 babies each year. Approximately 30% are outborn and approximately 30% weigh less than 1500 g at birth. Primary neonatal surgical and cardiac case are not admitted. Standard methods of management for sick infants include monitoring of urine output using self adhesive bags, continuous or sequential measurement of blood pressure via a pressure transducer connected to an intra-arterial line or by peripheral oscillometry and measurement of arterial blood gases approximately 4 hourly. Blood pressure is maintained in line with the standards of Versmold et al [1981] using colloid transfusion or infusion of pressor agents. Frusemide and other diuretics are not used routinely. Ampicillin and gentamicin are first line antibiotics. The patency of umbilical arterial catheters is maintained by infusing 5% dextrose solution and of peripheral arterial catheters by infusing 0.45% saline. Heparin is a standard additive at a concentration of 1 unit per ml. Intravenous sodium supplementation is begun on the second day of life at 4 mmol kg^{-1} day^{-1}. Infants are nursed under radiant warmers or in incubators.

Patients and study design

Three groups of patients were studied.

1. Renal function in the first week of life.

Infants were selected for study from the admissions to the Regional Neonatal Intensive Care Unit, Liverpool Maternity Hospital. The study requirements were for male neonates, 34 weeks gestation and under, who had suffered no major perinatal asphyxia (1 minute Apgar greater than 3), who required ventilatory support and who required admission for the problems of immaturity. Infants with surgical problems, congenital infections and congenital abnormalities were not studied. It was only possible to study one infant at any time because of limited equipment.

Continuous, sequential collections of urine in time blocks of approximately 4 hours each were made in these infants. Serial blood samples were obtained, consisting of 0.5 ml up to a maximum of 6 times a day and no more frequently than once every 4 hours. Urine sodium, creatinine, osmolality, glucose, chloride and potassium, plasma sodium, creatinine, osmolality, chloride and beta-2-microglobulin and blood glucose were measured.

The infants were weighed as often as possible, depending on clinical condition and upto a maximum of twice daily. A record was made of all intravenous and intraarterial fluids, including blood, blood products, flush fluids and drugs. The sodium content of fluid and drugs administered was recorded and in the case of blood and blood products, measured. Blood pressure and arterial blood gas measurements made 4 hourly were also recorded.

Each 'period' was approximately 4 hours duration; however the precise duration was noted in minutes. Each day consisted of 6 'periods'; period 2 thus represented the second four hours of the first day of life; period 9 the third four hours of the second day; period 18 the last four hours of the third day and so on.

The studies were begun as soon as possible after birth and were continued until leakage of urine from the collection system occurred.

2. Serum beta-2-microglobulin

Serum beta-2-microglobulin and serum creatinine were measured in infants of 34 weeks gestation and under, during the first three weeks of life. The infants were also selected from the admissions to the Regional Neonatal

Intensive Care Unit. They were male, healthy, breathing spontaneously in air, on full enteral feeds and receiving no antibiotic or diuretic therapy. Samples were obtained at the time of sampling for clinical purposes. further methodological details are to be found in chapter 10.

3. Renal failure

The incidence, aetiology and diagnostic characterization of acute renal failure, in a series of 388 consecutive admissions to the Regional Neonatal Intensive Care Unit, were determined. Methodological details are described in chapter 11.

Methods and measurements

Blood sampling

Blood samples, of 0.5 ml volume, were obtained from heelpricks or indwelling arterial lines, at times coinciding with blood sampling for clinical purposes and upto a maximum of one sample during each 4 hour urine collection period. Samples were collected into lithium heparin tubes, spun immediately and the plasma separated and stored at -20 C prior to assay in batches. Samples for glucose assay were collected into fluoride oxalate tubes.

Urine collection

Urine was collected continuously using a closed circuit system consisting of a small plastic pouch applied to the baby's perineum with medical adhesive (Dow Corning) after the application of a skin protector. This pouch was connected, via two narrow plastic tubes, to a collection bottle and a low grade suction pump. Collection bottles were changed at approximately four hourly intervals; the precise duration of the four hourly collections was, however, also noted in minutes. The volume of urine in each collection bottle was measured and recorded and an aliquot stored frozen at -20C prior to assay in batches.

Laboratory methods

All laboratory assays were performed by a single person (NR). Creatinine was measured in urine and plasma by the kinetic reaction rate Jaffe method using a Beckman analyser; sodium in plasma and urine and potassium in urine by flame photometry; glucose by the glucose oxidase method using a Beckman autoanalyser; osmolality by depression of freezing point; urea by the conductivity electrode urease method. Assay of serum beta-2-microglobulin was performed using the Enzygnost beta-2-microglobulin reagents from Behringwerke A.G., West Germany (supplied by Hoechst UK Ltd., Hounslow).

Records

A record was made of total fluid and sodium intake for each four hour period; this included the sodium content and volume of drugs, flush fluids and blood products. All drug administration was noted. Blood pressure measurements and arterial blood gas measurements made by the nursing and medical staff were recorded.

Weight

The babies were weighed once or twice daily, clinical condition permitting. All weighing was carried out by the investigator (NM). Electronic scales accurate to 2 g were used and weights were obtained net of intravenous lines, endotracheal tubes and other attachments.

Statistical analysis

Statistical analysis was performed using the standard computer packages, SPSSX (Statistical Package for the Social Sciences; SPSS inc., 444 North Michegan Avenue, Chicago, Illinois 60611) and SAS (Statistical Analysis Systems), accessing the University of Liverpool IBM 3083. The statistical methods used were linear regression, multiple linear regression, one way analysis of variance, multiple comparison procedures, multivariate analysis of variance, paired and two sample T tests, the Mann Whitney U test and spline fitting routines. Further discussion of the statistical methods used are to be found in individual chapters.

Presentation of data

'Box and whisker' plots have been used for presentation of the raw data. Scatterplots, regression plots and spline fitted curves have been used for visual presentation of data following analysis.

Numerical data relating to the sample studied have been presented as mean and standard deviation and median amd range. Confidence intervals have been quoted where appropriate.

Calculations

Creatinine clearance was calculated as creatinine excretion rate divided by plasma concentration. Excretion rates were calculated as the product of urine concentration and urine flow rate; filtered loads as the product of plasma concentration and creatinine clearance and fractional excretion as excretion rate divided by filtration rate.

Osmolar clearance was calculated as osmolar excretion rate divided by plasma osmolality and free water clearance as urine flow rate minus osmolar clearance. Osmolar clearance is converted to ml for the calculation of free water clearance in the standard manner [Haycock 1987], that is, an osmolality of 280 mosm kg^{-1} is virtually 0.28 mosm ml^{-1}. Tubular reabsorption of glucose is calculated as filtered glucose minus excreted glucose. Data are expressed per kg body weight.

Standardisation of results

Values have mainly been expressed in absolute terms and per unit weight. Where appropriate, values "corrected" for surface area have also been stated. In clinical practice expression of, for example, drug dosage, fluid allowances and electrolyte requirements, are standardised per unit body weight. The rationale of weight as the best standard is further discussed in chapter 5. Values

expressed per unit time are calculated per minute and if necessary standardised per hour or per day.

Surface area

The accurate measurement of height (length) in sick, low birth weight neonates is precluded by their clinical state. However the relationship of surface area to weight (W) during the perinatal period is represented by the self adjusting power equation [Boyd 1935].

$$S = 4.688W^{0.8168-0.0154\log W}$$

The standard deviation of the percentage deviation of calculated surface areas and 'true' measured surface areas using this equation is 7.8 +- 0.4%. The difference of 0.7% from the standard deviation of 7.1+- 0.3% using the height (H)- weight self adjusting power equation,

$$S = 3.207W^{0.7285-0.0188\log W}H^{0.3}$$

is so small as to be of little practical benefit [Boyd 1935; Brody et al 1928]. The self adjusting power equation incorporating weight alone has therefore been used for all estimates of surface area.

Data handling

Descriptive and numerical data for each infant were entered into a data file in free format on the mainframe Liverpool IBM 3083. Thirty two variables were entered into each line of data. Each line represented one period (approximately 4 hours) of urine collection for an individual baby. For example the data sequence

441193 28 1.2 1 0 4 3 5 250 5 3.5 89 1140 260 6.5 140 78 280 6.5 440 38 1.250 1 3.1 0.12 11.8 6 66 10.4 118 0.3

represented the following: identification number, gestational age, birth weight, maternal pre-eclampsia (no=0, yes=1), maternal antepartum haemorrhage (no=0, yes=1), one minute apgar score, day of life, period of day, duration in minutes of period, volume of fluid intake during this period (see explanation above), urinary output, urinary sodium, urinary creatinine, urinary osmolality, urinary glucose, plasma sodium, plasma creatinine, plasma osmolality, blood glucose, alveolar arterial oxygen gradient, mean blood pressure, present weight, pancuronium used (no=0, yes=1), serum beta-2-microglobulin, surface area, urinary urea, urinary potassium, urinary chloride, plasma urea, plasma chloride, sodium intake. Missing values were noted as -1.

Ethical approval

This study had the approval of the local ethical committee. Every attempt was made to discuss this study with the baby's parents though, as some infants were postnatal transfers, this was not always possible. Written consent was not obtained as the study did not alter or impinge on clinical management in any way and as blood samples were obtained at times of clinical sampling from indwelling lines.

Abbreviations and units

SI units are used throughout.

CCr	creatinine clearance	ml min^{-1}	
		ml min^{-1} kg^{-1}	
		ml min^{-1} m^2	
COsm	osmolar clearance	ml min^{-1} kg^{-1}	
CH2O	free water clearance	ml min^{-1} kg^{-1}	
FeNa	fractional sodium excretion	%	
FeUV	fractional urine flow	%	
PAO2	partial pressure of alveolar oxygen		
PaO2	partial pressure of arterial oxygen		mm Hg
PaCO2	partial pressure of arterial carbon dioxide		mm Hg
AaDO2	alveolar arterial oxygen gradient		torr
UCr	urinary creatinine	umol l^{-1}	
PCr	plasma creatinine	umol l^{-1}	
V	urine flow rate	ml kg^{-1} min^{-1}	
Uosm	urinary osmolality	mosm l^{-1}	
Posm	plasma osmolality	mosm l^{-1}	
UNa	urinary sodium	mmol l^{-1}	
PNa	plasma sodium	mmol l^{-1}	
Ugluc	urinary glucose	mmol l^{-1}	
Bgluc	blood glucose	mmol l^{-1}	
UCl	urinary chloride	mmol l^{-1}	
PCl	plasma chloride	mmol l^{-1}	
UK	urinary potassium	mmol l^{-1}	
SB2MG	serum beta-2-micoglobulin	mg l^{-1}	
Fi02	fractional inspired oxygen		
GFR	glomerular filtration rate		
ANP	atrial natriuretic peptide		
AVP	arginine vasopressin		
RFI	renal failure index		
ARF	acute renal failure		
ECFV	extracellular fluid volume		

Equations

$CCr = UCr.\ V/PCr$

$COsm = UOsm.\ V/POsm$

$CH_2O = V - COsm$

$FeNa = UNa/PNa.\ PCr/UCr.100$

$FeUV = PCr/UCr.100$

$PA0_2 = (713.Fi0_2) - PaC0_2/0.8$

$AaD0_2 = PA0_2 - Pa0_2$

$RFI = UNa.\ PCr/UCr$

weight change = (birth wt - actual wt).100/birth wt

4

CLINICAL DESCRIPTIONS

This chapter begins with a brief clinical account of the babies studied. In each case the clinical description is followed by a summary measure of the daily 4 hourly measurements of fluid and sodium intakes, urine output, weight change in relation to birth weight, sodium balance, mean daily plasma sodium and osmolality and mean daily alveolar-arterial oxygen difference. Specific points are made after each clinical description. 'Box and whisker' plots are then used to summarise mean daily fluid intake, plasma sodium and plasma osmolality for all the babies studied. The chapter concludes with a general commentary on the observations made. Further specific points are discussed in subsequent chapters.

Units of expression.

fluid intake	ml kg^{-1} day^{-1}
urine flow rate	ml kg^{-1} $hour^{-1}$
sodium intake	mmol kg^{-1} day^{-1}
sodium balance	mmol kg^{-1} day^{-1}
weight change	percentage of birth weight
mean posm	mosm l^{-1}
mean pna	mmol l^{-1}
mean uosm	mosm l^{-1}
mean una	mmol l^{-1}
mean AaDO2	torr

For explanation of abbreviations see p 45. Please note that a negative weight change implies weight gain (p 46).

Baby: 1

Gestational age: 28 weeks

Birth weight: 1.24 kg

The first of twins born by emergency caesarian section following antepartum haemorrhage and fetal bradycardia. Received fresh frozen plasma at birth for hypotension. Ventilated for 3 days. Normal at 4 year follow up.

day	**1**	**2**
fluid intake	104	107
urine flow rate	0.5	4.0
sodium intake	5.5	4.2
sodium balance	4.9	0.2
weight change	1.1	2.1
mean posm	272	285
mean pna	143	149
mean uosm	369	220
mean una	57	48
mean AaDO2	283	134

Baby: 2

Gestational age: 26 weeks

Birth weight: 1.008 kg

The second of twins born by vaginal vertex delivery following spontaneous onset of labour. In good condition at birth. Ventilated for 25 days; developed chronic lung disease with an additional oxygen requirement to day 50. Ventriculoperitoneal shunt inserted for posthaemorrhagic hydrocephalus. At 5 year follow up normal gross motor development but deaf with poor speech.

Note large sodium loss from day 2 and 27.2% weight loss by day 5.

day	**2**	**3**	**4**	**5**	**6**	**7**
fluid intake	136	106	132	152	158	175
urine flow rate	3.8	3.0	5.4	3.7	5.1	3.4
sodium intake	4.9	3.1	3.7	5.7	4.8	5.3
sodium balance	-4.7	-7.0	-13.7	-6.1	-6.6	-4.3
weight change	10.1	14.5	21.5	27.2	26.3	26.4
mean posm	295	298	292	300	309	
mean pna	139	143	140	140	140	123
mean uosm	511	520	409	367	305	395
mean una	106	138	131	129	95	120
mean AaDO2	316	323	272	190	157	51

Baby: 3

Gestational age: 32 weeks

Birth weight: 1.5 kg

The first of twins born in good condition by spontaneous vertex delivery. Ventilated from birth with an uncomplicated early course. Requiring CPAP alone by day 5. Deteriorated on day 7 with the onset of E. coli septicaemia complicated by disseminated intravascular coagulation and acute renal failure managed with peritoneal dialysis. Died on day 18.

Note the positive sodium balance on day 2 followed by negative balance on day 3 in association with improving respiratory function despite the similarity of sodium intakes and urine outputs on days 2 and 3.

day	**2**	**3**	**4**	**5**	**6**
fluid intake	99	101	143	181	148
urine flow rate	3.3	2.7	6.3	3.0	5.3
sodium intake	3.0	3.1	4.2	7.3	4.3
sodium balance	1.0	-0.6	-3.5	3.0	0.4
weight change	-2.8	-0.7	-0.7	5.6	1.0
mean posm	289	304	299	287	311
mean pna	139	144	141	143	146
mean uosm	432	562	401	264	174
mean una	26	59	57	58	27
mean AaDO2	326	179	75	39	40

Baby: 4

Gestational age: 27 weeks

Birth weight: 1.060

Vaginal vertex delivery following spontaneous onset of labour. In good condition at birth. No ventilation required. Died on day 8 following klebsiella septicaemia.

Note hypernatraemic dehydration with 13.8 % weight loss by day 2, large negative sodium balance and high urinary sodium concentration.

day	**2**	**3**
fluid intake	114	136
urine flow rate	4.5	3.2
sodium intake	2.7	3.4
sodium balance	-14.7	-7.6
weight change	13.8	24.7
mean posm	300	309
mean pna	159	149
mean uosm	419	442
mean una	159	139
mean AaDO2	122	28

Baby: 5

Gestational age: 32 weeks

Birth weight: 1.618 kg

Born by emergency caesarian section for preeclamptic toxaemia. In good condition at birth. Ventilated for 6 days. Normal at 5 year follow up.

Note good urine output from day 1, early positive sodium balance and low urine sodium concentration.

day	**1**	**2**	**3**	**4**	**5**
fluid intake	76	73	92	100	119
urine flow rate	1.5	2.0	2.3	3.1	2.9
sodium intake	0.5	1.5	2.5	3.0	3.6
sodium balance		0.7	0.9	-1.8	1.5
weight change		3.8	4.9		
mean posm	304	296	299	322	297
mean pna	132	141	140	141	142
mean uosm		221	216	218	104
mean una		16	40	74	28
mean AaDO2	596	599	543	514	472

Baby: 6

Gestational age: 30 weeks

Birth weight: 1.490 kg

Spontaneous vertex delivery. Apgar score of 10 at 1 minute. Ventilated for 3 hours. Normal at 4 year follow up.

Note low sodium intake, negative sodium balance and low urinary sodium concentration on day 1.

day	**1**	**2**	**3**	**4**
fluid intake	77	79	77	63
urine flow rate	1.3	2.5	2.7	1.9
sodium intake	0.3	1.4	2.3	2.0
sodium balance	-0.3	-1.2	-4.2	-3.7
weight change	2.8	4.3	12.2	16.4
mean posm	283	290	312	
mean pna	138	131	148	
mean uosm	209	206	313	411
mean una	19	49	119	125
mean AaDO2	123	75		

Baby: 7

Gestational age: 34 weeks

Birth weight: 1.632 kg

Delivered by emergency caesarian section for fetal distress following death of twin. Apgar score of 9 at 1 minute. Normal at 5 year follow up.

Note inability to excrete sodium on day 1.

day	**1**	**2**	**3**	**4**
fluid intake	72	81	92	90
urine flow rate	1.1	3.8	2.8	2.4
sodium intake	0.3	0.4	0.8	0.2
sodium balance	0	-4.0	-6.0	-2.1
weight change	0.3	4.5	5.2	6.9
mean posm		293	291	292
mean pna		142	145	143
mean uosm	230	242	307	225
mean una	9	60	106	42
mean AaDO2	48			

Baby: 8

Gestational age: 29 weeks

Birth weight: 1.488 kg

The second of twins delivered vaginally. Bruised at birth. Ventilated for 5 days. Uneventful course. Normal at 5 year follow up.

day	**1**	**2**	**3**
fluid intake	81	79	67
urine flow rate	0.7	2.7	2.6
sodium intake	4.4	2.6	2.2
sodium balance	3.6	-2.3	-2.6
weight change	-0.4	-1.3	3.0
mean posm	301	310	301
mean pna	139	144	138
mean uosm	296	355	416
mean una	44	74	80
mean AaDO2	584	578	485

Baby: 9

Gestational age: 29 weeks

Birth weight: 1.0 kg

Vaginal breech delivery following spontaneous rupture of membranes 5 days previously. Bruised at birth and received transfusion of blood and fresh frozen plasma. Ventilated for 5 days. Developed pulmonary interstitial emphysema. Poor urine output for 4 days. Discharged home but lost to follow up.

Note mean urine osmolality on day 1 of 708 mosm l^{-1}.

day	**1**	**2**	**3**	**4**
fluid intake	120	65	74	89
urine flow rate	0.3	0.6	0.8	0.8
sodium intake	6.5	2.6	2.7	5.4
sodium balance	5.8	0.6	1.1	4.2
weight change	-9.0	-10.0	-9.6	-12.6
mean posm	308	310	311	307
mean pna	146	137	145	141
mean uosm	708	547	523	544
mean una	115	127	83	63
mean AaDO2	449	406	421	311

Baby: 10

Gestational age: 31 weeks

Birth weight: 1.62

Delivered by emergency caesarian section for fetal bradycardia following antepartum haemorrhage. Received sodium bicarbonate on day 1. Ventilated for 7 days.
S. aureus septicaemia on day 2. Normal at 5 year follow up.

day	**1**	**2**	**3**	**4**
fluid intake	64	72	91	101
urine flow rate	0.05	2.7	2.7	2.1
sodium intake	1.5	2.3	3.4	4.2
sodium balance	1.4	-0.3	-2.8	-0.1
weight change	1.0	4.4	6.3	6.1
mean posm	279	284	298	297
mean pna	141	142	144	147
mean uosm	349	241	289	269
mean una	62	39	92	85
mean AaDO2	283	316	409	433

Baby: 11

Gestational age: 27 weeks

Birth weight: 1.12 kg

Precipitous vaginal vertex delivery. Ventilated uneventfully from birth. Developed posthaemorrhagic hydrocephalus. Died on day 16 of necrotising enterocolitis.

Note 21.2 % weight loss by day 7.

day	**6**	**7**
fluid intake	123	153
urine flow rate	0.7	3.1
sodium intake	7.5	3.5
sodium balance	6.1	-4.0
weight change		21.2
mean posm	300	297
mean pna	136	135
mean uosm	342	356
mean una	103	97
mean AaDO2	244	197

Baby: 12

Gestational age: 27 weeks

Birth weight: 0.780 kg

Delivered by emergency caesarian section for preeclampsia. Metabolic acidosis on day 2 treated with sodium bicarbonate. Ventilatory support discontinued at 11 days following major periventricular haemorrhage and anuria.

day	**2**	**3**	**4**	**5**	**6**
fluid intake	92	143	115	152	176
urine flow rate	0.5	1.6	2.9	4.6	2.6
sodium intake	4.8	12.3	5.6	7.7	6.8
sodium balance	4.2	9.2	-1.9	-5.1	-1.1
weight change	6.8			6.9	
mean posm	290	302	301	297	272
mean pna	139	144	143	139	137
mean uosm	390	357	335	334	370
mean una	66	77	106	119	127
mean AaDO2	560	576	516	529	572

Baby: 13

Gestational age: 30 weeks

Birth weight: 1.482

Vaginal vertex delivery following antepartum haemorrhage. No ventilatory support required. Died on day 8 of klebsiella septicaemia.

day	**1**	**2**
fluid intake	57	59
urine flow rate	1	4.4
sodium intake	0.3	0.3
sodium balance	-1.1	-5.5
weight change		3.5
mean posm	268	281
mean pna	139	141
mean uosm	213	228
mean una	46	56
mean AaDO2	69	16

Baby: 14

Gestational age: 30 weeks

Birth weight: 1.12 kg

In good condition following vaginal breech delivery. Ventilated uneventfully for 3 days. Lost to follow up.

day	**1**	**2**
fluid intake	74	102
urine flow rate	0.2	2.1
sodium intake	0.3	0.4
sodium balance	0.1	-1.6
weight change	-3.3	-8.1
mean posm		279
mean pna	140	132
mean uosm	553	266
mean una	87	64
mean AaDO2	388	182

Baby: 15

Gestational age: 28 weeks

Birth weight: 1.222 kg

Delivered by emergency caesarian section following spontaneous onset of preterm labour. Bruised at delivery but otherwise in good condition. Ventilated for 5 days. Normal at 5 year follow up.

Note early weight gain and sodium retention with low urine sodium concentration.

day	**1**	**2**	**3**	**4**
fluid intake	59	79	84	97
urine flow rate	0.2	0.7	3.8	1.7
sodium intake	1.5	5.7	1.9	4.7
sodium balance	1.3	5.0	-3.3	-0.1
weight change	-2.6	-5.1	-0.2	
mean posm	262	275	283	277
mean pna	128	128	140	135
mean uosm	332	419	306	318
mean una	41	44	55	120
mean AaDO2	602	601	341	44

Baby: 16

Gestational age: 25 weeks

Birth weight: 0.680 kg

Vaginal vertex delivery following placental abruption. Developed severe respiratory disease. Subsequent chronic lung disease complicated by transfusion acquired cytomegalovirus pneumonitis. At 5 year follow up, clumsy normal.

day	**1**	**2**	**3**
fluid intake	124	101	119
urine flow rate	0.4	0.9	1.5
sodium intake	5.1	3.8	2.4
sodium balance	4.6	1.7	-0.2
weight change	0	1.5	0.7
mean posm	282	300	308
mean pna	136	147	147
mean uosm	501	518	426
mean una	59	99	67
mean AaDO2	610	610	620

Baby: 17

Gestational age: 25 weeks

Birth weight: 0.800 kg

Vaginal vertex delivery. Developed severe respiratory disease. Received sodium bicarbonate and colloid on day 1. Hyperkalaemia at 24 hours treated sucessfully with dextrose and insulin. Died at 48 hours of respiratory failure.

Note the similarity of plasma and urine sodium concentrations in this profoundly hypernatraemic baby.

day	**1**	**2**
fluid intake	100	45
urine flow rate	0.6	0.3
sodium intake	12.0	1.1
sodium balance	9.5	0.1
weight change		
mean posm	379	387
mean pna	175	188
mean uosm	383	
mean una	178	187
mean AaDO2	617	644

Baby: 18

Gestational age: 26 weeks

Birth weight: 1.002 kg

Delivered by caesarian section for preterm labour. Bruised at birth. Developed chronic lung disease and required ventilation for 50 days. Ventriculoperitoneal shunt inserted for posthaemorrhagic hydrocephalus. Borderline normal at 4 year follow up.

Note hypernatraemic dehydration with almost 20 % weight loss by day 4 but inability to adequately concentrate urine.

day	**1**	**2**	**3**	**4**
fluid intake	82	98	104	90
urine flow rate	0.24	2.5	4.1	3.6
sodium intake	1.9	3.7	5.5	3.1
sodium balance	1.6	-2.1	-9.0	-9.8
weight change	0	4		19.6
mean posm	289	312	300	313
mean pna	136	143	142	149
mean uosm	467	335	409	435
mean una	60	90	145	147
mean AaDO2	423	269	214	222

Baby: 19

Gestational age: 31 weeks

Birth weight: 1.374 kg

Delivered by emergency caesarian section for fetal distress and antepartum haemorrhage. Ventilated for 4 days. Normal at 4 year follow up.

day	**1**	**2**	**3**
fluid intake	72	96	115
urine flow rate	1.9	3.4	3.9
sodium intake	1.1	3.1	3.5
sodium balance	-1.9	-4.2	-7.7
weight change	2.6	10.3	12.1
mean posm	282	299	271
mean pna	138	141	139
mean uosm	247	291	321
mean una	73	100	124
mean AaDO2	284	314	222

Baby: 20

Gestational age: 32 weeks

Birth weight: 1.832 kg

Vertex vaginal delivery following spontaneous onset of labour. In good condition at birth. Required head box oxygen for 24 hours but no ventilatory support.

day	**1**	**2**
fluid intake	48	73
urine flow rate	0.5	2.1
sodium intake	0.5	0.6
sodium balance	0	0
weight change	1.0	2.8
mean posm	269	279
mean pna	136	137
mean uosm	340	177
mean una	42	13
mean AaDO2	45	40

Baby: 21

Gestational age: 28 weeks

Birth weight: 1.022 kg

Vaginal breech delivery. Bruised at birth. Ventilated for 4 days. Developed post haemorrhagic ventricular dilatation. Exchange transfusion for jaundice carried out on day 7 but died the following day of kernicterus.

Note inability to maintain urinary sodium loss on day 2

day	**1**	**2**	**3**
fluid intake	100	117	114
urine flow rate	0.7	0.7	1.1
sodium intake	0.9	1.8	3.7
sodium balance	-0.6	1.2	2.6
weight change			
mean posm	297	279	277
mean pna	142	131	129
mean uosm	271	352	386
mean una	76	35	39
mean AaDO2	504	476	181

Baby: 22

Gestational age: 29 weeks

Birth weight: 0.988 kg

Delivered by emergency caesarian section for preeclamptic toxaemia. Developed chronic lung disease and required ventilation for 50 days. Died of respiratory failure precipitated by pneumonia at the age of 5 months.

day	2	3	4	5
fluid intake	97	90	93	105
urine flow rate	2.6	3.3	3.3	3.8
sodium intake	3.3	4.3	3.2	6.5
sodium balance	-0.2	-6.5	-7.3	-2.5
weight change	0.3	4.8	8.8	
mean posm		298	281	
mean pna	138	141	135	
mean uosm	228	343	345	242
mean una	56	134	133	99
mean AaDO2	521	583	488	342

Baby: 23

Gestational age: 28 weeks

Birth weight: 1.082 kg

Delivered by emergency caesarian section for fetal distress. Ventilated for 8 days. Developed enterobacter cloacae septicaemia on day 12 leading to death on day 18.

Note low sodium intake and negative sodium balance on day 1.

day	**1**	**2**
fluid intake	81	114
urine flow rate	1.4	1.5
sodium intake	0.9	5.0
sodium balance	-1.1	2.0
weight change	1.3	5.6
mean posm	284	299
mean pna	140	146
mean uosm	263	253
mean una	57	73
mean AaDO2	358	495

Baby: 24

Gestational age: 30 weeks

Birth weight: 1.480 kg

Delivered by emergency caesarian section for maternal preeclampsia and pyrexia. Ventilated for 5 days. Fluids restricted because of early oliguria and oedema. Discharged home but lost to follow up.

Note very low urine sodium concentration on day 2.

day	**2**	**3**	**4**	**5**
fluid intake	53	39	75	79
urine flow rate	0.1	2.4	4.8	1.6
sodium intake	1.3	1.8	4.2	2.6
sodium balance	1.2	-4.0	-8.1	-2.8
weight change	-3.9	-1.9	5.9	9.7
mean posm	282	256	282	
mean pna	135	135	136	138
mean uosm	355	387	369	425
mean una	29	71	116	142
mean AaDO2	474	211	84	40

Baby: 25

Gestational age: 25 weeks

Birth weight: 0.868 kg

Vaginal breech delivery. Developed chronic lung disease with ventilator dependence. Died on day 48 of serratia septicaemia.

Note relatively high early urine osmolality.

day	**1**	**2**	**3**
fluid intake	120	129	104
urine flow rate	0.1	0.5	2.1
sodium intake	2.9	4.2	4.5
sodium balance	2.7	2.6	-2.6
weight change	0	1.4	3.2
mean posm	293	299	
mean pna	134	142	
mean uosm	519	598	443
mean una	128	130	143
mean AaDO2	513	346	197

Baby: 26

Gestational age: 32 weeks

Birth weight: 1.46 kg

Born at home following concealed pregnancy and antepartum haemorrhage. On admission hypothermic and hypovolaemic from cord haemorrhage. Ventilated to day 32; pneumothoraces on days 2 and 3. Developed unilateral periventricular leukomalacia and post haemorrhagic hydrocephalus; ventriculoperitoneal shunt inserted; subsequent s.epidermidis septicaemia and ventriculitis. Spastic diplegia at 4 year follow up.

Note urine output in excess of 1 ml kg^{-1} $hour^{-1}$ from day 1 and early positive sodium balance.

day	**1**	**2**	**3**	**4**	**5**	**6**	**7**
fluid in	90	108	77	88	66	73	77
urine flow	1.2	1.4	1.7	1.9	1.7	0.6	1.4
sodium in	5.4	7.4	3.4	3.5	3.0	6.2	7.7
sodium bal		6.1	-0.5	0.1	-1.0	5.9	6.3
wt change	0	-6.7	-7.8		-7.1		-8.5
mean posm							
mean pna	138	138	137	137	140	137	139
mean uosm		361	345	450	408	438	422
mean una		40	98	75	97	24	43
mean AaDO2	504	514	617	621	603	609	544

Baby: 27

Gestational age: 28 weeks

Birth weight: 0.906 kg

Emergency caesarian section for pre-eclampsia and essential hypertension. Ventilated for 10 days. Ventriculoperitoneal shunt inserted on day 46 for post haemorrhagic hydrocephalus. Left hemiplegia and right retinopathy of prematurity at 3 year follow up.

day	**2**	**3**	**4**	**5**	**6**
fluid intake	131	88	109	104	129
urine flow rate	0.8	1.4	2.6	3.1	4.4
sodium intake	5.2	4.7	6.2	6.2	5.5
sodium balance	4.2	1.2	-0.6	-2.0	-7.4
weight change	-0.6	-3.1	-1.1	1.3	3.3
mean posm	273	270	286	257	296
mean pna	137	138	142	146	147
mean uosm	283	404	307	356	383
mean una	65	97	108	116	124
mean AaDO2	583	574	536	540	194

Baby: 28

Gestational age: 26 weeks

Birth weight: 0.884 kg

Spontaneous onset of labour following premature rupture of membranes after late amniocentesis for high alphafeto protein. Vaginal vertex delivery. Developed severe respiratory distress syndrome and chronic lung disease. Stable extubation achieved by day 42. Died at three months following s. epidermidis septicaemia and meningitis.

day	1	2	3	4	5	6	7
fluid in	136	129	110	90	112	107	120
urine flow	1.0	0.9	0.6	2.2	2.8	3.1	3.4
sodium in	7.8	9.6	5.1	2.5	6.0	3.7	4.0
sodium bal	5.5	8.1	4.4	-2.3	4.6		1.8
wt change	0	0.2	-1.2	1.1	4.1	11.3	
mean posm	274	298	304	295	313	298	308
mean pna	139	145	139	140	140	137	142
mean uosm	370	377	355	426	434		390
mean una	95	97	54	106	102		126
mean AaDO2	547	614	596	587	495	458	267

Baby: 29

Gestational age: 29 weeks

Birth weight: 1.260 kg

Delivered by emergency caesarian section following spontaneous rupture of membranes and antepartum haemorrhage to a 31 year old mother on holiday from South Africa. Developed severe respiratory distress syndrome and chronic lung disease requiring ventilation to day 19 and additional oxygen to day 41. No follow up.

Note relatively high early urine osmolality.

day	1	2	3	4	5	6	7
fluid in	111	65	71	54	82	89	104
urine flow	0.6	0.7	2.5	1.5	2.2	2.1	1.0
sodium in	5.2	2.9	5.6	1.6	0.3	2.4	6.6
sodium bal	3.7	1.8	-3.4	-3.5	-6.4	-3.2	5.2
wt change	-1.6	-4.1	-0.4	7.9	16	18.4	14.6
mean posm	262	292	286	290	290	307	299
mean pna	135	132	136	144	142	138	143
mean uosm	537	555	367	458	347	427	641
mean una	93	82	144	129	127	105	57
mean AaDO2	610	582	582	384	370	256	242

Baby: 30

Gestational age: 30 weeks

Birth weight: 1.004 kg

Born by emergency caesarian section for fetal distress and pre-eclampsia. In good condition at birth. Ventilated to day 8 and in air by day 9. Normal at 4 year follow up.

day	**1**	**2**
fluid intake	74	51
urine flow rate	0.3	0.6
sodium intake	3.1	0.8
sodium balance	2.6	0.2
weight change	-0.8	
mean posm	285	287
mean pna	134	130
mean uosm	287	234
mean una	61	35
mean AaDO2	253	35

Baby: 31

Gestational age: 26 weeks

Birth weight: 0.766 kg

Vaginal vertex delivery following spontaneous rupture of membranes. Extensive bruising at birth. Mother pyrexial and baby neutropenic but no organisms isolated. Early anuria. Ventilated to day 40; in additional oxygen to day 56. Developed post haemorrhagic hydrocephalus; ventriculoperitoneal shunt inserted. Myopic with left hemiplegia at 4 year follow up.

Note early and persistent weight gain and high urine osmolality on day 1.

day	**2**	**3**	**4**	**5**	**6**	**7**
fluid intake	80	70	170	162	132	118
urine flow rate	0.02	1.8	1.0	1.3	2.6	3.0
sodium intake	4.6	2.4	1.9	2.5	4.5	3.9
sodium balance	4.5	-4.7	-0.4	0	-0.7	-3.1
weight change	-19.1			-6.1	-6.0	-7.4
mean posm	302	338	322	284	277	
mean pna	138	153	150	130	122	
mean uosm	715	495	444	400	370	313
mean una	138	177	114	66	81	86
mean AaDO2	235	465	425	466	864	411

Baby: 32

Gestational age: 25 weeks

Birth weight: 0.824 kg

Vaginal vertex delivery following spontaneous onset of labour. Bruised at birth. Found to have a large posterior fossa haemorrhage; developed severe lung disease. Died on day 1.

Note extremely large sodium intake resulting from intensive resuscitation.

day	**1**
fluid intake	187
urine flow rate	1.2
sodium intake	24.5
sodium balance	19.8
weight change	0.4
mean posm	304
mean pna	141
mean uosm	366
mean una	164
mean AaDO2	599

Baby: 33

Gestational age: 27 weeks

Birth weight: 1.16 kg

The second of twins born by emergency caesarian section following maternal antepartum haemorrhage. Badly bruised at delivery. Ventilated for 9 days. Developed bilateral grade III periventricular haemorrhage on day 2; associated convulsions and metabolic acidosis treated with phenobarbitone and sodium bicarbonate. At 4 year follow up, myopic with motor clumsiness and cognitive delay.

Note large sodium intake on day 2 due to sodium bicarbonate administration and high urine osmolality on day 1.

day	**1**	**2**	**3**
fluid intake	95	126	123
urine flow rate	0.2	1.6	2.1
sodium intake	2.4	9.1	5.7
sodium balance	2.1	5.5	-1.9
weight change	0.8	0.9	7.1
mean posm	281	295	296
mean pna	136	137	137
mean uosm	739	398	531
mean una	71	104	167
mean AaDO2	92	104	107

Baby: 34

Gestational age: 28 weeks

Birth weight: 1.332 kg

The second of monozygotic twins born by emergency caesarian section in view of a bradycardia in twin I. Apgar score of 9 at 1 minute. Maternal rhesus isoimmunisation but no consequent neonatal problems. Ventilated for 2 days, in air by day 8. Normal at 4 year follow up.

Note 15.6 % weight loss on day 3 associated with hypernatraemia but no increase in urine osmolality.

day	**1**	**2**	**3**
fluid intake	82	99	132
urine flow rate	1.3	2.5	5.8
sodium intake	0.7	1.3	4.0
sodium balance	-1.2	-2.6	-6.3
weight change	3.6	11.6	15.6
mean posm	285	288	292
mean pna	141	148	149
mean uosm	226	239	221
mean una	62	68	74
mean AaDO2	167	99	120

Figure 4.1

Fluid intake (ml kg^{-1} day^{-1}) by postnatal age.

Box and whisker plot showing medians, interquartile range and extreme values.

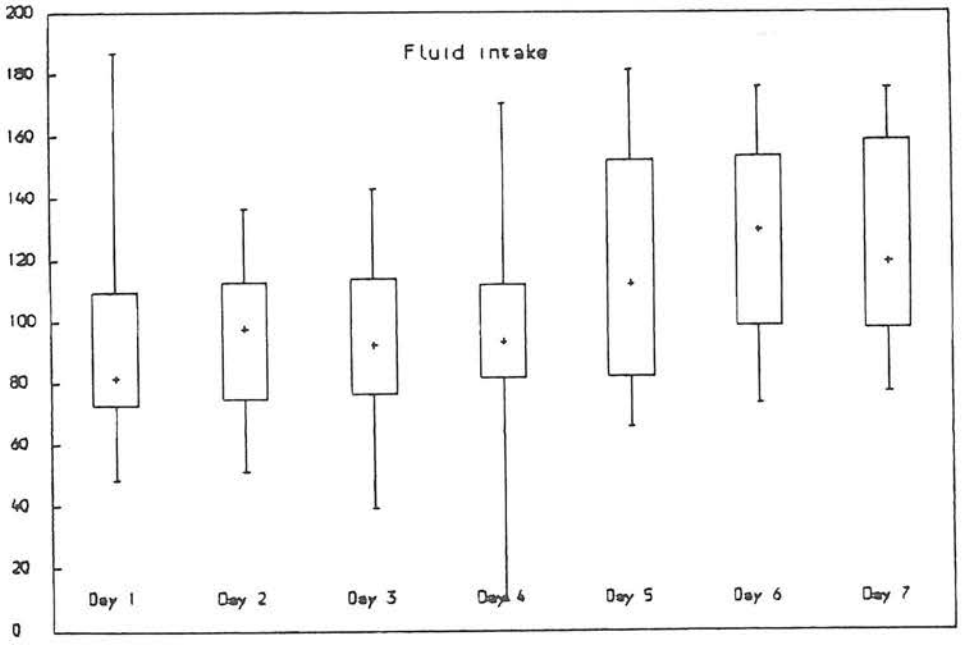


Figure 4.2

Plasma sodium (mmol l^{-1}) by postnatal age.

Box and whisker plot showing medians, interquartile range and extreme values.

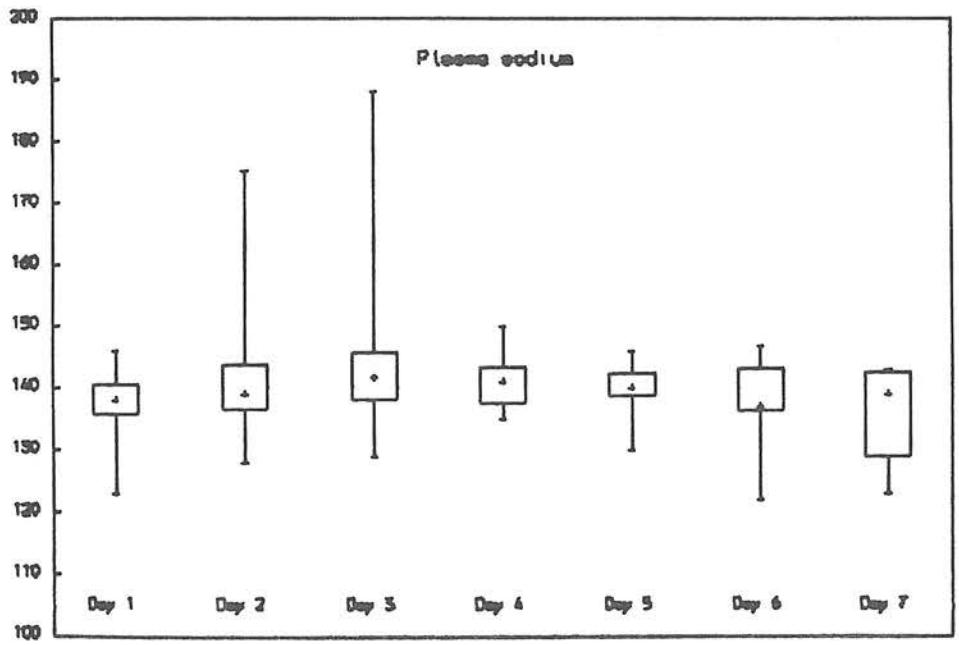
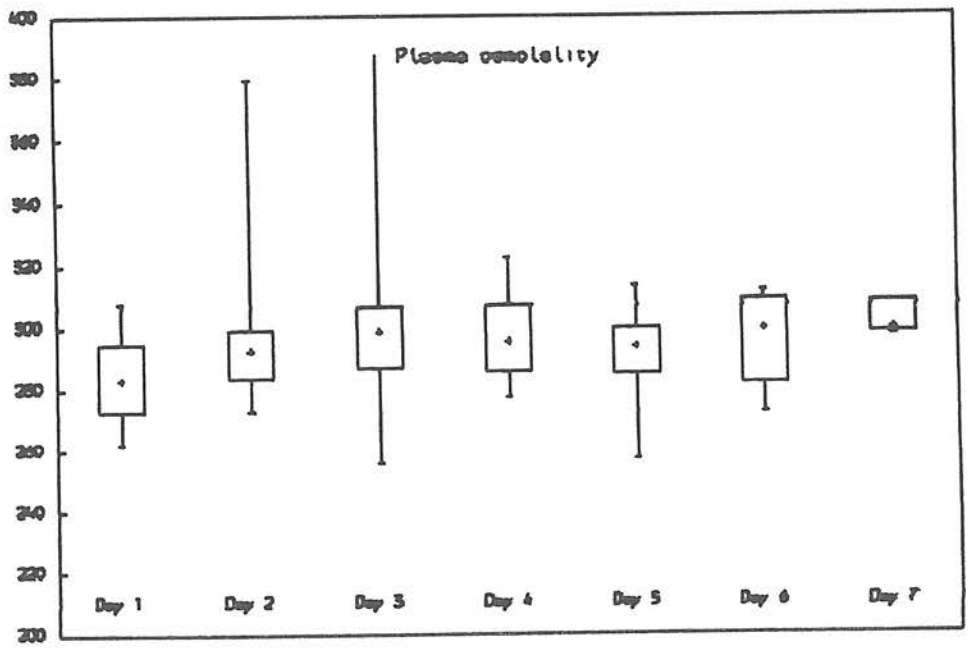


Figure 4.3

Plasma osmolality (mosm l^{-1}) by postnatal age.

Box and whisker plot showing medians, interquartile range and extreme values.



Discussion

The standard policy in this neonatal unit during the study period was, as in most others, to commence with a fluid intake of 60 ml kg^{-1} day^{-1}, increasing to 90, 120 and 150 ml kg^{-1} with alterations as clinically indicated. Infants nursed under radiant warmers were prescribed an increase of 30 ml kg^{-1}. Observation of actual fluid intakes showed that the infants rarely received this regime. A variable water requirement is understandable given the very variable insensible water losses. Infants might be nursed under radiant warmers, in incubators and under a variety of coverings such as bubble wrap, polythene sheeting or perspex shields all of which would influence transcutaneous losses and add to the inherant variation between babies. The 60-90-120-150 formula, so widely used and incorporated into teaching lore, is probably not appropriate for the neonatal intensive care setting. Probably a better guideline would be to suggest a starting volume based on estimated insensible water losses and one and a half times the minimum urine output of 30 ml kg^{-1} day^{-1}. Adjustments should then be made every 6-8 hours based on urine output, clinical condition and serum electrolytes.

Urine flow rate was very often less than 1 ml kg^{-1} h^{-1} on the first day of life. It is unclear whether this reflected a transient period of renal impairment or normal

first day physiology. Healthy babies are known to be relatively oliguric immediately following birth. This is further discussed in subsequent chapters.

True sodium intake varied considerably. Despite a unit policy to begin with 4 mmol kg^{-1} day^{-1} on the second day of life, every baby received some sodium from the first day and many received appreciable amounts. Positive sodium balance was frequently seen on the first day of life and many babies failed to show the expected early weight loss and indeed showed an inappropriate weight gain. Daily weight loss should be of the order of 1% in such babies.

Hypernatraemia occurred in 11 babies in conjunction with weight loss and was due to dehydration. Hypernatraemia in association with weight gain was seen in only two babies (9 and 31). Inappropriate weight gain occurred frequently together with a normal plasma sodium and this suggested expansion of the extracellular space. These babies appeared to have been given too much sodium. The babies obviously retained too much water but they do not appear to have been given too much water. Certainly hyponatraemia was uncommon; it occurred in baby 15 in association with weight gain and in baby 2 in association with weight loss.

The babies were also generally hyperosmolar; this would have resulted in a stimulus to vasopressin secretion

which in turn could explain a poor urine output. It is possible therefore that an explanation for the abnormalities seen is that the babies received too much sodium and normal to low amounts of water resulting in avid water retention and a poor urine output.

It is immediately apparent that the administration of sodium bicarbonate results in a large sodium intake as a 4.2% solution contains 0.5 ml sodium ml^{-1}. However appreciable inapparent intakes sometimes resulted from the normal saline used to flush lines. The use of normal saline to maintain patency of peripheral or umbilical lines as opposed to dextrose for an umbilical line and 0.45% saline for peripheral arterial lines was another contributory factor.

Urine sodium concentration and osmolality considered alone were unlikely to assist clinical management. Urinary sodium concentrations were almost invariably high, exceeding 50 mmol l^{-1}; any decision based on this parameter alone to increase sodium intake would have been questionable given the frequence concurrence of inappropriate positive sodium balance. Baby 24 had an unusually low mean urinary sodium concentration of 29 mmol l^{-1} on day 2 with positive sodium balance and weight gain; a decision to increase sodium intake solely on the basis of this information would again have been inappropriate.

Urine osmolality lay most often between 200 - 450 mosm l^{-1} and seemed to be a poor reflection of hydration. Eleven babies developed hypernatraemic dehydration and during these episodes mean urine osmolality ranged from 174 - 518 mosm l^{-1}.

What improvements might be made to fluid and electrolyte management in the newborn baby? In terms of clinical practice four suggestions should be made: we require the means to accurately and easily monitor urine output; to accurately weigh sick infants without disturbance; the clinical resolve to ensure that sodium and water are prescribed independently and the ability to rapidly and precisely calculate true water and electrolyte intakes inclusive of all sources. This last could easily be computed at the cotside using a programmable hand held calculator.

These observations are discussed in detail in the chapters which follow.

5

GLOMERULAR FILTRATION RATE

The value of glomerular filtration rate (GFR) as an index of renal function is sometimes controversial, but it remains an accepted standard. Several studies have been made of GFR in neonates but these have, on the whole, been confined to 'healthy' infants not requiring ventilatory support or intravenous fluids. The rationale for this approach is understandable. Nevertheless, it has resulted in an inevitable paucity of data pertaining to the typical

immature infant to be found in intensive care units. In addition, where utilised, urine collections have often been of short duration and measurements expressed as absolute values or 'corrected' for surface area; raw data has generally not been published. The aim of this section of the study was to determine GFR as endogenous creatinine clearance during the first week of life in a typical population of preterm infants requiring intensive care and to compare these measurements with published data relating to 'well' preterm neonates.

The measurement of glomerular filtration rate

Inulin clearance remains the 'gold standard' for the measurement of GFR. Coulthard (1983) has studied several methods of measuring GFR in the neonate, using inulin. Given the slower equilibration period of substances handled by the newborn kidney he found two methods reliable; a constant infusion technique over 24 hours or a single injection method with sampling over 5 hours combined with urine collection. Both methods are difficult to perform, especially in the preterm neonate receiving intensive care.

Coulthard et al [1985] found agreement between inulin clearance and 'true' creatinine clearance. 'True' creatinine was measured following adsorption onto Dowex-50

resin - a method that is laborious and unsuited to routine use. Under ideal circumstances the preferred method would be measurement using high pressure liquid chromatography (HPLC) or dilution mass spectroscopy but these methodologies are not readiliy available. In clinical practice today creatinine is usually measured following its reaction with alkaline picrate. However other chromogens in plasma also react with alkaline picrate falsely elevating levels. Automated methods have therefore been developed which use reaction rate analysis - measuring the generation of colour during incubation with picrate. Such methods reduce [Coulthard et al 1985] and may eliminate [Arant 1978] interference from non-creatinine chromogens. Though there is thus a possibility of overestimating plasma creatinine, on the whole correlation is good [Stonestreet et al 1979]. As the purpose of the present study was to obtain data of use in everyday clinical practice, measurement of plasma creatinine was made with the widely available Beckman autoanalyser which utilises the kinetic reaction rate Jaffe method and which was in standard clinical use at the time of this study. Plasma creatinine measured by Beckman autoanalyser shows minimal positive bias versus dilution mass spectroscopy [Schwartz et al 1987].

Methods

Glomerular filtration rate, as endogenous creatinine clearance, was measured during the first week of life in the study population described in chapter 3. Calculations were only performed when the urine flow rate equalled or exceeded 0.5 ml kg^{-1} h^{-1} so as to minimise the chances of including data from infants with unrecognised renal impairment.

Absolute daily GFR was calculated for each baby as the product of mean daily urinary creatinine and total daily urine output divided by the product of mean daily serum creatinine and total duration of daily urine collection.

Absolute GFR was also calculated for each baby individually as the product of mean urinary creatinine for the whole collection period and total urine output divided by the product of mean serum creatinine and total duration of urine collection in minutes.

GFR expressed per kilogram was calculated using birthweight, as opposed to actual weight on the day of study. The rationale for this is discussed below. Surface area (SA) was estimated from birthweight (BW) using Boyd's self-adjusting power equation [Boyd 1935] as described in chapter 3 - Methods.

Statistical analyses were by linear regression, one-way analysis of variance, multivariate analysis of variance and multiple comparison procedures.

Results

Glomerular filtration rate, as endogenous creatinine clearance, was measured on 103 days in 34 male infants during the first week of life. The mean gestational age of the babies was 28.5 weeks (median 28; range 25 - 34); the mean birth weight was 1.18 kg (median 1.12; range 0.680 - 1.832). The mean urine flow rate was 2.57 ml kg^{-1} h^{-1} (median 2.58; range 0.64 - 4.44).

The mean duration of daily urine collection was 1241 minutes (median 1420; range 105 - 1800). The mean duration of total urine collection was 2.45 days (median 2.38; range 0.2 - 7).

The mean GFR for the 34 infants was 0.57 ml min^{-1} kg^{-1} (median 0.51, range 0.09 - 1.11; 95% confidence interval 0.49 - 0.66).

GFR was first assessed in relation to postnatal age. GFR (ml min^{-1} kg^{-1}), calculated for each of the first seven days of life, is presented for visual inspection in boxplot

format (Fig 5.1). The corresponding numerical values are shown in Table 5.1. Visual inspection suggests that GFR increases between the first and the third days of life and then remains relatively constant. The Tukey multiple comparison procedure showed that no two groups were significantly different at the 0.05 level. Analysis using the less rigorous least significant difference multiple comparison procedure suggested that GFR on day 1 differed from GFR on days 3 and 4. However mutivariate analysis of variance failed to substantiate this impression, showing no effect of postnatal age, having allowed for between baby variation and variation due to gestational age ($F=0.89$, $p=0.5$).

GFR was then examined in relation to gestational age. Absolute GFR (ml min^{-1}), GFR factored by body weight (ml min^{-1} kg^{-1}) and GFR factored by surface area (ml min^{-1} $m^{2\,-1}$) are presented as regression plots against gestational age (Fig 5.2 - 5.4). Absolute GFR increased significantly with gestational age ($r=0.64$, $p<0.0001$) (Fig 5.2) as did GFR factored by surface area ($r=0.4$, $p<0.05$) (Fig 5.4); when factored by body weight a positive correlation was shown which failed to reach significance ($r=0.28$, $p=0.1$) (Fig 5.3).

Discussion

The measurement of GFR in neonates has been the subject of numerous investigators. Published data have however, often been conflicting. GFR is believed to alter with postconceptional and postnatal age, yet the pattern of maturation has been variably described. There is also disagreement over the effect of several clinical circumstances on GFR. Engle et al [1983] found no change in GFR during the course of hyaline membrane disease, unlike Guignard et al [1976] and Costarino et al [1985]. Artificial ventilation [Leslie et al 1986] has also been held to influence GFR. Coulthard and Hey [1985] and Stonestreet et al [1983], studying the effect of varying fluid intakes, found that this did not change glomerular filtration rate.

Expression of GFR

Confusion has arisen in the interpretation of measurements, in part because of the use of differing methods of expression. The conventional "correction" of GFR for surface area, used by "adult" nephrologists, would appear to have been incorectly applied to the neonate. As long ago as 1952, McCance and Widowson questioned the use, in paediatric practice, of surface area to standardize GFR.

It would be logical to relate GFR to the size of the fluid pool affected by the kidney. In the neonate all fluid compartments are changing fairly rapidly and correlate closely with body weight. Coulthard and Hey [1984] have argued elegantly in favour of weight as the best standard for glomerular filtration in the newborn. They point out that whereas the ratio of surface area to weight changes little in adulthood, it falls by one third between 27 weeks and term (Fig 5.5). A 70 kg, 1.73 m^2 adult, filters approximately 140 ml min^{-1}; this is equivalent to 80 ml min^{-1} $m^{2\,-1}$ and 2 ml min^{-1} kg^{-1} (Table 5.2). To achieve a GFR of 80 ml min^{-1} $m^{2\,-1}$, an infant weighing 1 kg and with a surface area of 0.1 m^2,would need to filter 8 ml min^{-1} kg^{-1}. Such an infant actually filters around 0.5 ml min^{-1} kg^{-1}.

GFR is generally held to be extremely low in the preterm infant in comparison to adult values: however when GFRs standardized by body weight are compared, the magnitude of difference between the 1 kg infant and the 70 kg adult is closer to fourfold rather than to the sixteenfold difference suggested when surface area corrected GFRs are compared.

Maturation of GFR

There is general agreement that GFR correlates with gestational and postconceptional age [Leake et al 1976 i]. The precise pattern of maturation has however been described in conflicting ways. Arant [1978], Al-Dahhan et al [1983] and Coulthard [1985] describe a shallow gradient until 34 weeks becoming abruptly steeper thereafter. These authors expressed their results in absolute terms of ml min^{-1}. Another group of workers, expressing their measurements of GFR corrected for surface area as ml min^{-1} $m^{2\,-1}$, describe the converse, that is a rapid increase to 35 weeks gestation slowing down till term [Guignard 1982; Guignard and John 1986; Fawer et al 1979]. They suggest that this may be explained by the completion of nephrogenesis at 35 weeks. This pattern of maturation has not been confirmed by other workers. It has been suggested that the apparent slowing of maturation at 35 weeks is an analysis related artefact [Coulthard 1985]. When expressed per kg body weight, the rate of increase in GFR decreases [Coulthard 1985] or disappears. Coulthard has analysed data on GFR from 14 previous studies in addition to his own. An "overview" of the published data, following presentation in similar format, allowed him to draw the conclusion that GFR in newborns (measured from the third postnatal day), expressed per unit body weight, increases linearly in a programmed way which is determined

by postconceptional age (Fig 5.6). Data from the present study are consistent with these observations (Fig 5.2 - 5.4).

Influence of birth on GFR

The data presented here suggest that GFR may increase over the first two days of life but then remains relatively constant between days 3 - 7. It should be appreciated however that GFR on the first two days of life was found to be significantly lower only when applying the less rigorous least significance difference multiple comparison procedure. A similar pattern of essentially unchanging GFR during the first week of life in preterm infants has been described by others [Stonestreet et al 1983; Arant 1978]. More mature infants display a clear increase in GFR during the first week of life [Guignard et al 1975; Aperia et al 1981]. This is likely to be due to the decrease in renal vascular resistance and increase in renal blood flow that has been demonstrated in animal studies of the immediate postnatal period [Gruskin et al 1970].

During the first few weeks of postnatal life GFR has been believed to show a more rapid rate of increase [Aperia et al 1981 ; Fawer et al 1979]. Coulthard [1985] has replotted this data, expressing GFR by projected weight

rather than by actual weight and has shown this apparent sharp rise after birth is an artefact due to a temporary slowing of growth. It is in order to avoid any artefactual increase in GFR during the first week of life due to postnatal weight loss that GFR has been expressed by birth weight rather than actual weight in the study described here.

Comparison with published data derived from "healthy" newborns.

It is widely believed that preterm infants requiring ventilatory support are in a state of relative renal impairment. It is of interest, therefore, to compare the values for GFR obtained in this study, with measurements made in healthy infants. Coulthard [1985] measured GFR in 39 healthy infants using the prolonged inulin infusion technique and constructed a formula predicting GFR (ml min^{-1} kg^{-1}) in the first month of life from postnatal age (PNA, weeks) and birthweight (BW, kg):

$$\mathbf{GFR = 0.24BW + 0.18PNA + 0.45}$$

The standard error for this prediction was 0.09. The mean birthweight and postnatal age for the infants in the present study were 1.18 kg and 0.47 weeks respectively. The

95% confidence interval derived following insertion of these values into Coulthard's equation is:

0.64 - 0.99 **(1)**

The 95% confidence interval for GFR (ml min^{-1} kg^{-1}) derived from the present study is:

0.49 - 0.66 **(2)**

Coulthard et al [1985] suggest, however, that creatinine clearance measured by reaction rate analysis (as in the present study) underestimates inulin clearance by approximately 25%. Correction of interval (2) above on the assumption that it represents only 75% of 'true' GFR produces the following confidence interval:

0.65 - 0.88 **(3)**

Furthermore Coulthard [1985] compared his measurements with data from 14 other published studies of GFR in healthy babies and found close agreement. There is close agreement between confidence interval 1 (Coulthard; heathy infants) and confidence interval 3 (present study; 'sick' infants). Agreement is also found in Coulthard's regression equation describing the

correlation between GFR (ml min^{-1} kg^{-1}) and conceptional age (CA,weeks), in babies aged 2-7 days (Fig 5.6),

$$\mathbf{GFR = 0.0414CA - 0.4}$$

and the regression equation derived from the present study (Fig 5.3),

$$\mathbf{GFR = 0.03GA - 0.23}$$

where GA = gestational age in weeks.

It would appear, therefore, from the arguments presented above that there is little difference between estimates of GFR obtained from healthy preterm infants and those representing the typical preterm population of a neonatal intensive care unit.

Changes in GFR in relation to postnatal respiratory adaption are discussed in chapter 8.

Conclusions

1. The 95% confidence interval for glomerular filtration rate, expressed as endogenous creatinine clearance and measured during the first week of life, in infants between 25 - 34 weeks gestation, was 0.49 - 0.66 ml min^{-1} kg^{-1}.

2. Infants between 25 -34 weeks gestation may show an increase in GFR over the first two days of life but show no significant increase from days 3 - 7.

3. When expressed in absolute terms of ml min^{-1}, GFR, measured between 25 - 34 weeks gestation, showed a highly significant positive correlation with gestational age; when factored by body weight a positive correlation was also found, which failed to reach significance.

4. Comparison of published estimates of GFR measured in healthy preterm infants and those from the population of infants receiving intensive care, studied here, show little overall difference.

Figure 5.1

Glomerular filtration rate by postnatal age.

Box and whisker plot showing medians, interquartile range and extreme values. The numerical values are listed over (Table 5.1)

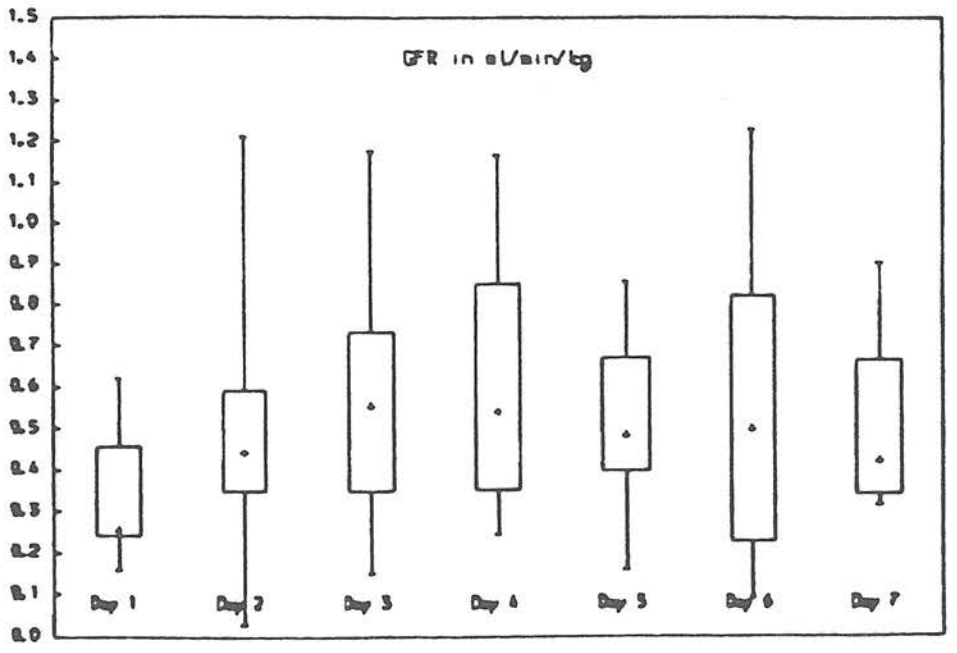


Table 5.1

Glomerular filtration rate by postnatal age.

(medians, interquartile range & extreme values)

day	n	minimum	Q_1	median	Q_3	maximum
1	11	0.16	0.24	0.25	0.46	0.62
2	29	0.03	0.35	0.44	0.59	1.21
3	24	0.15	0.35	0.53	0.73	1.17
4	16	0.24	0.35	0.54	0.85	1.17
5	10	0.16	0.40	0.48	0.67	0.85
6	8	0.09	0.23	0.50	0.82	1.23
7	5	0.31	0.34	0.42	0.66	0.90

(GFR, glomerular filtration rate in ml min^{-1} kg^{-1})

Figure 5.2

Regression of glomerular filtration rate (ml min^{-1}) on gestational age.

GFR = 0.094GA - 1.99, SE of estimate = 0.27

r = 0.64, p<0.0001

Figure 5.3

Regression of glomerular filtration rate (ml min^{-1} kg^{-1}) on gestational age.

GFR = 0.03GA - 0.23, SE of estimate = 0.23

r = 0.28, p = 0.1

Figure 5.4

Regression of glomerular filtration rate (ml min^{-1} $m^{2\,-1}$) on gestational age.

GFR = 0.46GA - 7.0, SE of estimate = 2.5

r = 0.4, p<0.05

Regression of Glomerular Filtration Rate on gestational age

(with 95% confidence limits for regression line)

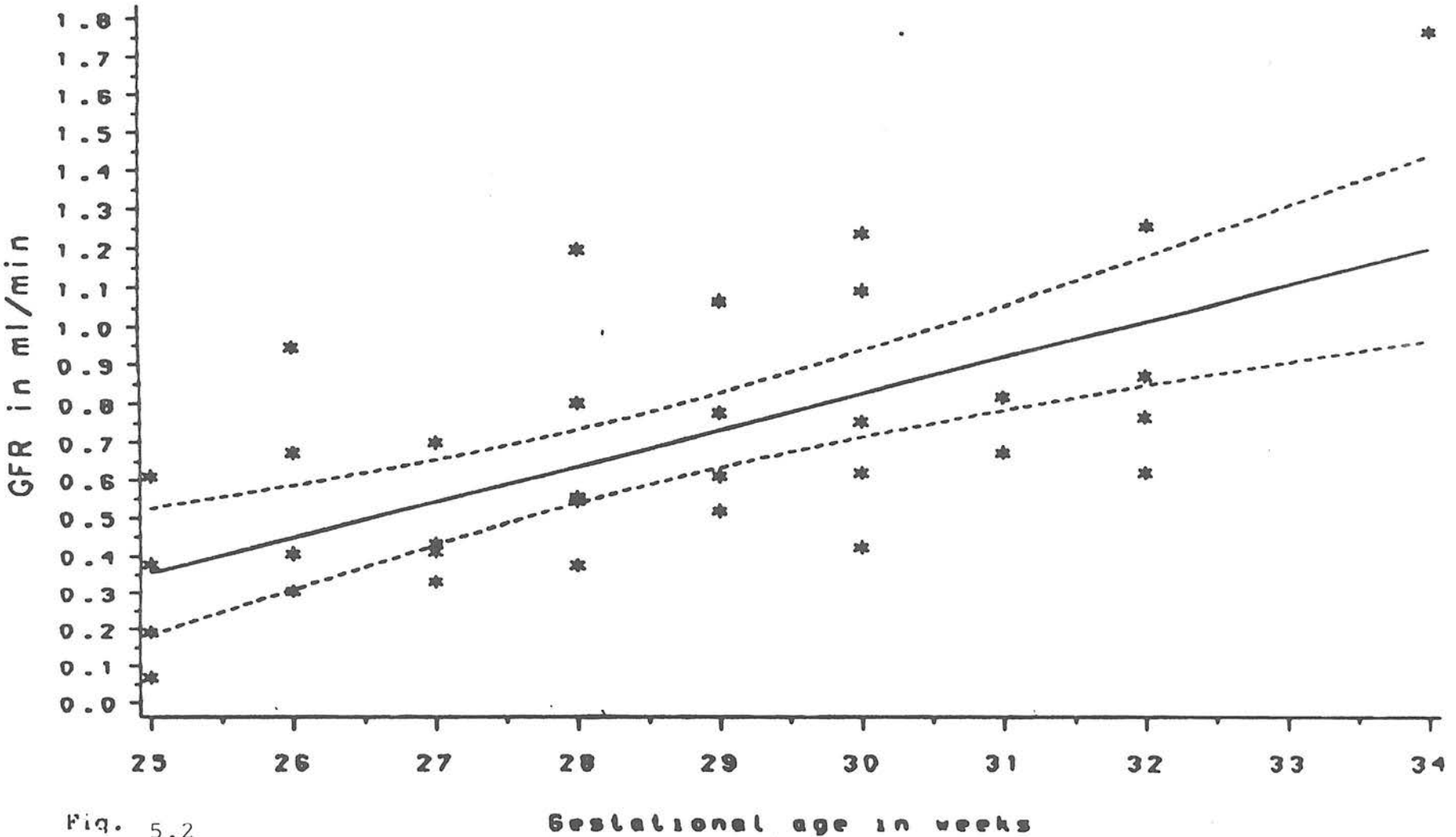


Fig. 5.2

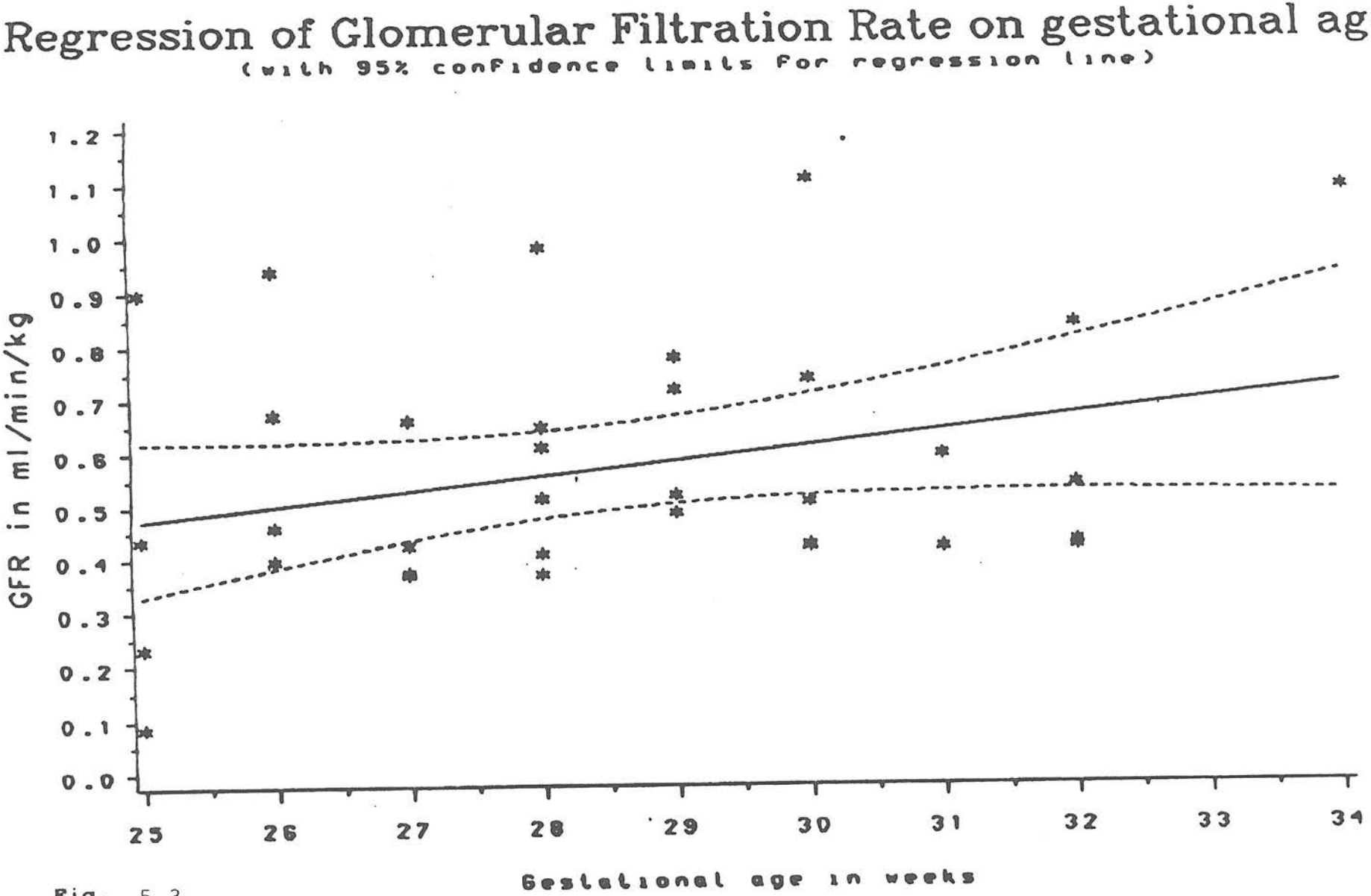

Regression of Glomerular Filtration Rate on gestational age
(with 95% confidence limits for regression line)
GFR in ml/min/kg
1.2
1.1
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
25
26
27
28
29
30
31
32
33
34
Gestational age in weeks

Fig. 5.3

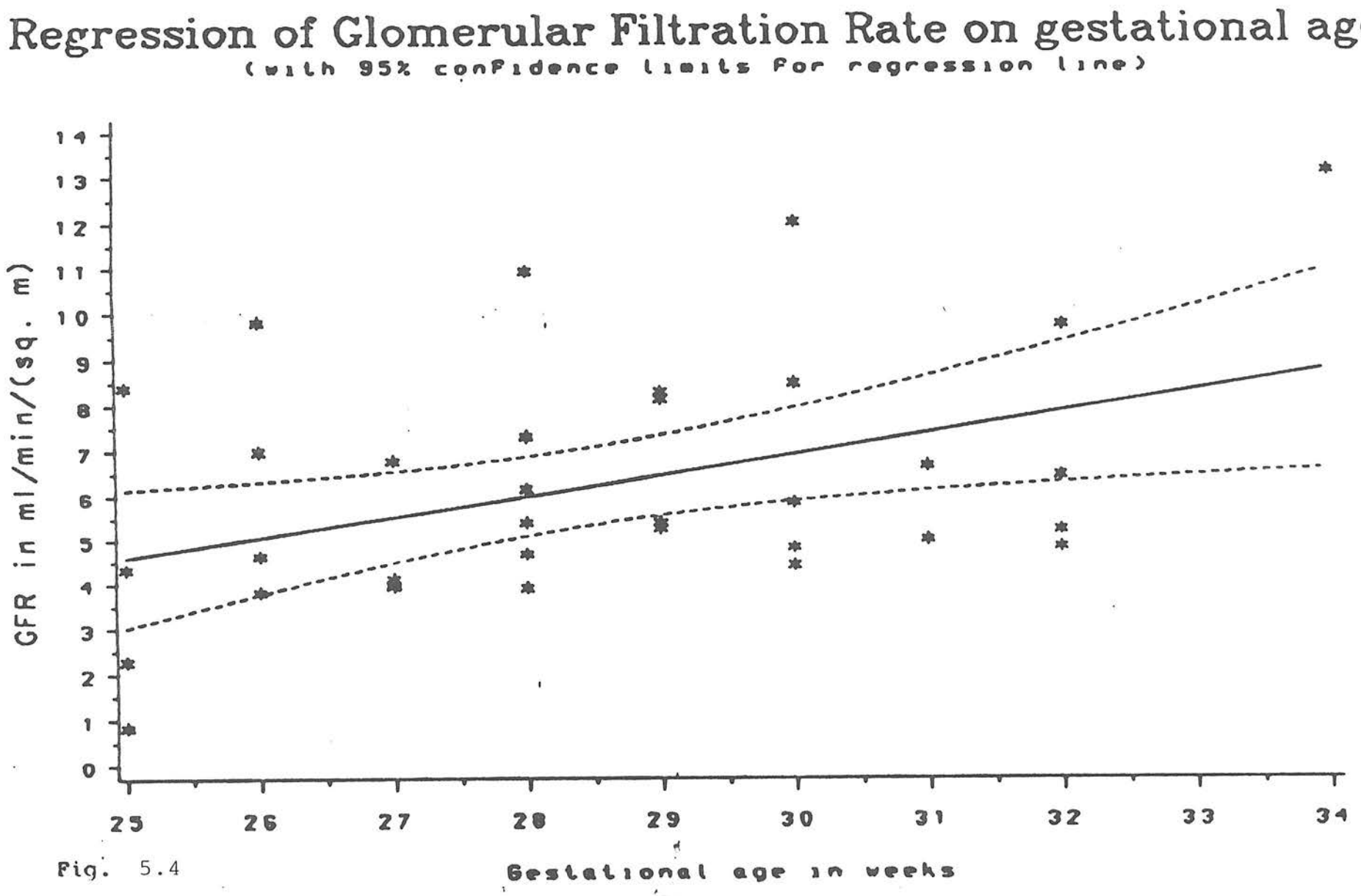

Regression of Glomerular Filtration Rate on gestational age
(with 95% confidence limits for regression line)
GFR in ml/min/(sq. m)
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
25
26
27
28
29
30
31
32
33
34
Gestational age in weeks

Fig. 5.4

Figure 5.5

Surface area to weight ratio by body weight.

(From Coulthard MG, Hey EN, Arch Dis Child 1984 59:374; reproduced with permission)

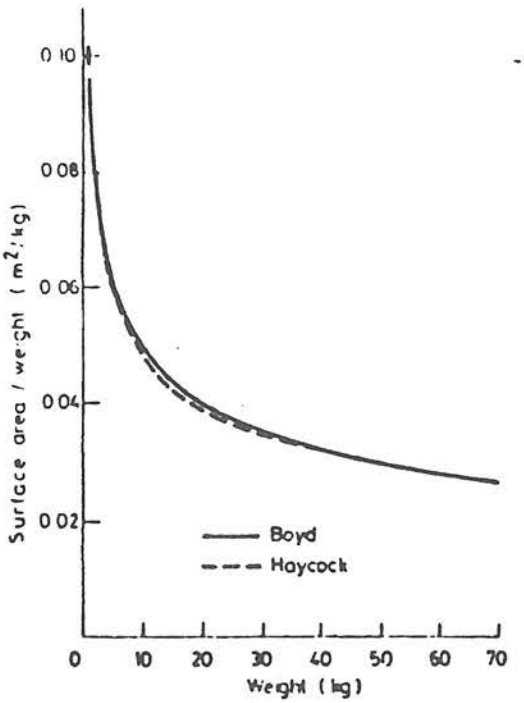


Table 5.2

"Corrected" glomerular filtration rate.

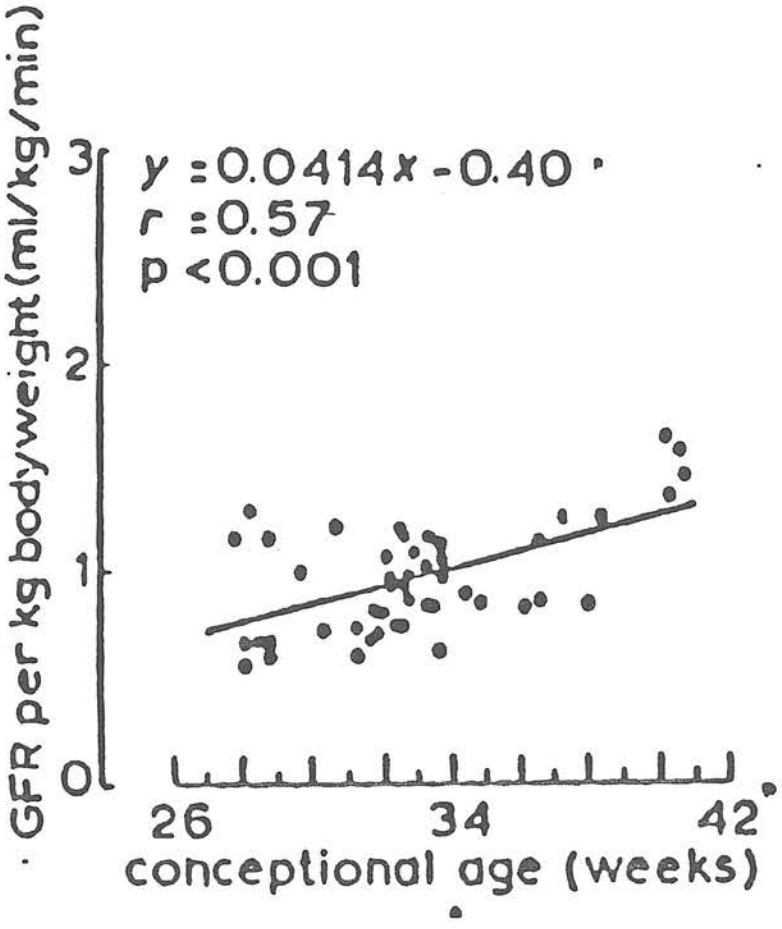
GFR	adult weight 70 kg SA 1.7 m^2	preterm neonate weight 1 kg SA 0.1 m^2
ml min^{-1}	140	0.5
ml min^{-1} $m^{2\,-1}$	80	5
ml min^{-1} kg^{-1}	2	0.5

(SA, surface area)

Figure 5.6

Glomerular filtration rate by conceptional age.

(From Coulthard MG, Earl Hum Dev 1985 11:288;
reproduced with permission)



6

URINARY CREATININE EXCRETION AND ESTIMATION OF MUSCLE MASS

Creatinine is derived from phosphocreatine by a non enzymatic process occurring in muscle [Bloch & Schoenheimer 1939]. In 1947 Borsook and Dubnoff reported that 98% of total body phosphocreatine is located in muscle and that 2% is converted daily to creatinine and excreted in the urine. At steady state therefore, creatinine excretion is an indirect measure of muscle mass. The urinary excretion rate of creatinine was first used in anthropometric studies

as an indirect index of muscle mass in 1938 [Talbot 1938]. Creatinine excretion factored by body weight is similarly a reflection of the relative amount of muscle in the body [Graystone 1968].

A knowledge of urinary creatinine excretion has several applications; it has been used as an index of muscle mass and nutritional status [Heymsfield et al 1983], to estimate urine flow rate and to relate the excretion of other metabolites [Coulthard et al 1985]. There is limited information relating to creatinine excretion in extremely immature infants. This chapter presents data relating to a typical group of preterm infants.

Methods

Continuous urine collections were obtained from the study population described in chapter 3 - Methods.

Mean daily urine flow rate was calculated for each infant for each study day using aggregated data from the 4 hourly time periods of urine collection. In order to minimise the risk of inadvertently including infants with unrecognised impairment in renal function, data was only analysed in infants in whom mean daily urine flow rate equalled or exceeded 0.5 ml kg^{-1} h^{-1}.

Urinary creatinine excretion was calculated as the product of urine volume and urinary creatinine concentration. Creatinine excretion in daily time periods was aggregated and standardised to excretion per 1440 minutes to produce a daily excretion rate. Creatinine excretion was factored by body weight on the day of study.

The relationships between daily creatinine excretion and postconceptional age, daily creatinine excretion and weight, daily creatinine excretion factored by body weight and postconceptional age and daily creatinine excretion factored by body weight and weight were studied. As repeated measurements were made [O'Brien Smith 1987], multivariate analysis of variance was used, allowing for between baby differences. Values for daily creatinine excretion and daily creatinine excretion factored by body weight are analysed following logarithmic transformation to stabilise the variances. To assist conceptualisation, these data are presented for visual inspection as scatterplots. The influence of postnatal age on daily creatinine excretion was assessed and found not to vary within the study period of seven days having allowed for between baby differences and actual weight; data from each infant was therefore aggregated to provide a single mean daily creatinine excretion rate for each infant in order to estimate muscle mass as described below. These results are analysed using simple linear regression.

Muscle mass was estimated using the factor of 20 suggested by Graystone [1968]; i.e. the excretion of 1 g of creatinine per 24 hours derives from 20 kg muscle. (1 mg = 8.8 umol creatinine).

Results

Continuous urine collections were obtained over 89 days in 31 babies during the first week of life. The mean duration of each daily urine collection was 1276 minutes (median 1425; range 105 - 1800). The mean duration of each total urine collection was 3744 minutes (median 3465; range 630 - 9930). Mean daily urine flow rates of less than 0.5 ml kg^{-1} h^{-1} occurred on a total of 13 days in 13 babies.

The median daily creatinine excretion was 71.4 umol kg^{-1} day^{-1} (mean 71.4; 95% confidence interval 65.16 - 77.64).

The median muscle mass as a percentage of birth weight was 14.3% (mean 15; 95% confidence interval 13.4 - 16).

Log creatinine excretion (umol day^{-1}) was found to have a significant positive association with actual weight ($F=5.80$, $p<0.05$) and postconceptional age ($F=8.08$, $p<0.01$) allowing for between baby differences. There was no

significant change with postnatal age (F=2.54, p=0.12) having allowed, in addition, for actual weight.

Log of the ratio of creatinine excretion to body weight also showed a significant correlation with both weight (F=11.96,p=0.001) and postconceptional age (F=12.35,p=0.001). There was no correlation with postnatal age (F=2.55, p=0.12).

These data are presented for visual inspection, without logarithmic transformation, as scatterplots (Figs 6.1- 6.6).

Muscle mass showed a highly significant positive correlation with birthweight (r=0.8, p<0.0001) (Fig 6.7) and gestational age (r=0.8, p<0.0001) (Fig 6.8). Percentage muscle mass showed a positive correlation with birthweight (r=0.35, p=0.05) (Fig 6.9) and gestational age (r=0.43, p=0.01) (Fig 6.10). The regression equations summarizing the relationships between creatinine excretion, muscle mass, percentage muscle mass, birthweight and age are presented in Table 6.1.

Birth weight (BW) and gestational age (GA) together accounted for 64% of the variance for muscle mass. The following regression equation was constructed:

muscle mass (g) = 0.145 BW (g) + 10 GA (weeks) - 275

Analysis of the published summary statistics (Table 6.2) reveals that creatinine excretion factored by body weight does increase with postconceptional age ($r=0.8$, $p=0.01$)(Fig 6.11). The relationship is described by the following equation, which was derived using weighted least squares, with the sample sizes used as weights:

creatinine excretion = 55.2 + 0.13 post conceptional age

(umol kg^{-1} day^{-1}) (days)

The coefficient of postconceptional age is significant at less than 2%. This is consistent with the results of the more detailed analysis presented above.

Discussion

The benefits accruing from a knowledge of urinary creatinine excretion rate have been mentioned above. However there is limited data relating to creatinine excretion in immature neonates given the problems of accurate urine collection; neonates empty their bladders incompletely necessitating prolonged collection periods; further difficulties are posed by skin breakdown, secure perineal adhesion and leakage. There would appear to be only three reported studies [Sutphen 1982, Brion et al

1986, Al-Dahhan et al 1988] relating to the direct measurement of urinary creatinine excretion rate in immature infants.

Coulthard et al [1985] estimated creatinine excretion rate from a knowledge of "spot" urinary creatinine concentration and urine flow rate in babies of 26 - 40 weeks gestation during the first week of life. Each of these studies, including that reported here, relates to a relatively small sample size. An important criticism that may be levelled at the studies of Coulthard et al [1985] and Al-Dahhan et al [1988] is the use of simple linear regression when repeated measurements made on the same individual are combined with those from different individuals [O'Brian Smith 1987]. Measurements made on the same individual on separate occasions are correlated with one another and the inclusion of such measures in a simple linear regression violates the assumption on which the analysis is based. P values thus derived are meaningless.

The published summary statistics have been analysed together with data from this study. Coulthard et al [1985], state that the per kg creatinine excretion rate showed no relation to gestation and describe a mean excretion rate of 104 umol kg^{-1} day^{-1} in the first week of life. Unfortunately these authors have not included the statistical data, the raw data nor details of the babies postconceptional age and

it has therefore not been possible to include their observations in the pooled analysis.

In analysing pooled published data the relationship of creatinine excretion factored by body weight with postconceptional age, i.e. a significant positive correlation, has emerged; this is in keeping with the conclusions of this study. Issue must therefore be taken with the conclusion of Al-Dahhan et al that "infants of postconceptional age 198 - 290 days may be regarded as a single population with respect to the excretion of creatinine factored by weight" and that of Coulthard et al that the per kg creatinine excretion rate is not influenced by gestation [Modi & Hutton, **In press,** 1990].

In the examples discussed above, inappropriate analysis has led to erroneous conclusions. It is also a fundamental statistical precept that an acceptable estimation of a "normal" range demands, in the first instance, a large sample size; further, given the wide dispersion of values about the mean seen with most biological data, the validity of attempts to define "normal" ranges from samples of small size is questionable [Al-Dahhan et al 1988]. Collaboration between workers in this field would seem a better approach to estimate population characteristics with reasonable accuracy.

If creatinine excretion factored by body weight increases with postconceptional age it may be inferred that the relative amount of muscle in the body increases over the age range studied in keeping with changes known to occur in older age groups. The classic dissection studies of the early German anatomists showed muscle mass to be 25% of body weight in full term newborns which increases to the adult level of 45% at puberty [Graystone 1968]. The regression equation deriving percentage muscle mass from gestational age (GA) (Table 6.1) is in striking agreement, predicting an infant of 40 weeks gestation to have a muscle mass of 24% body weight.

% muscle mass = 0.8GA - 7.93

The regression equation also predicts a 12% muscle mass in the 25 week infant and 19% at 34 weeks. However these figures may be underestimates as there is a greater proportion of connective tissue in preterm muscle; in addition the coefficient of 20 suggested by Graystone [1968] has not been validated for application in the extremely immature infant.

Percentage muscle mass was shown to have a better correlation with gestational age than with birth weight. This suggests that birth weight is a poor reflection of relative muscle mass and is in keeping with the parallel

observation that body water content is both variable and strongly correlated with birth weight [Shaffer et al 1986 i].

Conclusions

1. The median daily creatinine excretion in the first week of life in babies of gestational ages 25 - 34 weeks was 71.4 umol kg^{-1} day^{-1} (mean 71.4, 95% confidence interval 65.16 - 77.64).

2. Creatinine excretion and creatinine excretion factored by body weight showed a significant positive correlation with weight and postconceptional age. Pooled analysis of published data together with that from this study, also revealed that this correlation is significant. This correlation is not evident when inappropriate methods of analysis are used.

3. Muscle mass is estimated from creatinine excretion rate. A regression equation is derived predicting muscle mass from birth weight and gestational age. Muscle mass increases from 12% of birth weight at 25 weeks gestation to 19% at 34 weeks and 24% at 40 weeks. This is in agreement with classic dissection studies which showed muscle mass to be 25% of body weight at term.

Figures 6.1 - 6.6

Scatterplots of creatinine excretion (umol day^{-1} and umol kg^{-1} day^{-1}) by weight (kg), postconceptional age (days) and postnatal age (days).

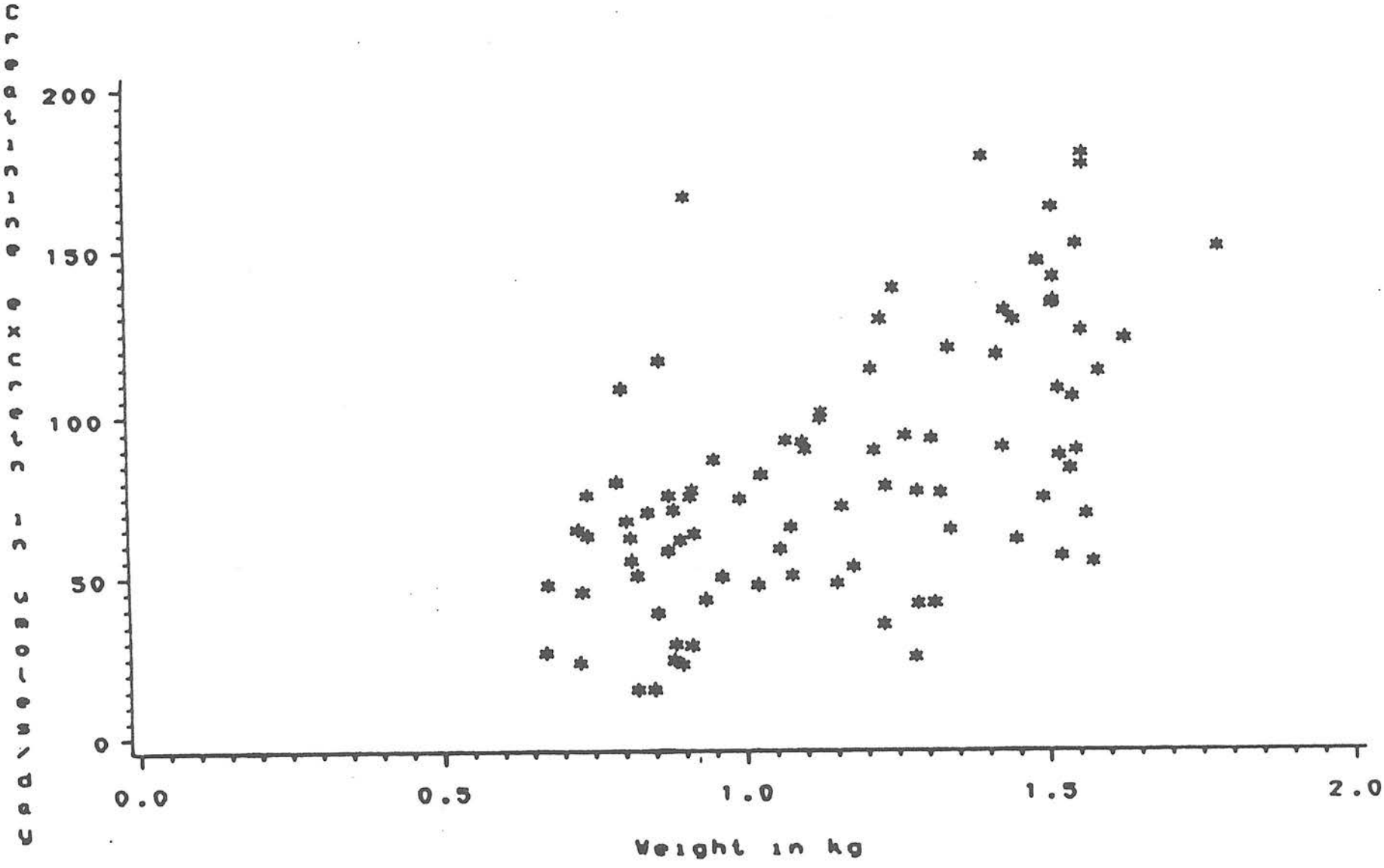

Creatinine excretion in mg/day
200
150
100
50
0
0.0
0.5
1.0
1.5
2.0
Weight in kg

Fig 6.1

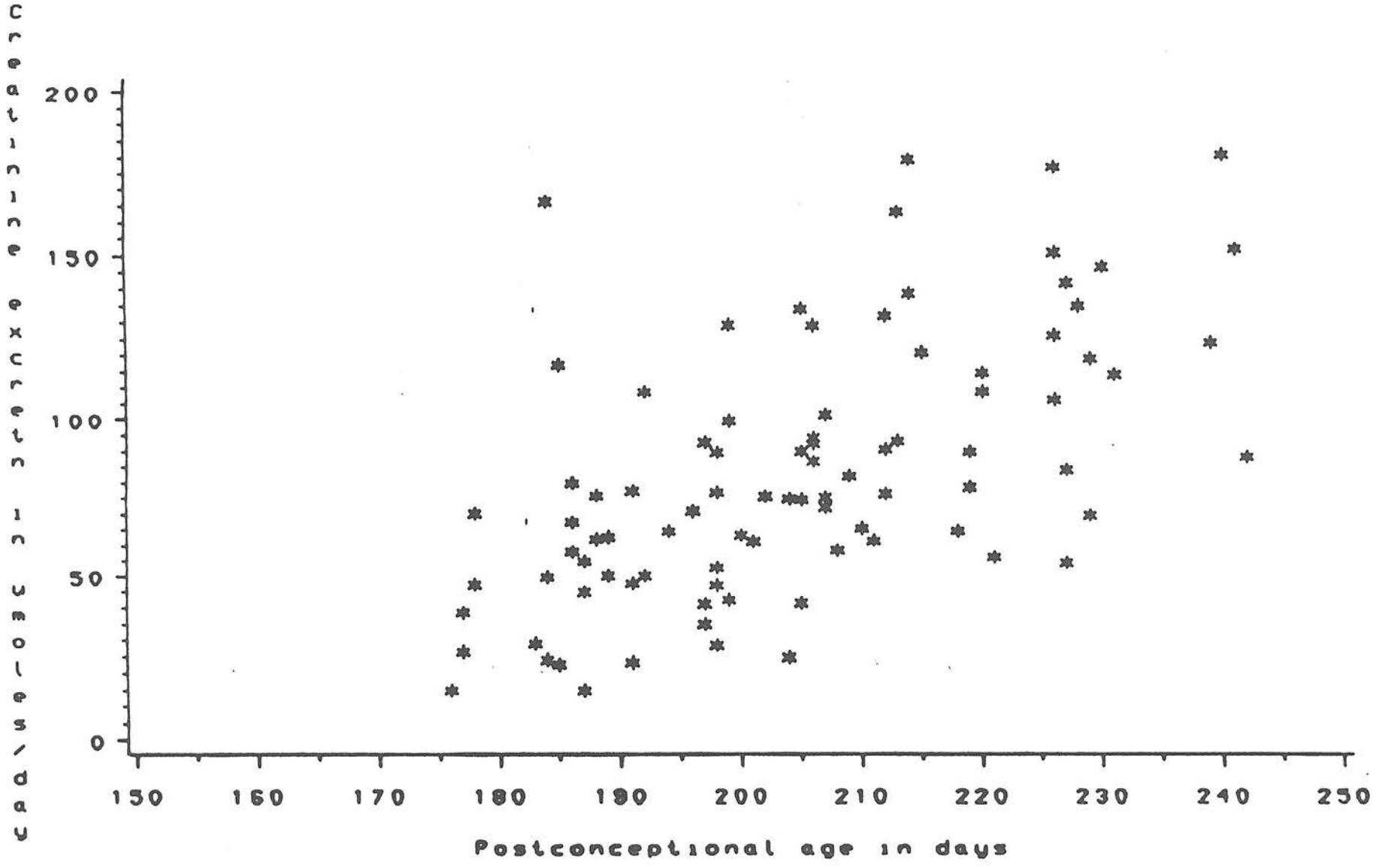

Creatinine excretion in umol/kg/day
200
150
100
50
0
150
160
170
180
190
200
210
220
230
240
250
Postconceptional age in days

Fig 6.2

Fig 6.3

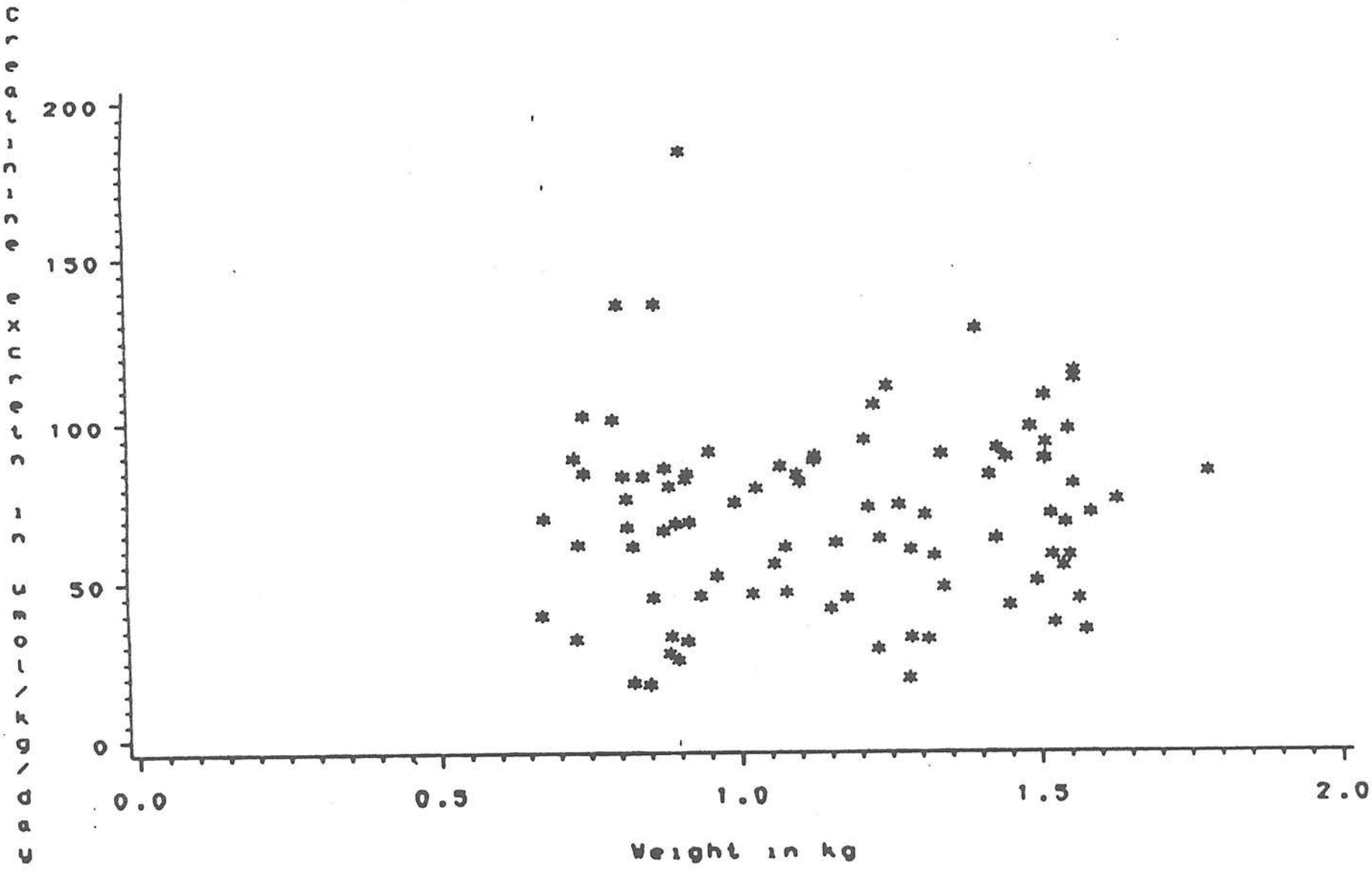

Creatinine excretion mg/kg/day
200
150
100
50
0
0.0
0.5
1.0
1.5
2.0
Weight in kg

Fig 6.4

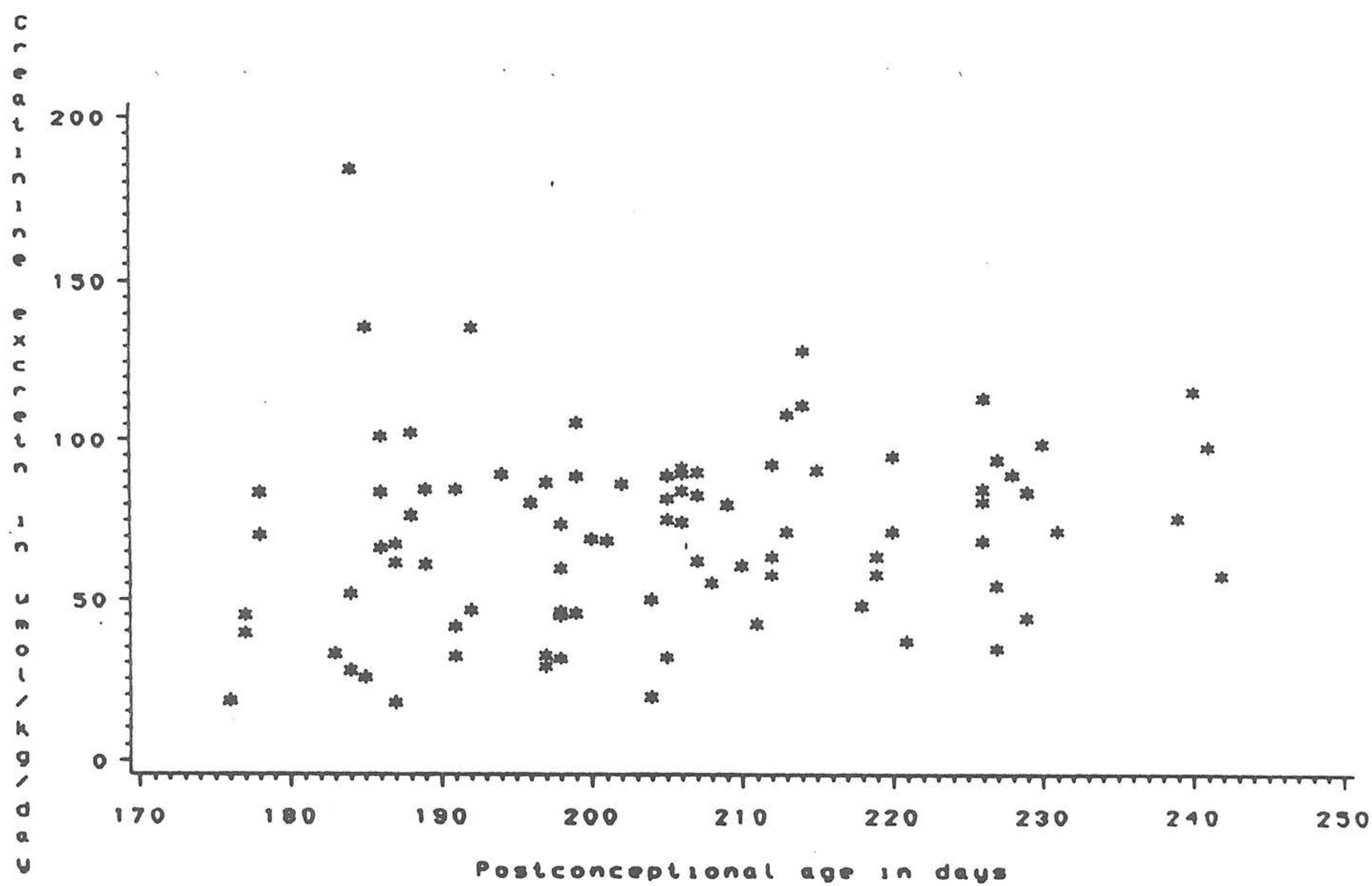

Creatinine excretn in umol/kg/day
200
150
100
50
0
170
180
190
200
210
220
230
240
250
Postconceptional age in days

Fig 6.5

Clearance excretion of urea/kg/day
200
150
100
50
0
0
1
2
3
4
5
6
7
8
postnatal age in days

Fig 6.6

Figures 6.7 - 6.8

Regression plots , with 95% confidence interval for the points, of muscle mass (g) on birthweight (kg) and gestational age (weeks). The regression statistics are listed in Table 6.1.

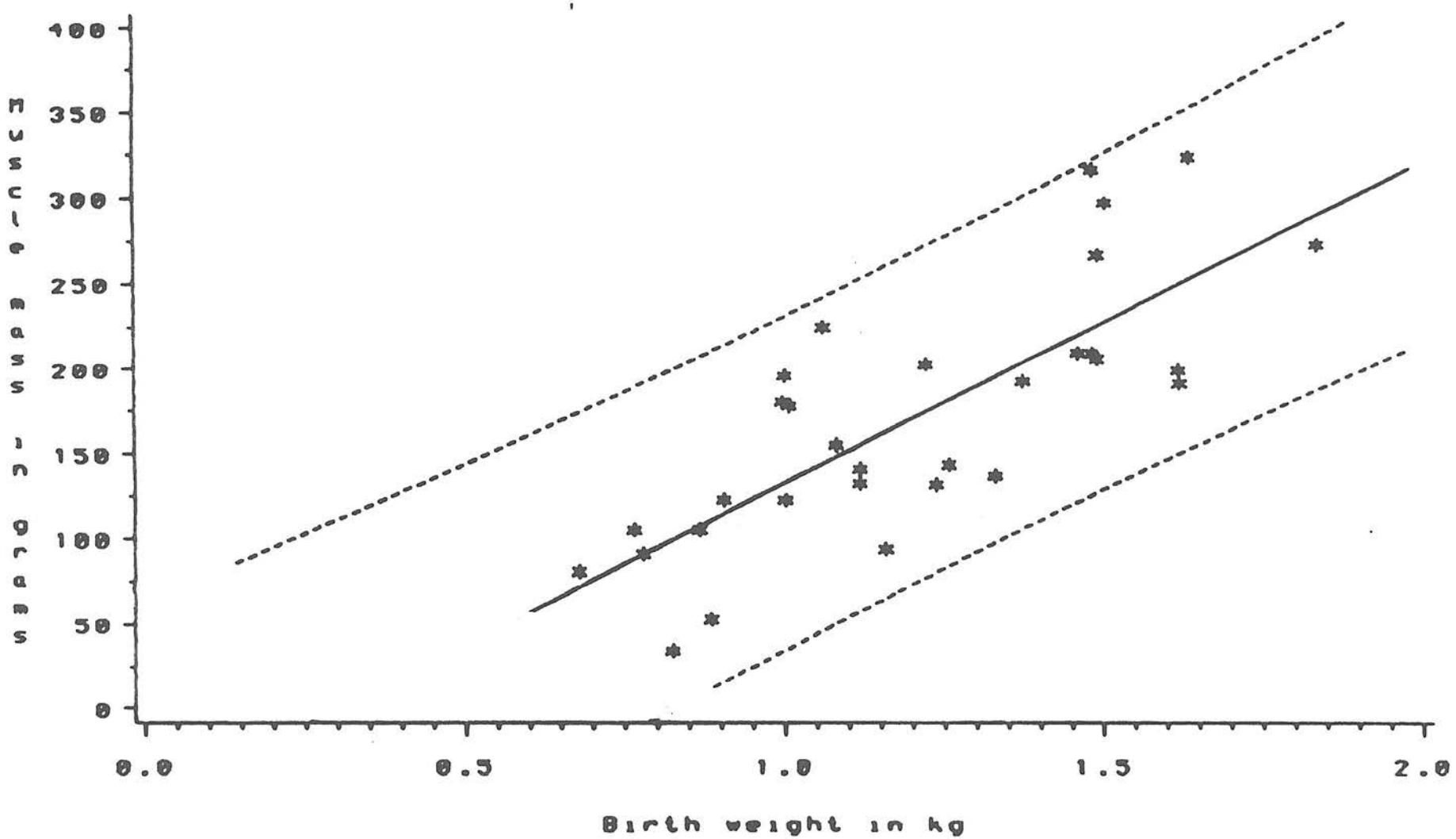

Muscle mass in gms
400
350
300
250
200
150
100
50
0
0.0
0.5
1.0
1.5
2.0
Birth weight in kg

Fig 6.7

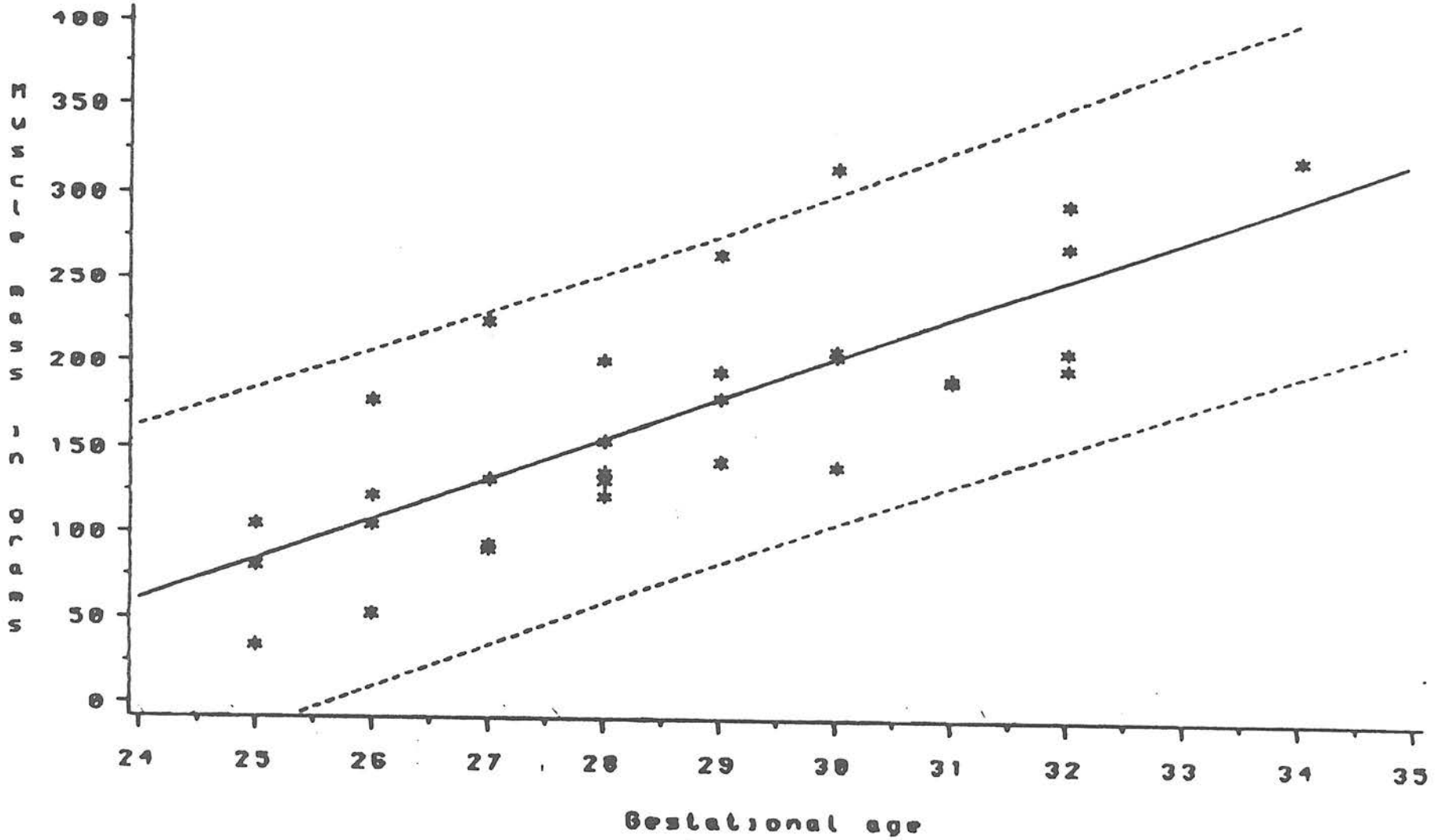

Muscle mass in grams
400
350
300
250
200
150
100
50
0
24
25
26
27
28
29
30
31
32
33
34
35
Gestational age

Fig 6.8

Figures 6.9 - 6.10

Regression plots of muscle mass as a percentage of birth weight on birth weight (kg) and gestational age (weeks). The regression statistics are listed in Table 6.1.

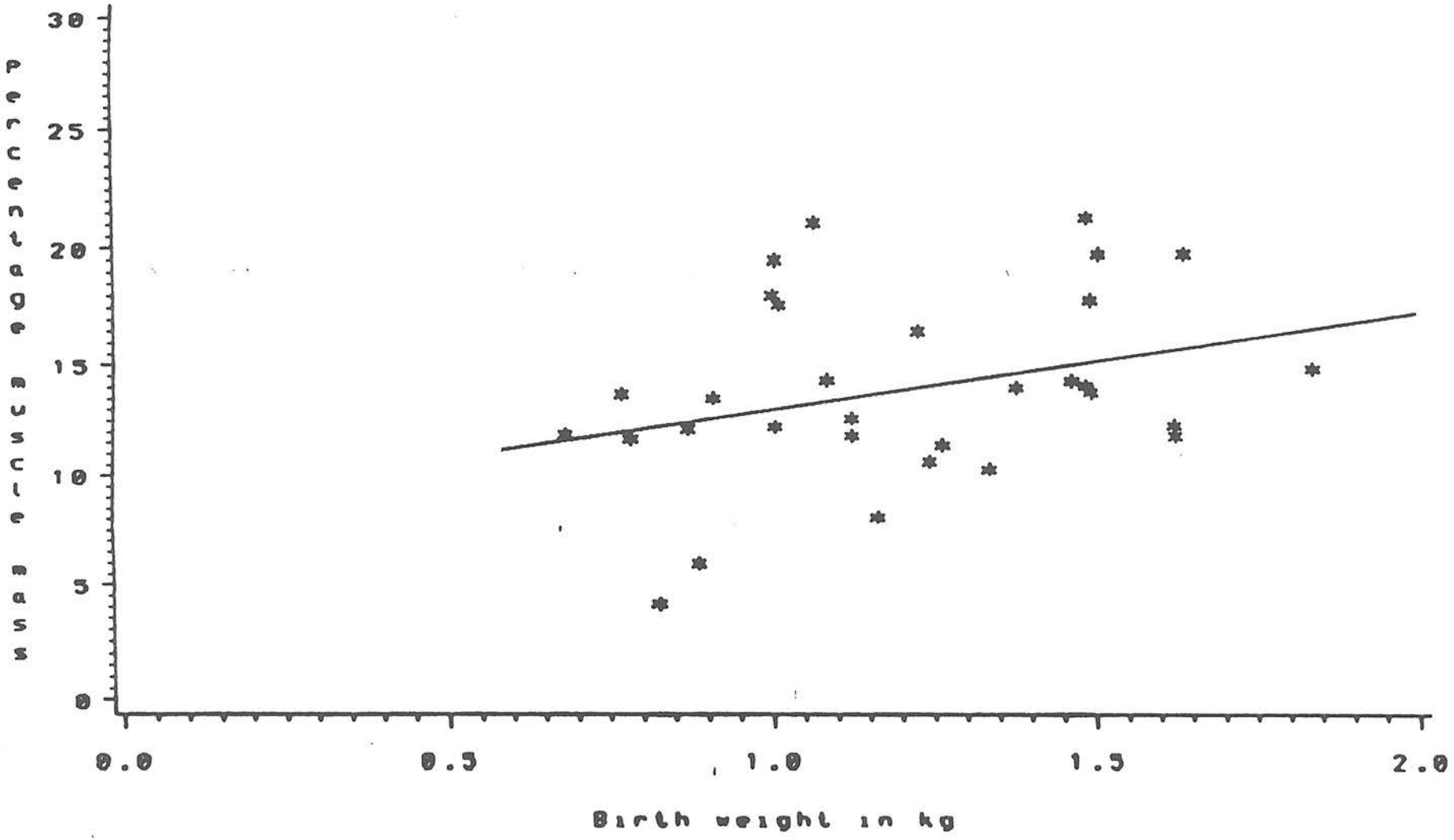

Mean e-mucus egestence p
30
25
20
15
10
5
0
0.0
0.5
1.0
1.5
2.0
Birth weight in kg

Fig 6.9

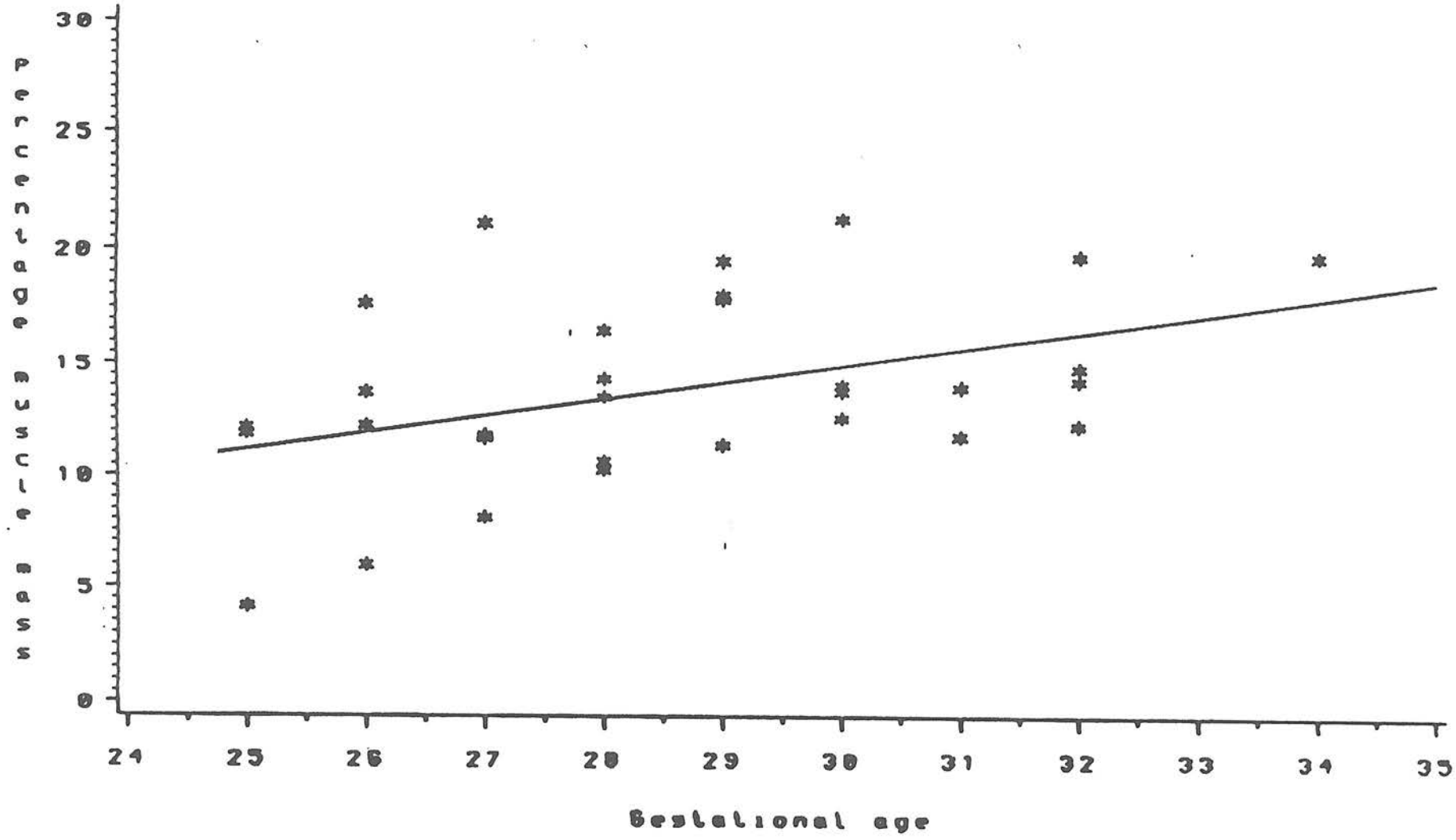

Percentage muscle mass
0
5
10
15
20
25
30
24
25
26
27
28
29
30
31
32
33
34
35
Gestational age

Fig 6.10

Figure 6.11

Regression plot of pooled published data; daily creatinine excretion (umol kg^{-1} day^{-1}) on postconceptional age (days).
y = 55.2 + 0.13x, r=0.8, p=0.01

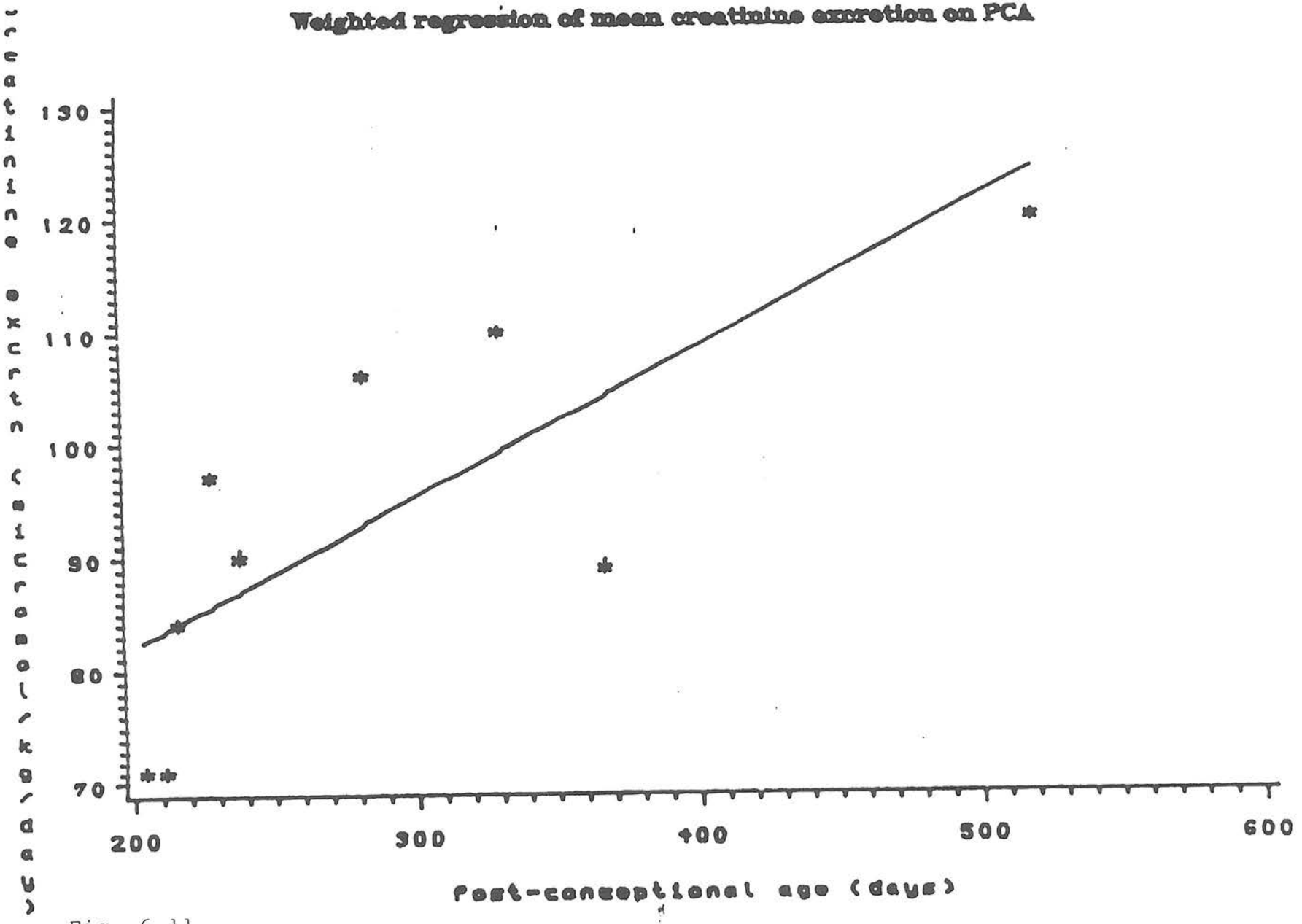

Weighted regression of mean creatinine excretion on PCA
Mean weighted creatinine excretion (mg/kg/day)
130
120
110
100
90
80
70
200
300
400
500
600
Post-conceptional age (days)

Fig. 6.11

Regression statistics of muscle mass and muscle mass as a percentage of birthweight on birthweight and gestational age

SUMMARY OF RELATIONSHIPS

Dependent Variable (y)	Fig	Explanatory Variable (x)	Intercept (a)	Coefficient (b)	Correlation	SE	'p'
Muscle Mass (g)	5.7	Birthweight (kg)	-71.41	213.07	0.8	51.2	0.0001
	5.8	Gestational age (weeks)	-551.49	25.73	0.8	54.5	0.0001
Percentage muscle mass	5.9	Birthweight (kg)	8.75	5.18	0.35	4.3	0.05
	5.10	Gestational age (weeks)	-7.93	0.80	0.43	4.2	0.01

$Y = a + bx$

Table 6.1

Table 6.2

Published summary statistics of mean creatinine excretion rate at varying postconceptional ages.

	n	mean creatinine excretion	PCA
Modi & Hutton [In press]	89	71	204
Sutphen [1982]	15	71	211
Brion et al [1986]	42	85	216
Brion et al [1986]	63	97	228
Al-Dahhan et al [1988]	84	90	238
Brion et al [1986]	27	106	282
Brion et al [1986]	22	110	330
Brion et al [1986]	13	89	367
Brion et al [1986]	35	120	519

(creatinine excretion, umol kg^{-1} day^{-1}; PCA, postconceptional age in days)

7

URINE FLOW RATE AND OSMOLALITY

Urine flow rate

The measurement of urine flow rate is an important part of the assessment of renal function in the neonate. Unfortunately, as discussed elsewhere in this thesis, it is difficult to carry out accurately because of the problems of urine collection and because neonates frequently do not void completely. Urine osmolality is a frequently measured

parameter on 'spot' urine specimens; it has been suggested that optimal hydration is assured if urine osmolality is maintained within predefined limits [Coulthard & Hey 1985]. Immature neonates are regarded as having a limited concentrating and diluting capacity. In view of the risks in this group of vulnerable infants, of acute volume overload if subjected to a high infusion rate and conversely prerenal, potentially leading to intrinsic renal failure if dehydrated, it cannot be ethical to observe maximum and minimum urinary concentrations under such controlled conditions. The aim of this part of the study was therefore to observe maximum and minimum urine osmolalities achieved in the course of routine clinical management and to examine postnatal changes in urine flow rate and osmolality. The effects of respiratory function on these parameters are described in chapter 8.

Methods

Urine osmolality was measured in each of the individual sequential time periods throughout the entire study duration in the manner described in chapter 3 - Methods.

Mean daily urine osmolality and mean daily urine flow were calculated for each baby for each of the first seven days of life.

Results

Five hundred and twenty one measurements of urine osmolality were made in 34 infants in the first 7 days of life. The minimum urine osmolality recorded was 90 mosm l^{-1} on the fifth day of life in an infant of 32 weeks gestation. The maximum recorded osmolality was 1225 mosm $^{-1}$ on the second day of life in an infant of 29 weeks gestation; this infant had a urine flow rate at the time of less than 0.5 ml kg^{-1} h^{-1}.

Mean daily urine osmolality for each infant is expressed in boxplot format by postnatal age in figure 7.1; the numerical values are shown in table 7.1. There appears to be little fluctuation with postnatal age, with the median osmolality remaining between 345 - 401 mosm l^{-1}. Overall, the mean daily urine osmolality was 370 mosm l^{-1} (median 366, range 104 - 739).

Mean daily urine flow rate is shown in boxplot format in figure 7.2 (numerical values, table 7.2). There appears to be an increase between the first and second postnatal days. This has been further evaluated using multivariate analysis of variance allowing for between baby differences which confirms that there is a significant change in urine flow rate with postnatal age ($F_{6,116} = 8.04$, $p<0.001$).

Discussion

The observations here confirm that urine flow rate is low on the first day of life and rises subsequently. This is believed to be secondary to the increase in GFR that occurs at this time (chapter 5) and may also in part be due to the high circulating levels of arginine vasopressin (AVP) present in the infant in the perinatal period (chapter 2).

It is generally held that a urine output less than 1 ml kg^{-1} h^{-1} is suggestive of impaired renal function. This is because in the presence of a renal solute load of 15 mosm kg^{-1} day^{-1} and an approximate maximum urinary concentration of 500 - 700 mosm kg $water^{-1}$, solute retention might be expected to occur if urine flow rate is less than 1 ml kg^{-1} day^{-1} [Ziegler & Fomon 1971]. Extremely immature infants have considerably smaller solute loads on the first day of life, and in these infants it may be more appropriate to regard a urine flow rate of less than 0.5 ml kg^{-1} h^{-1} on day one of life and 1 ml kg^{-1} h^{-1} thereafter as abnormal.

High urine flow rates in the immediate newborn period are seen in infants with tubular damage, as a physiological response to fetal overhydration such as in maternal fluid overload and in the presence of polyhydramnios. The author [Modi 1988] has observed an infant who was noted to have a

high intrauterine urinary flow rate and in whom polyhydramnios was present. This infant was born at 28 weeks gestation and developed moderately severe hyaline membrane disease; despite this she had a high urinary flow rate of approximately 7 ml kg^{-1} hr^{-1} on the first day of life which persisted to five days.

It has been estimated that the most immature preterm infants might achieve a maximum urine flow rate of around 7 ml kg^{-1} h^{-1} [Coulthard & Hey 1985].

Water balance is maintained by altering urine volume and concentration. The ascending limb of the loop of Henle and the distal tubule function as the 'diluting' segments where reabsorption of solute takes place without water. The ability to form a concentrated urine is dependent on the hypertonic medullary interstitium established by the loop of Henle countercurrent system. The permeability to water of the distal tubule and collecting duct is controlled by the action of antidiuretic hormone. It has been shown that the peak urine flow of mature infants given a water load is the same as that of adults when expressed per unit body water [McCance et al 1954]. Coulthard and Hey [1985] have also recently challenged the widely held view that newborns have a reduced capacity for water excretion. They demonstrated that healthy preterm (29 to 34 weeks) babies were able to cope with

water intakes ranging from 96 -200 ml kg^{-1} day^{-1} from the third day of life, sodium intake remaining constant. Other studies of the effect of varying fluid loads in tiny babies have failed to maintain a constant sodium intake. It is likely that the morbidity associated with increased fluid intakes is in fact attributable to the increased sodium load [Bell et al 1980], mediated by failure to achieve a contraction in extracellular fluid volume [Stonestreet et al 1983]. Water and sodium should be prescribed independently and in particular, the use of 'fixed formula' parenteral solutions is ill advised.

Coulthard and Hey [1985] describe a minimum osmolality of 45 mosm kg^{-1} in a group of healthy infants, of less than 34 weeks gestation, receiving a liberal fluid intake. They estimate that the smallest babies are likely to have an upper limit of urine flow of around 7 ml kg^{-1} h^{-1}, with larger babies achieving double this rate. In contrast, in the study here involving a group of babies of similar gestational and postnatal age but who required ventilatory support, a minimum urine osmolality of 90 mosm kg^{-1} is noted. It may, of course, be that maximal diuresis was never achieved in this group of babies but in view of the risks of acute volume overload in such a clinically compromised group, it would be ethically unacceptable to subject these infants to such a procedure.

Urine osmolality is known to increase and free water clearance to decrease in hypoxic fetal lambs [Robillard et al 1981]. However the renal response to hypoxia appears to be gestation dependent. In lamb fetuses near term, hypoxia has been shown to result in a decreased renal blood flow, concomitant rise in plasma renin activity, increased AVP secretion, decreased heart rate and rise in mean arterial pressure. During the reactive hyperaemia seen following hypoxia urinary prostaglandin E and F2a rose. In contrast, lamb fetuses of greater immaturity showed none of these responses other than a rise in AVP in only half the animals studied [Robillard et al 1981]. AVP is present in the posterior pituitary of the eleven week old human fetus [Levina 1968]; concentrations increase up to 28 weeks gestation with relatively little increase thereafter [Schubert et al 1981]. Nephron sensitivity to vasopressin increases with maturity [Svenningsen & Aronsen 1974]. High renal prostaglandin E production in the newborn may interfere with cyclic AMP production and so diminish the cellular action of vasopressin [Joppich et al 1979].

The immature medulla is characterised by a limited osmotic gradient, a consequence of short loops of Henle , low urea production and high blood flow through the vasa recta. There is evidence to suggest that the renal solute gradient is the most important factor limiting the renal response to

vasopressin in that maximum urine osmolality achieved is higher during hypernatraemic dehydration [Svenningsen & Aronsen 1974]. Rees et al [1984] have shown that osmotic and volume stimuli are able to stimulate the secretion of vasopressin in preterm infants from 26 to 35 weeks gestation. In addition peaks of vasopressin secretion occurred in response to non osmotic stimuli, resulting in inappropriately concentrated urine. They show that despite the immature response to AVP the preterm neonate is at frequent risk of developing the syndrome of inappropriate AVP secretion during, for example, the development of pneumothoraces and large periventicular haemorrhage. The maximum urine osmolality achieved during their observations was 550 mosm kg^{-1}. The data presented here suggest that, given an appropriate stimulus, even extremely immature infants are able to produce urine of much higher osmolality.

Changes in urine flow rate and osmolar clearance are further discussed in chapter 13 and in relation to changing respiratory function in chapter 8.

Conclusions

1. Urine flow rate was seen to increase between the first and second day of life in a group of infants between 25 - 34 weeks gestation, whereas urine osmolality remained relatively constant.

2. The range of urine osmolality observed in this group of sick infants was 90 - 1225 mosm l^{-1}; the median was 366 mosm l^{-1}.

Figure 7.1

Daily urine osmolality (mosm l^{-1}) for each infant by postnatal age.

Box and whisker plot showing medians, interquartile range and extreme values. The numerical values are listed over (Table 7.1).

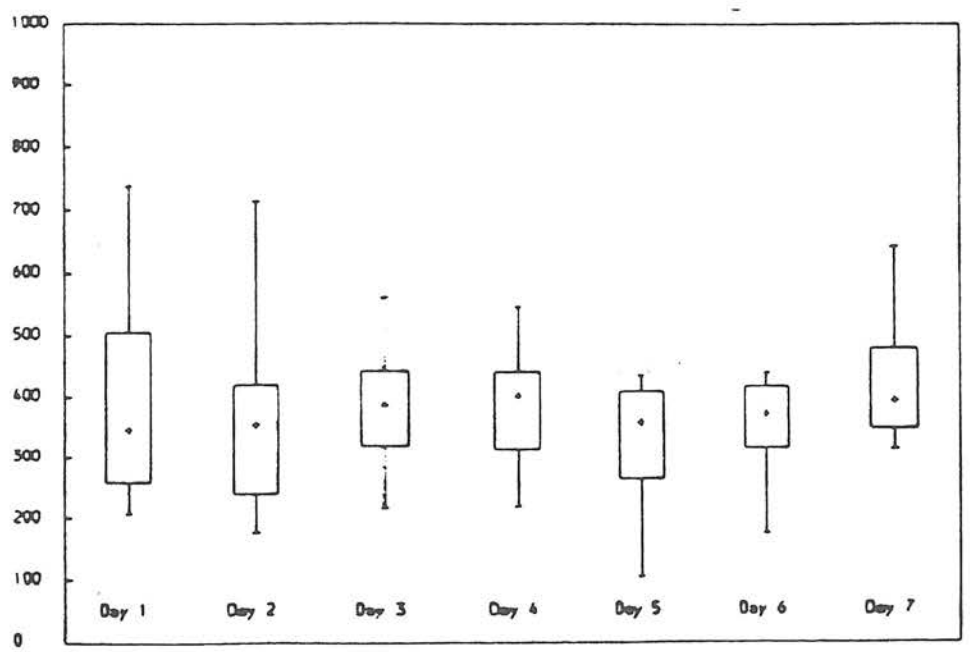


Table 7.1

Daily urine osmolality (mosm l^{-1}) for each infant by postnatal age.

(medians, interquartile range & extreme values)

day	minimum	Q_1	median	Q_3	maximum
1	209	259	345	506	739
2	177	239	353	419	715
3	216	318	386	443	562
4	218	313	401	439	544
5	104	264	356	408	434
6	174	314	370	416	438
7	313	345	393	477	641

Figure 7.2

Daily urine flow rate (ml kg^{-1} h^{-1}) for each infant by postnatal age.

Box and whisker plot showing medians, interquartile range and extreme values. The numerical values are listed over (Table 7.2).

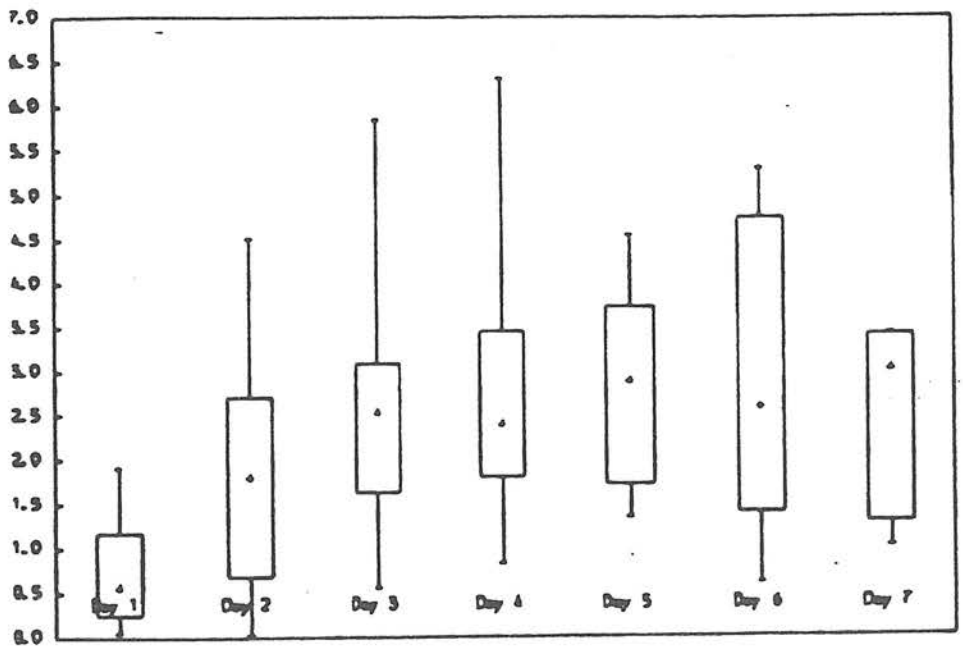


Table 7.2

Daily urine flow rate (ml kg^{-1} h^{-1}) for each infant by postnatal age.

(medians, interquartile range & extreme values)

day	minimum	Q_1	median	Q_3	maximum
1	0.05	0.24	0.56	1.17	1.9
2	0.02	0.68	1.79	2.71	4.52
3	0.55	1.62	2.52	3.08	5.83
4	0.81	1.79	2.39	3.44	6.31
5	1.33	1.71	2.87	3.71	4.55
6	0.60	1.39	2.57	4.74	5.30
7	0.99	1.28	3.00	3.40	3.42

8

SODIUM

Sodium homeostasis is dependent on the interplay between sodium and water balance. Derangements of water and sodium balance are commonplace in the preterm infant. There continues to be much discussion as to optimal fluid and sodium administration in very low birth weight infants [Costarino & Baumgart 1986, Lorenz et al 1982].

Sodium retention is a prerequisite of growth and characterises the developing fetus and infant. Yet urinary sodium losses are high in the preterm infant and in immature infants with respiratory disease, are widely held to be even higher [Hirsch et al 1980].

The early newborn period is characterised, in infants of all gestational ages, by a contraction of extracellular fluid volume. In preterm infants with respiratory disease this contraction is delayed and is marked by the diuresis that accompanies improving respiratory function. The loss of extracellular fluid entails the loss of sodium, the principal extracellular electrolyte. The trigger that initiates these postnatal adaptations is not known. The purpose of this part of the study was to investigate sodium handling during the first week of life and further, to examine the influence of respiratory disease.

Methods

Thirty four male neonates, of less than 34 weeks gestation and requiring ventilatory support from birth, formed the initial study group. This initial group is fully described in chapter 3 - Methods.

The volume and sodium content of all intravenous and intraarterial fluids, including blood products and flush

fluids, was recorded. Blood samples were collected at times of clinical sampling upto a maximum of one sample in each 4 hour period. Urine was continuously collected; infants were weighed at birth and at intervals thereafter; these techniques and those of sodium, potassium, osmolality and creatinine assay and four hourly arterial blood gas measurements are described in chapter 3 - Methods.

Meconium/stool loses were not measured. Frusemide is not administered routinely in this neonatal unit and only three doses were given during the entire period of study observations. Each individual study was terminated when leakage of urine from the collection system occurred.

Sodium intake, sodium output, sodium balance, fractional sodium excretion, urinary sodium concentration, urinary potassium concentration, the ratio of urinary sodium to potassium and the percentage of sodium exchanged for potassium in the distal tubule were calculated for each baby for each of the first seven days of life. The calculation of alveolar-arterial oxygen gradient ($AaDO_2$) and fractional sodium excretion (FeNa) are as described in chapter 3 - Methods.

The percentage of sodium exchanged for potassium in the distal tubule, which may be considered to reflect the

action of aldosterone, was estimated from the following formula [Kaloyanides et al 1969]:

(UK.100)/(UK + UNa)

Weight loss as a percentage of birth weight was calculated daily for each baby and expressed in relation to postnatal age.

(birth weight - actual weight).100/birth weight

Analysis in relation to respiratory disease

Infants who develop respiratory problems secondary to immaturity frequently do not display a clear improvement in respiratory function in the days following birth. Instead hyaline membrane disease may merge into chronic lung disease, complicated by patent ductus arteriosus, infection and cor pulmonale and ultimately lead to death. The second part of this study was designed to examine changes in sodium handling in preterm infants who demonstrated a clear and sustained improvement in respiratory function. From the initial group of 34 infants, 26 were suitable for further analysis in relation to respiratory disease on the basis of a clear and sustained improvement in respiratory function, during the study period, as described below.

Aggregated mean daily $AaDO_2$ was initially plotted against day for each of the 34 babies individually. Babies in whom there was a clear and sustained improvement in respiratory function were subjected to further analysis (n=26). This point of improvement was defined as the first day on which the mean daily $AaDO_2$ was less than that of the preceding day but greater than that of the subsequent day. The use of mean daily $AaDO_2$ was used to smooth the within day variation to allow this precise definition; subsequent analysis was based on 4 hourly time periods.

Initial data exploration involved the use of linear regression and two sample T testing. Final analysis utilised multivariate analysis of variance, allowing for differences between babies, respiratory phases and actual $AaDO_2$. The simplest adequate model was chosen.

Multivariate analysis of variance, having allowed for between baby differences, was also used to compare the following variables during the periods of deteriorating and improving respiratory function: $AaDO_2$, urine flow rate, creatinine clearance, osmolar clearance, free water clearance, fractional sodium excretion, urinary sodium to potassium ratio, percentage distal sodium exchange, plasma sodium, creatinine and osmolality, urinary osmolality.

Sodium retention and $AaDO_2$ were then plotted against time period for each baby individually. Smooth curves were fitted through the points using the spline fitting routine of SAS (Statistical Analysis System) with a parameter value of 50.

The possibility that any change in sodium "retention" was due to the effect of postnatal maturation was explored in two ways. Age (as 4 hourly period) was examined in an analysis of variance together with respiratory phase and an analysis of covariance was performed for the eight babies who did not show an improvement in respiratory function during the study period.

Results

The mean birthweight of the 34 babies comprising the initial study group was 1.18 kg (median 1.12, range 0.680 - 1.832) and mean gestational age 28.5 weeks (median 28, range 25 - 34).

Sodium intake and output, urinary sodium concentration, sodium balance, fractional sodium excretion, urinary sodium to potassium ratio, percentage distal sodium exchange, urinary potassium concentration and weight loss as a percentage of birth weight, for the first seven days of life, are depicted as box plots showing median,

interquartile and extreme values and in tabular form (Figs 8.1 - 8.9) (Tables 8.1 - 8.9).

Sodium intake increased over the first five days of life (Fig 8.1); sodium output increased over days 1 through 3 but then appeared to stabilise (Fig 8.2). Though the median sodium intake was 3.61 mmol kg^{-1} day^{-1} (mean 4.04) and median urinary loss 3.96 mmol kg^{-1} day^{-1} (mean 4.95) over this period, the range of values was wide, intake ranging from 0.20 mmol kg^{-1} day^{-1} to 24.45 mmol kg^{-1} day^{-1} and output from 0.25 mmol kg^{-1} day^{-1} to 17.42 mmol kg^{-1} day^{-1}.

The median urinary sodium concentration was 88 mmol l^{-1} (mean 87) with a range of values from 9 mmol l^{-1} to 187 mmol l^{-1} (Table 8.3). Multivariate analysis of variance, allowing for between baby variation and gestational age influences, demonstrated a significant difference between mean urinary sodium concentration on days 1 - 2 (71.3 mmol l^{-1}, 95% confidence interval 58.8 - 83.8) and days 3-7 (97.7, 95% confidence interval 88.9 - 106.4) ($F = 16.74$, $p<0.0001$). Although analysis of grouped data showed higher urinary sodium concentrations to be associated with higher total daily sodium loss, the estimation of daily sodium loss from spot urinary sodium concentration, a common clinical practice, is likely to be extremely inaccurate. The range of measured total daily sodium loss is presented for four ranges of urinary sodium in Table 8.10.

Median sodium balance was positive for the first two days of life but negative on days 3 through 7. A plot of cumulative sodium balance for the first week of life shows positive balance for the first three days of life, negative for the next three and with decreasing negative balance attained by day 7 (Fig 8.10).

Median fractional sodium excretion (Fig 8.5) was 4.6% (mean 5.2%, 95% confidence interval 4.5-6.3). Linear regression showed FeNa to fall with increasing gestational age; this effect was confirmed on multivariate analysis of variance allowing for postnatal age and between baby differences ($F = 12.44$, $p<0.0001$).

Multivariate analysis of variance, allowing for gestational age and between baby differences, also showed mean FeNa on days 1-2 (4.44, 95% confidence interval 2.56 - 6.32) to differ from that on days 3-7 (6.06, 95% confidence interval 5.2 - 6.92) ($F = 15.3$, $p<0.0001$).

The influence of gestational age and postnatal age was also examined in relation to the ratio of urinary sodium to potassium and percentage distal sodium exchange using multivariate analysis of variance. Urinary sodium to potassium ratio increased significantly with postnatal age

(F=4.14, p=0.001) (Fig 8.6) but was not influenced by gestational age F = 0.48, p = 0.87) having allowed for between baby differences. The median ratio over the first week was 2.72 (mean 3.69, 95% confidence interval 1.83 - 5.55); the median ratio on day 1 was 2.08 (mean 2.52, 95% confidence interval 1.02-4.02) increasing to 6.00 (mean 6.89, 95% confidence interval 0.71 - 13.07) on day 7.

Percentage distal sodium exchange decreased significantly with postnatal age (F=3.18, p<0.01) (Fig 8.7) and was not influenced by gestational age (F=1.82, p=0.09); the median value during the first week was 26.89 (mean 30.24, 95% confidence interval 27.02 - 33.46); the median value on day 1 was 32.84 (mean 39.27, 95% confidence interval 27.15 - 51.39): the median value on day 7 was 15.9 (mean 24.87, 95% confidence interval -0.5 - 49.99).

Urinary potassium concentration showed no significant change with postnatal age (F=1.98, p=0.08) (Fig 8.8). Median urinary potassium concentration was 30.03 $mmol^{-1}$ (mean 35.87, 95% confidence interval 31.57 - 40.17).

Weight loss as a percentage of birth weight was extremely variable, with many infants showing a failure to achieve any postnatal weight loss (Fig 8.9). The median weight loss by day 7 was 14.6% (mean 9.24%).

Influence of respiratory function on sodium handling.

The median birthweight of the 26 babies suitable for analysis of sodium handling in relation to respiratory function was 1.170 kg (range 0.780 - 1.830) and median duration of total study time 3.18 days (range 1.04 - 11.00). The median birthweight and duration of study for the eight babies unsuitable for analysis in relation to respiratory function was 1.070 kg (range 0.680 - 1.632) and 1.56 days (range 0.5 - 3.02).

Initially a linear regression analysis of pooled data for all infants was performed (Fig 8.11). This showed sodium balance to increase with $AaDO_2$; i.e. suggested that the poorer the respiratory function and greater the $AaDO_2$, the greater the sodium retention. The relationship is summarised by the regression equation

$$\textbf{sodium balance} = -3.69 + 0.00923\ AaDO_2$$

sodium balance, mmol kg^{-1} day^{-1}; $AaDO_2$, torr

The coefficient of $AaDO_2$ is positive, $p<0.0001$; i.e. the correlation of 0.4 is highly significant.

In the second stage of the analysis, sodium balance before the point of improvement in respiratory function was compared with sodium balance after the point of improvement

using a two sample T test. Sodium balance changed from positive (mean 1.42 mmol kg^{-1} day^{-1}; SD 3.97) during the phase of worsening respiratory function to negative (mean - (minus) 1.99 mmol kg^{-1} day^{-1}; SD 3.92) during improving respiratory function. The T statistic of 3.98 is highly significant when compared with a T distribution with 99 degrees of freedom, $p<0.0001$. This suggests that the decrease in sodium balance is real despite the non independence of the daily values.

Sodium handling during the periods of deteriorating and improving respiratory function was then analysed using analyses of variance of sodium balance in 4 hourly periods. This confirms that the difference before and after the improvement in respiratory function is significant (31.85 cf. $F_{1, 390}$, $p<0.0001$), having allowed for between baby differences (3.65 cf. $F_{25, 390}$, $p<0.0001$).

The correlation of sodium balance with $AaDO_2$, noted initially, is accounted for by the influence of respiratory phase, i.e. whether prior to or after the point of improvement. Within each respiratory phase there was no correlation between sodium balance and $AaDO_2$. This association is also presented for visual inspection in the form of plots of sodium balance and $AaDO_2$ against time period for individual infants. These plots reveal, in 18 of the 26 cases, a temporal relationship between change in

sodium balance and change in $AaDO_2$ despite the variation in values; changes in sodium handling parallel the changes in $AaDO_2$ with relative sodium retention occurring during deteriorating respiratory function, changing to relative sodium loss with the start of improving function. The plots are presented in figures 8.12 - 8.18.

In view of the possibility that any change in sodium "retention" might be a consequence of postnatal maturation, analysis of variance of sodium "retention" by respiratory phase was performed, allowing for postnatal age (as 4 hourly period). This confirms the highly significant effect of respiratory phase (17.65, cf. $F_{1,431}$, $p<0.001$) having allowed for postnatal age. In addition an analysis of covariance for the eight babies who did not show an improvement in respiratory function during the study period, failed to show any decrease in sodium "retention" with postnatal age (1.87, $F_{1,72}$, $P=0.176$).

Values for sodium balance, $AaDO_2$ and other parameters of renal function by respiratory phase are presented in Table 8.11. Comparison was made using multivariate analysis of variance having allowed for between baby differences. The "estimated contrasts" are estimates of the "true" difference, having allowed for between baby variation. An increase in sodium loss, fractional sodium excretion and osmolar clearance is shown during the improving phase of

respiratory function with no change in free water clearance.

Discussion

Sodium handling in the immature infant is characterised by three features: urinary sodium losses are high, the natriuretic response to a salt load is blunted and there is a net stimulus to conserve sodium - a prerequisite of growth.

The first step in the process of sodium reabsorption occcurs in the proximal tubule. Here the absorption of sodium and water is isotonic and governed by both active and passive forces. Physical factors affecting peritubular capillary fluid resorption influence sodium transport at the proximal tubule [Giebisch 1969]. These factors have not been studied in the human preterm neonate. However animal studies do not suggest that proximal tubular reabsorption is responsible for the sodium retention that characterises the infant [Spitzer 1982]. Micropuncture studies of "late proximal" tubules at various stages of maturation also suggest that the fraction of filtrate reabsorbed is no greater than in the adult nephron [Spitzer & Brandis 1974]. The sodium retention of infancy must therefore be presumed to be due to enhanced reabsorption at the distal tubule. Coulthard and Hey [1985] have estimated distal sodium

delivery in babies under 34 weeks gestation to be between 17 and 20% of the glomerular filtrate, a similar value to that reported by Rodriguez-Soriano et al [1983].

The renin-angiotensin-aldosterone system rather than physical forces appear to be significant with regard to sodium reabsorption at the distal tubule. Aldosterone secretion is relatively elevated in the newborn [Dillon et al 1976, Sulyok et al 1979 i]. There is evidence to suggest a limited responsiveness of the distal tubule to aldosterone in extremely immature infants which increases with maturation. The retention of sodium during growth and the blunted natriuretic response of the preterm neonate to a saline infusion is thus believed to be due to the high level of activity of the renin-angiotensin-aldosteone system. Conversely the high renal sodium losses of the extremely immature infant appear to be due in part to the limited responsiveness of the distal tubule to aldosterone stimulation [Spitzer 1982]. Sulyok et al [1979 ii], have shown that though preterm infants, in response to negative sodium balance, are able to augment plasma renin activity to values above those found in full term infants, their adrenals fail to respond adequately. The high urinary sodium losses of the preterm baby [Engelke et al 1978, Ross et al 1977, Sulyok et al 1979 ii] have also been attributed to poor proximal reabsorption [Sulyok et al 1979 iii]. In the newborn rat kidney, both the total reabsorbtive

capacity of the proximal tubule and the activity of Na/K ATPase, the enzyme determining active sodium transport, increase postnatally [Larsson et al 1983]. Fractional sodium excretion decreases with increasing gestational age to around 0.2% in full term neonates [Siegel & Oh 1976]. The wide range of values for fractional sodium excretion shown here, with a mean of 5.4%, accords with the findings of other workers [Ross et al 1977, Siegel & Oh 1976].

Sodium balance in the first week of life is similarly held to be consistently negative [Al-Dahhan et al 1983, Butterfield et al 1960, Engelke et al 1978] though a criticism that can be levelled at these studies is the paucity of data relating to the first two days of life. In addition the studies of Al-Dahhan et al and Butterfield et al were confined to healthy newborns. Such reports have led to the suggestion that infants of less than 35 weeks gestation should receive sodium supplements of 4-5 mmol kg^{-1} day^{-1} during the first two postnatal weeks [Al-Dahhan et al 1983] and recommendations to this effect are now to be found in standard textbooks of neonatal care [Roberton 1986]. In marked contrast, the data presented here show cumulative sodium balance to be positive for the first three days of life.

In the fetus in utero a urinary sodium concentration in excess of 100 umol l^{-1} is predictive of poor renal

function [Golbus et al 1985], yet, postnatally, such levels are often seen in the presence of ostensibly normal function. An increased GFR, such as occurs in the postnatal period, without a concomitant increase in tubular resorptive capacity would explain this observation and has been used as evidence of functional glomerulotubular imbalance [Aperia et al 1981, Aperia et al 1983]. A morphological imbalance is known to exist in the preponderance of glomerular over tubular development [Fetterman et al 1965]. The postnatal urine flow rate, after the period of initial oliguria, is however similar to the intrauterine flow rate despite the increase in GFR. Tubular resorptive capacity for water therefore appears to have matured pari passu with glomerular filtration, suggesting an alternative explanation for the high urinary sodium losses in the immediate postnatal period.

Aldosterone increases sodium absorption and potassium excretion at the distal tubule and thus the urinary sodium potassium ratio is an index of aldosterone dependent distal tubular activity [Ganong & Mulrow 1958]. Similarly the percentage of sodium exchanged for potassium in the distal tubule may be considered to reflect the action of aldosterone. Preterm infants with respiratory disease have also been shown to have high aldosterone levels. This study has shown a rise in urinary sodium/potassium ratio and fall in the percentage of sodium exchanged for potassium in the

distal tubule with postnatal age in preterm infants with respiratory disease, during the first week of life. This might imply a decrease in aldosterone concentration, decreasing tubular responsiveness to aldosterone or another natriuretic stimulus. Siegel et al [1973] found aldosterone levels to be similarly elevated in infants both with and without hyaline membrane disease. Tubular responsiveness is believed to rise with maturation and to be accelerated after birth [Al-Dahhan 1983].

It would appear therefore that an alternative natriuretic stimulus is responsible for the increased urinary sodium losses in this group of infants. This conclusion is further strengthened by the finding that urinary potassium losses show no change with postnatal age. The question of an alternative natriuretic stimulus is further discussed in the next section.

The influence of respiratory function.

Following birth, the neonate experiences a contraction in extracellular fluid volume [Shaffer et al 1986 i] , with concomitant net loss of sodium, the principle extracellular electrolyte. It thus appears that the stimulus to retain sodium that characterises the growing infant is temporarily overruled during the period of postnatal adaptation. It is not known what triggers the postnatal contraction in

extracellular fluid volume. It may be argued however, that a negative sodium balance in the first day or days of life is an appropriate response to the onset of postnatal existence.

In healthy, mature infants the postnatal contraction in extracellular fluid volume occurs rapidly and relatively imperceptibly, only marked in some measure by varying degrees of weight loss. In the immature infant with respiratory disease, the postnatal contraction in extracellular fluid volume is delayed and occurs with the well recognised diuresis that accompanies improving respiratory function. The mechanism of this diuresis has been the subject of several studies but has not yet been adequately explained [Costarino et al 1985, Engle et al 1983, Heaf et al 1982].

The data presented here suggest that the diuresis that accompanies improving respiratory function in preterm infants may be consequent on an increase in sodium excretion. Earlier suggestions that the diuresis represented an improvement in renal function consequent on improved oxygenation [Cort 1962, Guignard et al 1976] were refuted when it was shown that the diuresis was not initiated subsequent to the improvement in respiratory function [Engle et al 1983, Heaf et al 1982, Langman et al 1981]. Certain authors [Costarino et al 1985, Engle et al

1983, Heaf et al 1982, Langman et al 1981] have concluded from their findings that diuresis precedes the improvement in respiratory function. However careful examination shows that their data may equally be interpreted as showing that the start of diuresis follows the start of improvement in respiratory function and that continuing diuresis then accompanies continuing respiratory improvement.

The data presented here characterise the alterations with respiratory improvement as that of a natriuresis, with increased sodium loss, fractional sodium excretion and osmolar clearance but with no increase in free water clearance (Table 8.11). Costarino et al [1985] interpret their data as characterising a water diuresis and the elimination of an endogenous water load. They refute the possibility that the increased urine flow follows an increase in solute excretion despite data showing an increase in sodium excretion during the diuretic phase and a change in mean sodium balance from -0.1 mEq kg^{-1} day^{-1} in the prediuretic phase to -0.9 and -1.1 mEq kg^{-1} day^{-1} in the diuretic and post diuretic phases. Although this difference is not significant the sample size of six infants lacks power; given a standard deviation of 2.0 and if the difference of 0.8 mEq kg^{-1} day^{-1} were real, at least 30 babies would be needed to achieve a 50% chance of reaching 10% significance. Their data may therefore be interpreted as lending support to the findings presented here.

Changes in sodium excretion cannot be attributed to changes in urine flow rate. Coulthard and Hey [1985] have shown that preterm babies are able to maintain a stable sodium balance despite fluctuations in urine flow rate. Engle et al [1983] ruled out a primary effect on water handling mediated by arginine vasopressin, showing no change in plasma or urinary levels during the diuretic phase. It has been argued that the reduction in sodium excretion is secondary to a fall in GFR. However a reduced capacity for sodium excretion cannot be attributed per se to a low GFR [Spitzer 1982]; a GFR of 0.25 ml kg^{-1} min^{-1} will, in a 1 kg infant, still result in the hourly filtration of approximately 2 mmol of sodium. A hypoxic renal insult is, in addition, likely to result in tubular loss of sodium. In contrast it has been shown here, that during deteriorating renal function there is a net stimulus to retain sodium.

Recently there has been much speculation as to the role of human atrial natriuretic peptide (ANP) during postnatal adaptation [Shaffer et al 1986 ii, Tulassay et al 1987, Kojima et al 1987]. ANP is, in the neonate, released from the left atrium in response to increases in left atrial pressure [Andersson et al 1988]. It may be postulated that the postnatal fall in pulmonary vascular resistance and increased left atrial return will lead to

ANP release. Kojima et al [1987] report a rise in concentration of ANP during the diuretic phase of respiratory distress syndrome; these workers did not however study the relationship between respiratory function and level of ANP. They suggest instead that endogenous water overload and an expanded extracellular volume may be responsible for the release of ANP in the newborn. Tulassay et al [1987], though showing that plasma ANP, in full term neonates, rises during the period of early postnatal weight loss and falls as weight gain commences, failed to examine sodium handling during these changes. Shaffer et al [1986 ii] also describe raised levels of ANP in ventilated, preterm infants, but claim no correlation exists between ANP concentration and sodium excretion. This interpretation is open to criticism given the lack of longitudinal data; sequential measurements in individual babies are necesssary for, as we have shown, there is considerable between baby variation in sodium excretion.

Negative sodium balance, in infants of less than 34 weeks gestation, is held to be the norm in the first two weeks of life [Judd et al 1987]. This belief is based on studies in healthy infants. Equally, infants with respiratory distress are held to have a greater degree of renal salt loss [Hirsch et al 1980]. This study shows that changes in sodium handling closely follow changes in respiratory function as measured by $AaDO_2$ [Modi & Hutton

1990]. Prior to the improvement in respiratory function, these infants continued to exhibit a net stimulus to retain sodium, behaving as though still in utero. After the improvement in respiratory function sodium retention changed to sodium loss. This change in sodium handling is highly statistically significant; the temporal relationship has also been demonstrated in the form of longitudinal data for individual infants presented as small scale time plots.

During postnatal respiratory adaptation, including recovery from hyaline membrane disease, pulmonary vascular resistance falls, increasing left atrial return. It may be speculated that the association demonstrated here, between sodium handling and respiratory function, may be explained by the rise in the level of a natriuretic agent triggered by an increase in pulmonary venous return; in other words that a change in sodium handling, caused by a primary natriuretic stimulus, brought about by postnatal respiratory adaptation, may be the trigger that initiates the contraction in extracellular fluid volume that characterises early postnatal existence in all gestational age groups; if so, these observations lend support to the suggestions that the natriuretic agent, atrial natriuretic peptide, is important in postnatal adaptation. Further studies are clearly necessary to clarify these relationships.

Estimated changes in extracellular fluid volume.

A plot of cumulative sodium balance for the first week of life shows positive balance for the first three days of life, negative balance for the next three days and then decreasing negative balance on day seven (Fig 8.10). By the end of the first week of life the infants had lost approximately 10% of their birth weight. The cumulative sodium balance at this time was - (minus) 4.7 mmol kg^{-1} (Fig 8.10). As extracellular fluid is isotonic, such a sodium loss corresponds to an extracellular volume loss of approximately 30 ml kg^{-1} or 3%. The additional 7% weight loss must therefore presumably represent catabolic losses. Stonestreet et al [1983], studying a comparable group of low birth weight infants receiving a 'high' sodium intake of 4.5 mmol kg^{-1} day^{-1}, describe a weight loss of 11.8%, but similarly to the study reported here, only a slight decrease in extracellular fluid volume (ECFV) as measured by inulin space. It is uncertain what constitutes optimal postnatal extracellular space contraction but it is likely that it should be in excess of 3%. Friis-Hansen [1971] showed the extracellular fluid compartment in infants of 28 - 32 weeks gestation to be aproximately 52% of total body weight and Kagan et al [1972] describe this space, at 6 days of age, in a similar group of infants, to be of the order of 40%, suggesting a 12% reduction. In the study by Stonestreet et al, the group of infants receiving a 'low'

sodium intake of 3.1 mmol kg^{-1} day^{-1} achieved an ECFV contraction of about 7%

Inappropriate sodium and water administration will eventually lead to volume overload and expansion of the extracellular space [Janovsky et al 1967]. Stonestreet et al [1983] have shown a high sodium and water intake to inhibit the normal postnatal contraction of the extracellular fluid compartment. Atrial natriuretic peptide is known to be increased in the presence of volume overload [Rascher et al 1985; Lang et al 1985]. Iatrogenic expansion of the extracellular space stimulating natriuresis may thus be responsible for the large sodium losses often seen in sick, preterm babies who are also strikingly oedematous. In addition, a delay in ECFV contraction may underly the increased morbidity in terms of patent ductus arteriosus, respiratory disease and necrotising enterocolitis, described in infants receiving high rate intravenous infusions of sodium and water [Bell et al 1980; Bell & Oh 1983]. Vanpee et al [1988] have recently presented evidence to show that the high sodium losses of immature infants may not be due to renal wastage; they suggest that extrarenal factors may be responsible.

The infants in the study reported here received a mean daily sodium intake of 4.04 mmol, a figure similar to the high intake group of Stonestreet et al. The data presented

here suggest that a high catabolic weight loss masks the restricted extracellular fluid loss. It would seem that in view of the possible consequences of an expanded extracellular fluid space discussed above, sodium supplementation should be delayed until after the period of physiological diuresis and should then be instituted at a rate sufficient to allow for the high urinary salt losses.

Conclusions

1. The median urinary sodium concentration in the group of infants studied was 88 mmol l^{-1} (mean 87); the median fractional sodium excretion was 4.6% (mean 5.4%); the median urinary sodium to potassium ratio was 2.72 (mean 3.69); urinary sodium concentration, fractional sodium excretion and urinary sodium to potassium ratio showed a significant increase with postnatal age during the first week of life.

2. Fractional sodium excretion fell significantly with increasing gestational age; urinary sodium to potassium ratio and percentage distal sodium exchange were uninfluenced by gestational age.

3. Positive sodium retention is seen in preterm babies with respiratory disease; sodium retention changes to sodium loss at a point coinciding with improvement in respiratory function.

4. The diuresis that accompanies the improvement in respiratory function in infants with hyaline membrane disease, is characterised as a natriuresis, with increased creatinine clearance and osmolar clearance but unchanged free water clearance.

5. Contraction in extracellular fluid volume probably accounts for an estimated 3% of weight loss during the first week of life in this group of infants - who received early sodium supplementation; the remaining weight loss may represent excessive catabolism.

Hypotheses

1. The diuresis that signals improving respiratory function during the course of hyaline membrane disease is brought about by a change in sodium handling. This may be mediated by the release of atrial natriuretic peptide triggered by the fall in pulmonary vascular resistance and increased left atrial return, that characterises improving hyaline membrane disease. This may also be the mechanism triggering the extracellular fluid volume contraction that is a feature of postnatal adaptation in newborn infants of all gestational ages.

2. The high urinary sodium losses that are a feature of early postnatal life, in extremely immature infants, may be a consequence of delayed contraction of the extracellular space brought about by inappropriate early sodium supplementation.

Figure 8.1

Sodium intake (mmol kg^{-1} day^{-1}) by postnatal age.

Box and whisker plot showing medians, interquartile range and extreme values. The numerical values are listed over (Table 8.1).

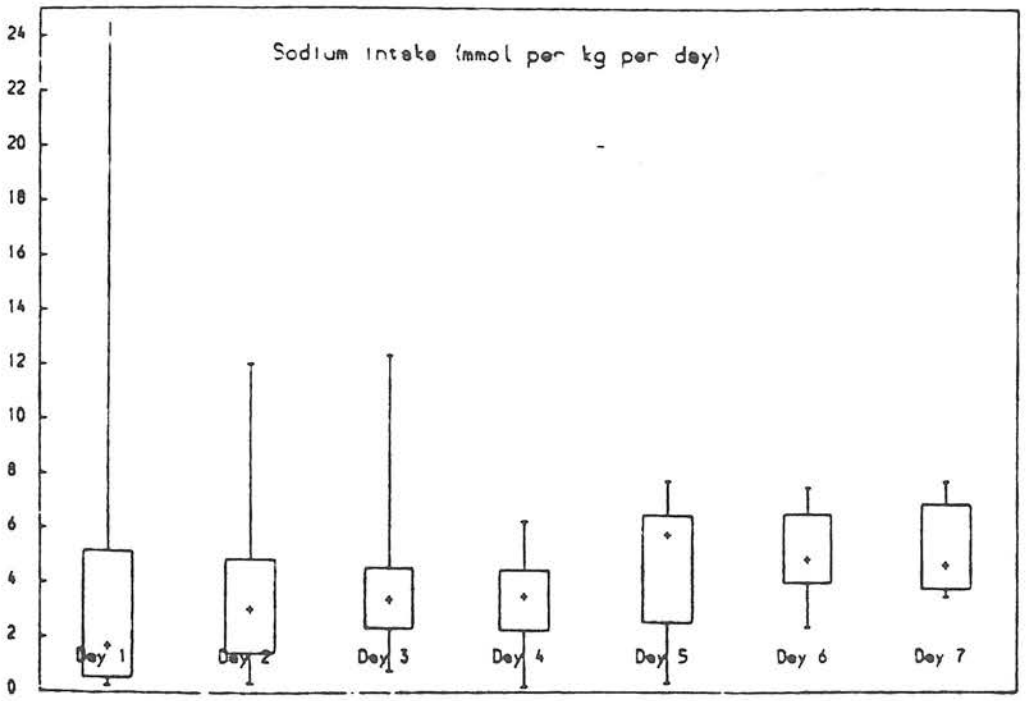


Table 8.1

Sodium intake (mmol kg^{-1} day^{-1}) by postnatal age.

(medians, interquartile range & extreme values)

day	minimum	Q_1	median	Q_3	maximum
1	0.26	0.48	1.11	5.47	24.45
2	0.35	1.46	3.04	4.92	12.00
3	0.78	2.42	3.40	4.60	12.30
4	0.20	2.27	3.50	4.45	6.24
5	0.34	2.56	5.73	6.46	7.48
6	2.38	4.00	4.84	6.50	7.48
7	3.47	3.77	4.63	6.85	7.69

Figure 8.2

Sodium output (mmol kg^{-1} day^{-1}) by postnatal age.

Box and whisker plot showing medians, interquartile range and extreme values. The numerical values are listed over (Table 8.2).

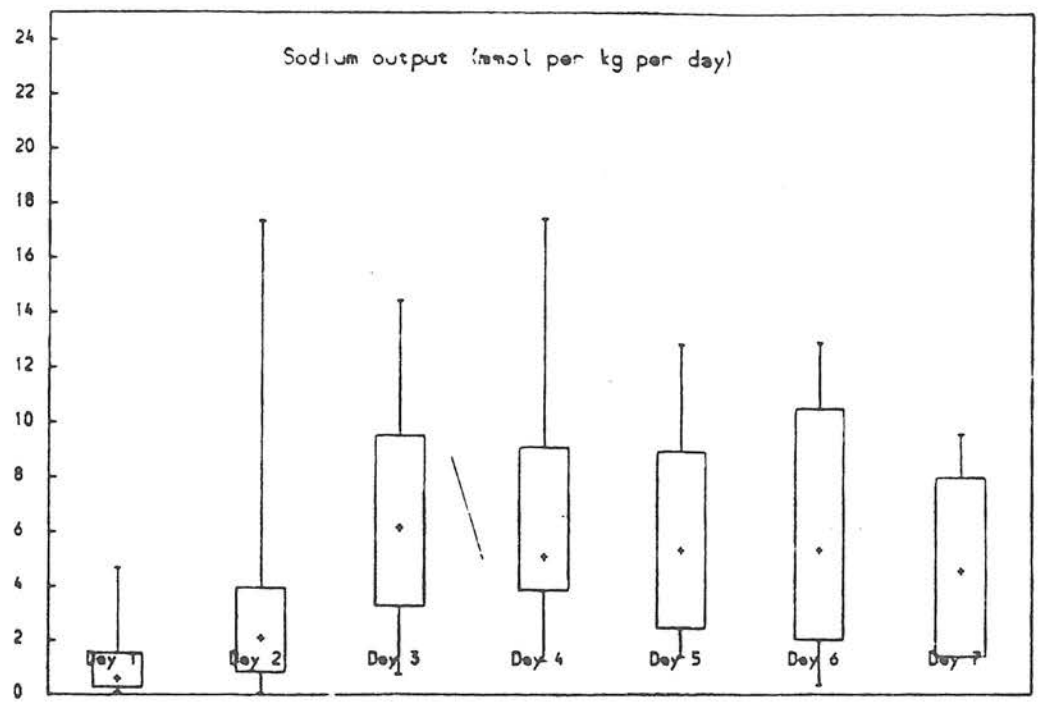


Table 8.2

Sodium output (mmol kg^{-1} day^{-1}) by postnatal age.

(medians, interquartile range & extreme values)

day	minimum	Q_1	median	Q_3	maximum
1	0.25	0.64	1.43	1.78	4.69
2	0.54	1.20	2.54	4.18	17.34
3	0.73	3.30	6.16	9.52	14.45
4	1.24	3.87	5.09	9.08	17.42
5	1.39	2.47	5.34	8.94	12.85
6	0.35	2.04	5.35	10.52	12.92
7	1.38	1.41	4.57	8.00	9.58

Figure 8.3

Urinary sodium concentration (mmol l^{-1}) for each baby by postnatal age.

Box and whisker plot showing medians, interquartile range and extreme values. The numerical values are listed over (Table 8.3).

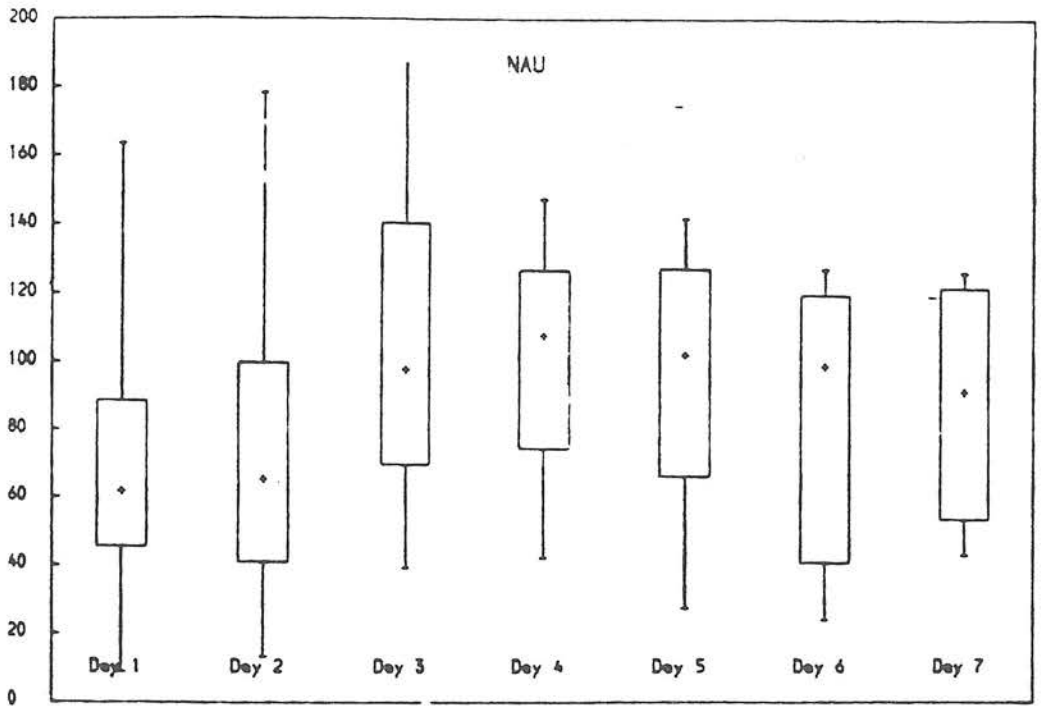


Table 8.3

Urinary sodium concentration (mmol l^{-1}) for each baby by postnatal age.

(medians, interquartile range & extreme values)

day	minimum	Q_1	median	Q_3	maximum
1	9	44	59	88	163
2	13	42	65	99	178
3	39	69	97	139	187
4	42	74	108	127	147
5	28	66	102	127	142
6	24	41	99	119	127
7	43	54	91	122	126

Figure 8.4

Daily sodium balance (mmol kg^{-1} day^{-1}) by postnatal age.

Box and whisker plot showing medians, interquartile range and extreme values. The numerical values are listed over (Table 8.4).

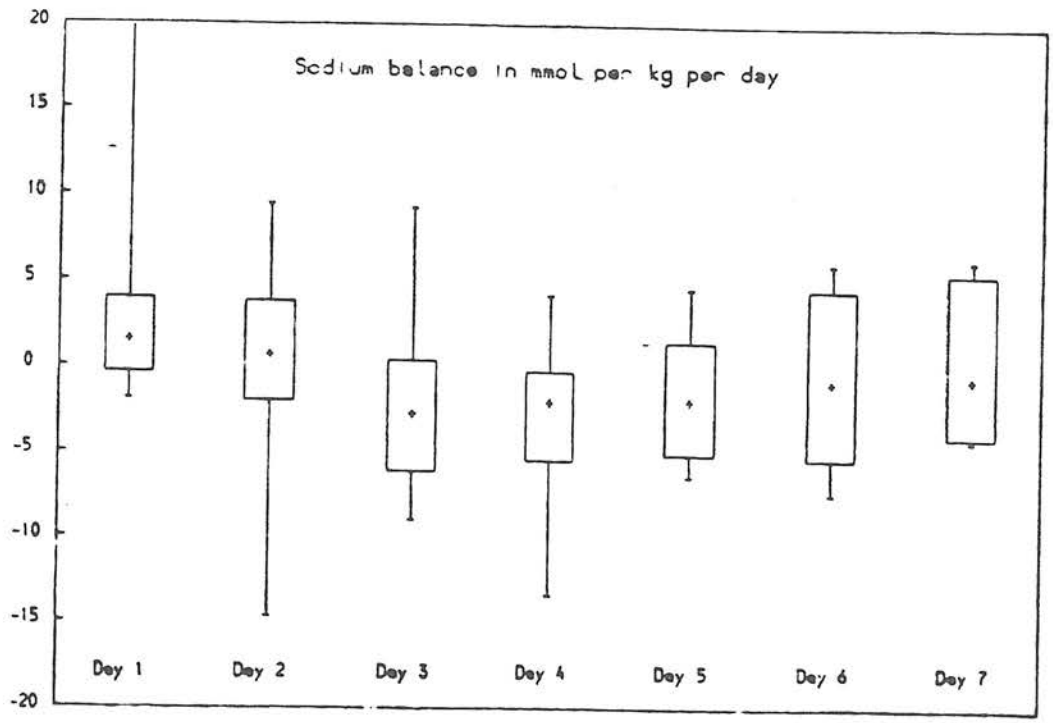


Table 8.4

Daily sodium balance (mmol kg^{-1} day^{-1}) by postnatal age.

(medians, interquartile range & extreme values)

day	minimum	Q_1	median	Q_3	maximum
1	-1.90	-0.14	1.15	4.65	19.76
2	-14.67	-2.20	0.23	4.30	9.46
3	-8.98	-6.12	-2.76	0.34	9.25
4	-13.70	-5.49	-2.08	-0.30	4.16
5	-6.40	-5.12	-1.96	1.47	4.59
6	-7.40	-5.74	-0.86	4.34	6.06
7	-4.29	-4.07	-0.66	5.46	6.28

Figure 8.5

Fractional sodium excretion by postnatal age.

Box and whisker plot showing medians, interquartile range and extreme values. The numerical values are listed over (Table 8.5).

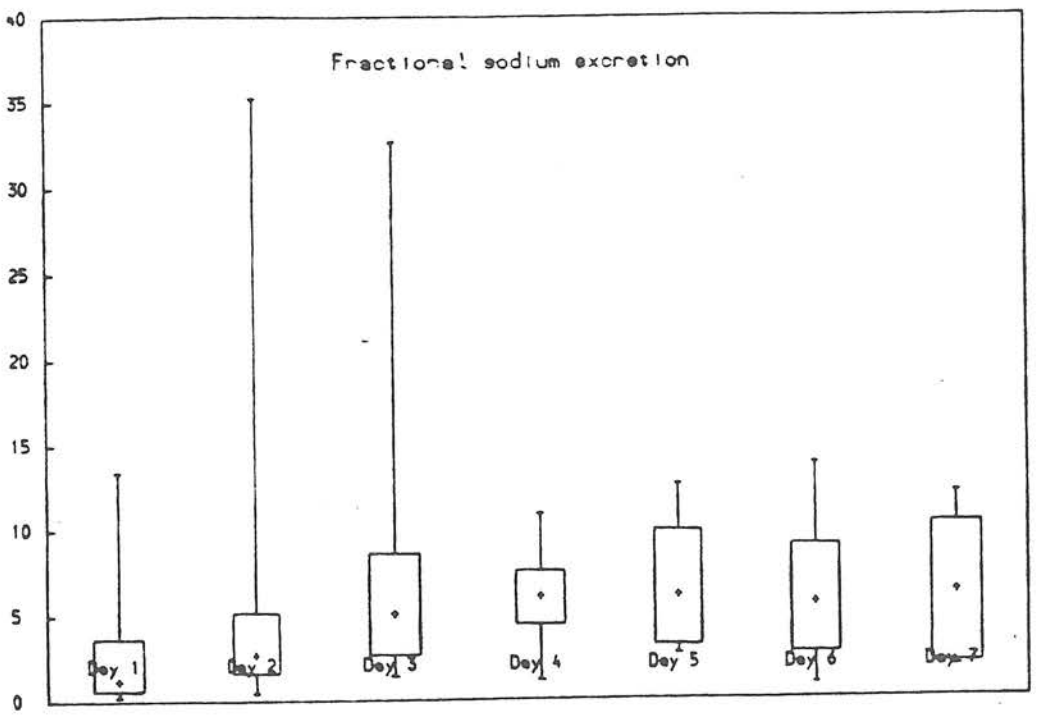


Table 8.5

Fractional sodium excretion by postnatal age.

(medians, interquartile range & extreme values)

day	minimum	Q_1	median	Q_3	maximum
1	0.93	1.31	2.46	3.40	13.40
2	0.45	1.66	3.14	5.33	35.21
3	1.42	2.55	4.86	8.13	32.42
4	1.13	4.39	6.00	7.51	10.87
5	2.67	3.17	6.04	9.86	12.57
6	0.86	2.71	5.58	8.99	13.78
7	1.81	2.03	6.17	10.28	12.03

Figure 8.6

Urinary sodium to potassium ratio by postnatal age.

Box and whisker plot showing medians, interquartile range and extreme values. The numerical values are listed over (Table 8.6).

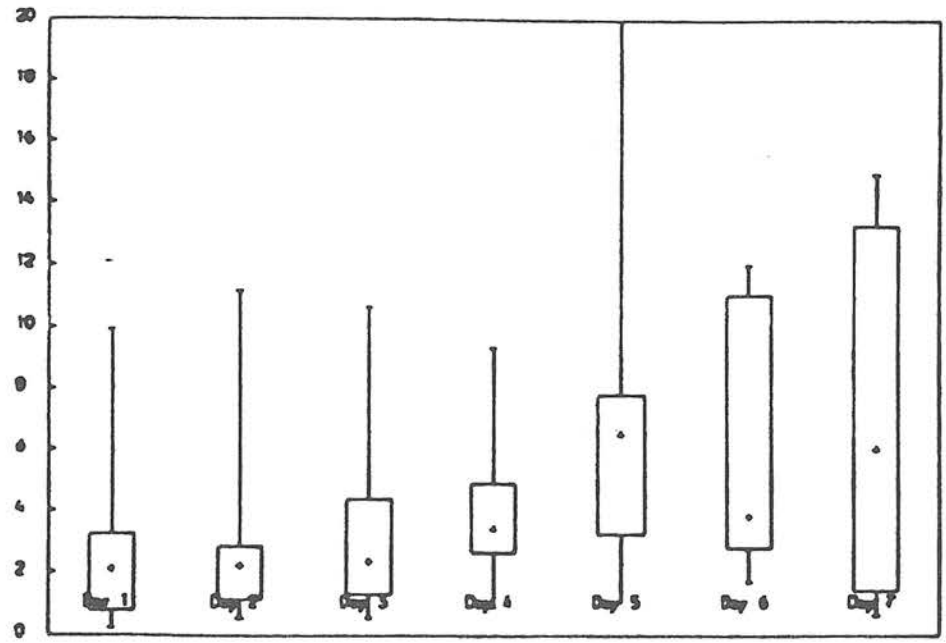


Table 8.6

Urinary sodium to potassium ratio by postnatal age.

(medians, interquartile range & extreme values)

day	minimum	Q_1	median	Q_3	maximum
1	0.22	0.79	2.08	3.19	9.91
2	0.54	1.14	2.20	2.82	11.14
3	0.54	1.31	2.31	4.37	10.61
4	0.90	2.60	3.38	4.87	9.30
5	1.03	3.21	6.49	7.77	30.40
6	1.69	2.76	3.80	11.03	11.98
7	0.63	1.41	6.00	13.24	14.91

Figure 8.7

Percentage distal sodium exchange by postnatal age.

Box and whisker plot showing medians, interquartile range and extreme values. The numerical values are listed over (Table 8.7).

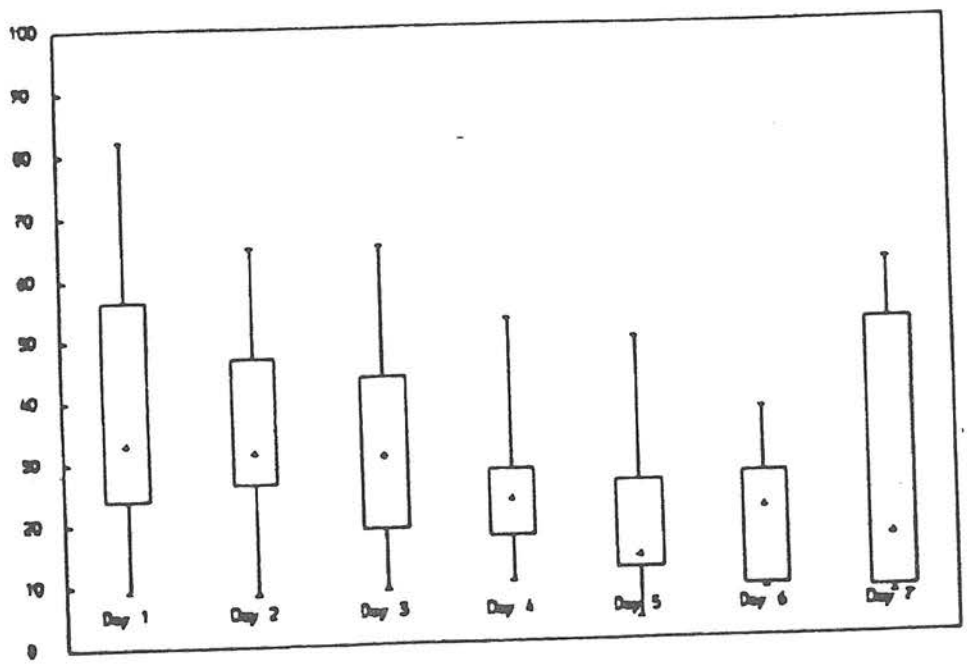


Table 8.7

Percentage distal sodium exchange by postnatal age.

(medians, interquartile range & extreme values)

day	minimum	Q_1	median	Q_3	maximum
1	9.17	23.89	32.84	56.36	82.00
2	8.24	26.17	31.24	46.68	64.92
3	8.61	18.60	30.29	43.33	64.88
4	9.71	17.03	22.87	27.78	52.56
5	3.19	11.43	13.35	25.68	49.16
6	7.70	8.31	20.84	26.59	37.21
7	6.28	7.42	15.90	51.29	61.40

Figure 8.8

Daily urinary potassium concentration (mmol l^{-1}) for each baby by postnatal age.

Box and whisker plot showing medians, interquartile range and extreme values. The numerical values are listed over (Table 8.8).

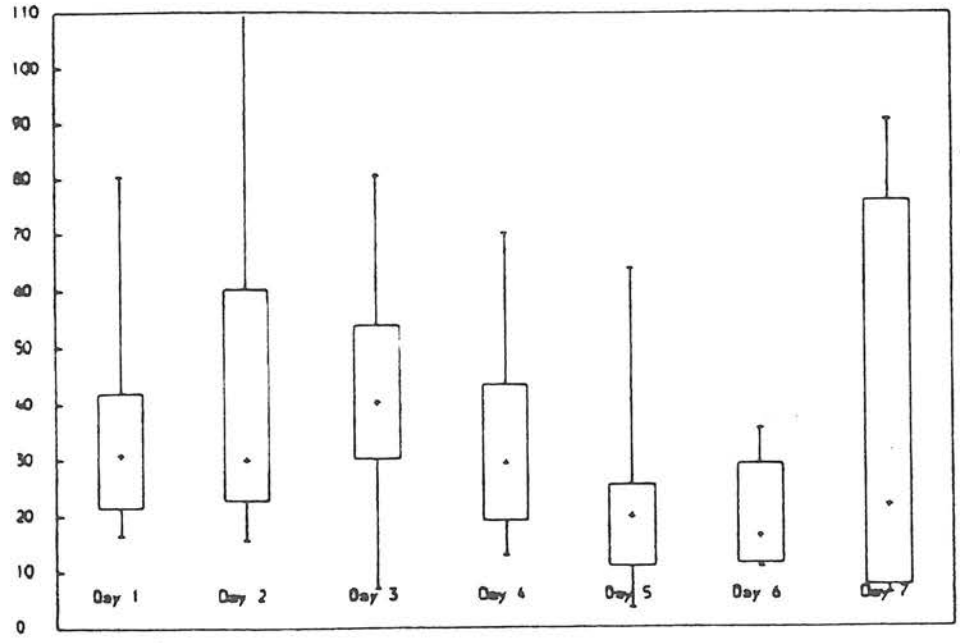


Table 8.8

Daily urinary potassium concentration (mmol l^{-1}) for each baby by postnatal age.

(medians, interquartile range & extreme values)

day	minimum	Q_1	median	Q_3	maximum
1	16.5	21.5	30.9	41.9	80.4
2	15.6	22.9	30.2	60.2	109.3
3	6.9	30.3	40.3	53.9	80.7
4	12.9	19.2	29.5	43.5	70.2
5	3.4	10.8	19.9	25.5	63.9
6	10.6	11.3	16.2	29.4	35.7
7	5.7	7.2	21.8	75.9	90.7

Figure 8.9

Weight loss (birthweight - actual weight) as a percentage of birth weight by postnatal age.

Box and whisker plot showing medians, interquartile range and extreme values. The numerical values are listed over (Table 8.9).

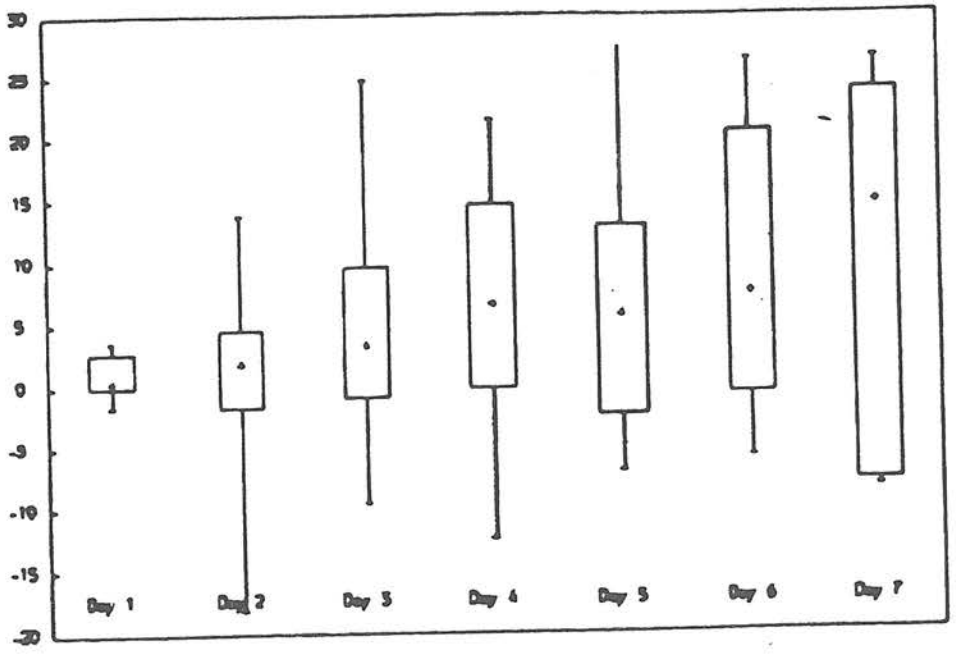


Table 8.9

Weight loss as a percentage of birth weight by postnatal age.

(medians, interquartile range & extreme values)

day	minimum	Q_1	median	Q_3	maximum
1	-1.59	0.00	0.36	2.62	3.60
2	-18.13	-1.71	1.78	4.47	13.77
3	-9.60	-0.96	3.23	9.58	24.72
4	-12.60	-0.22	6.46	14.49	21.47
5	-7.12	-2.41	5.60	12.88	27.24
6	-6.01	-0.75	7.31	20.40	26.34
7	-8.49	-7.97	14.60	23.78	26.39

Table 8.10

Range of measured daily sodium excretion compared with urinary sodium concentration noted on "spot" samples obtained on the same days.

Range of daily sodium excretion (mmol kg^{-1})	urinary sodium concentration (mmol l^{-1})
0.11 - 11.57	<50
0.09 - 18.72	50 - 100
0.44 - 18.72	100 - 150
1.64 - 14.28	>150

Figure 8.10

Cumulative sodium balance (mmol kg^{-1}) for the first week of life; mean (standard deviation).

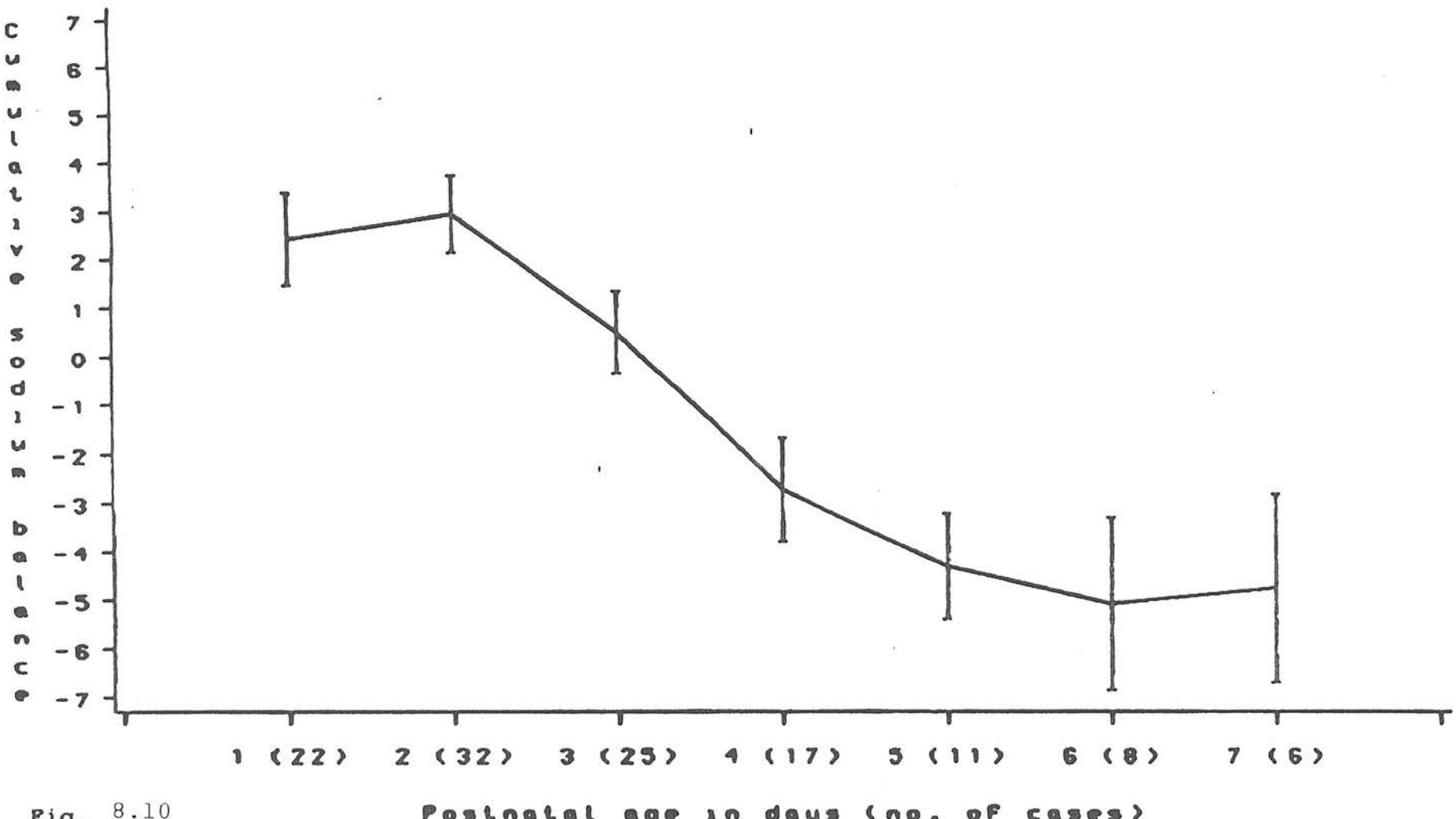

Cumulative response deficit
7
6
5
4
3
2
1
0
-1
-2
-3
-4
-5
-6
-7
1 (22)
2 (32)
3 (25)
4 (17)
5 (11)
6 (8)
7 (6)
Postnatal age in days (no. of cases)

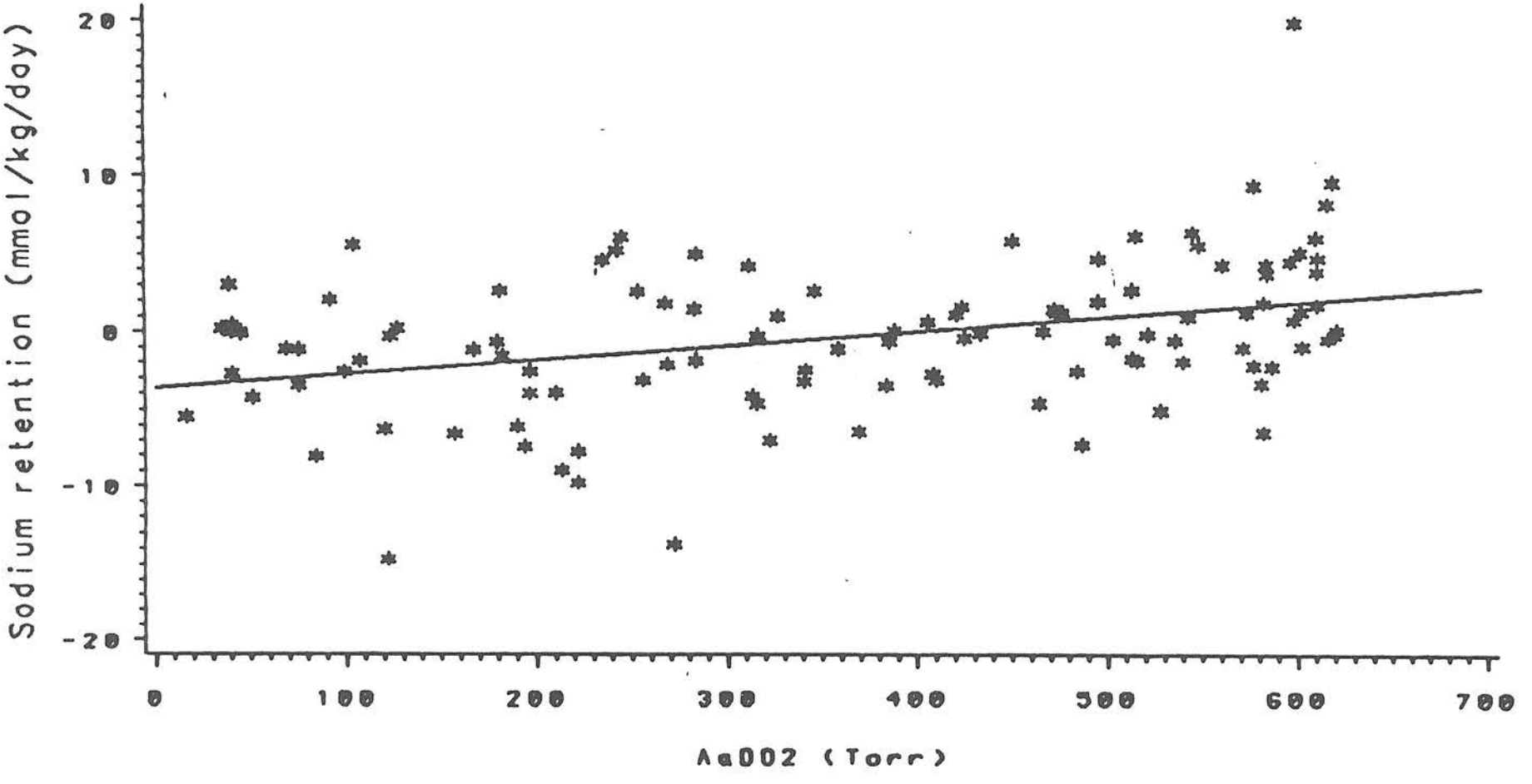
Fig. 8.10

Figure 8.11

Sodium balance by $AaDO_2$.

Fig. 8.11

Regression of sodium retention on AaDO2

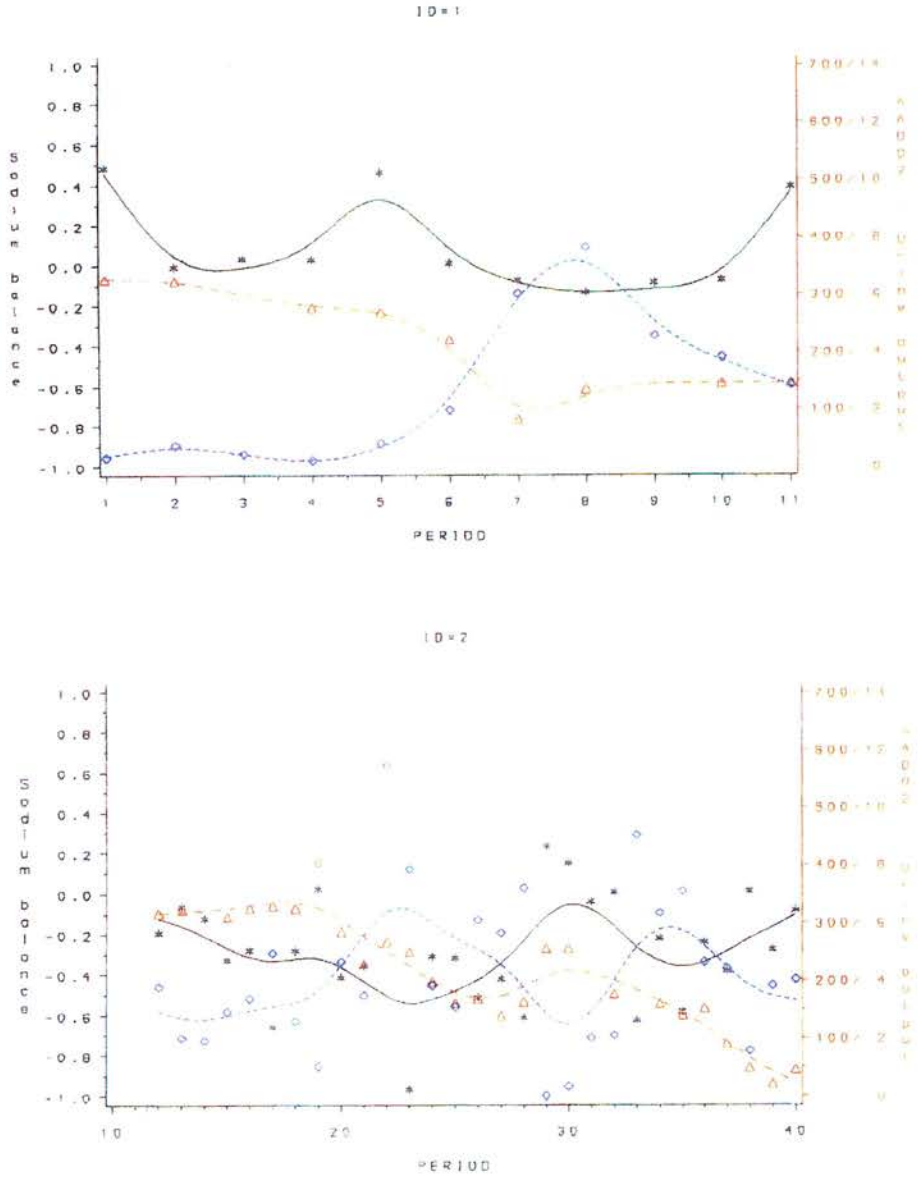


Regression equation: sodium retention = -3.69 + 0.00923*AaDO2

Figures 8.12 - 8.18

Time plots of $AaDO_2$, urine flow rate and sodium retention by time period in individual babies.

Fig 8.12



* Sodium balance (mmol/kg/day)
△ AADO2 (torr)
◇ Urine flow rate (ml/kg/hour)

Fig 8.13

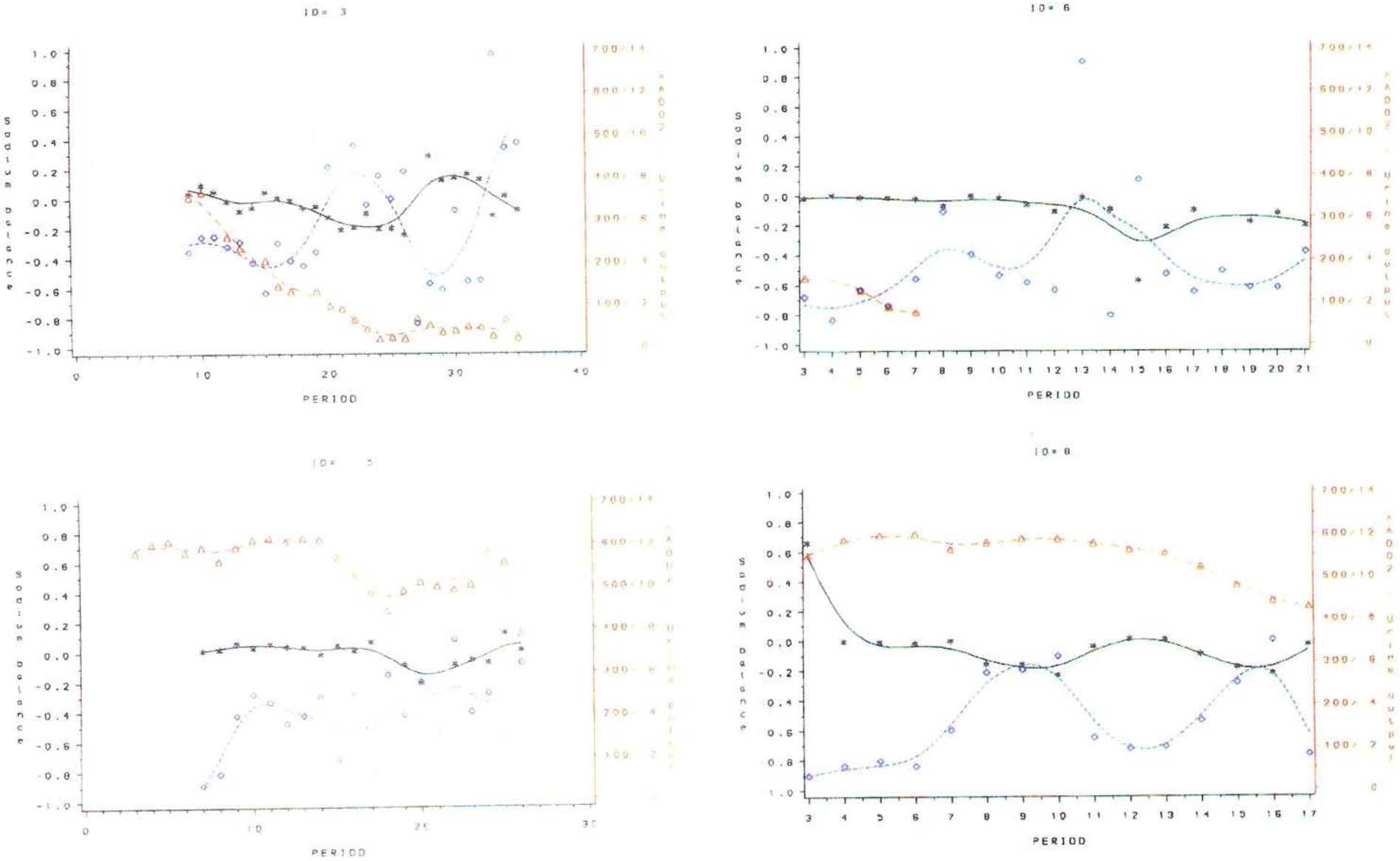


Fig 8.14

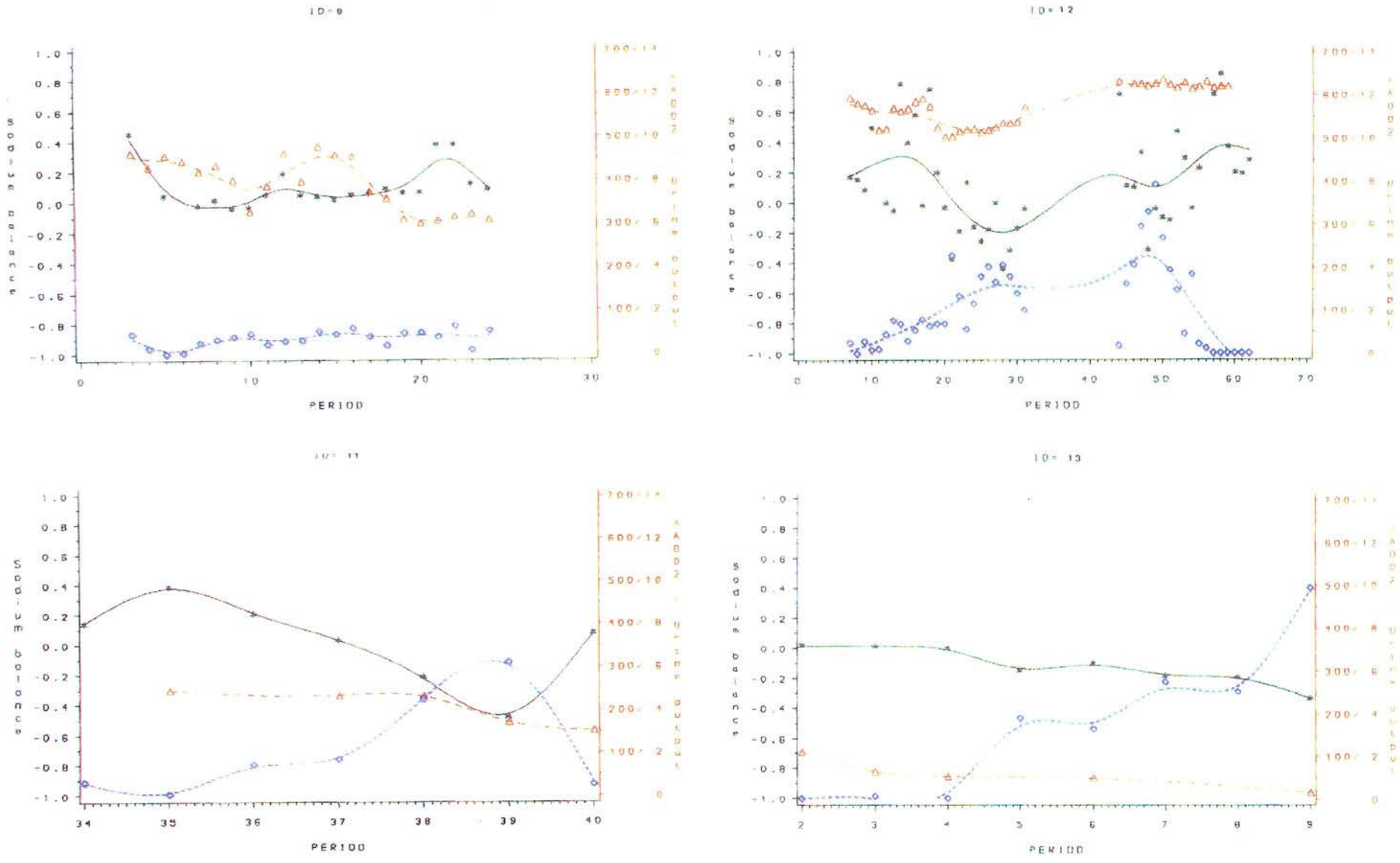


Fig 8.15

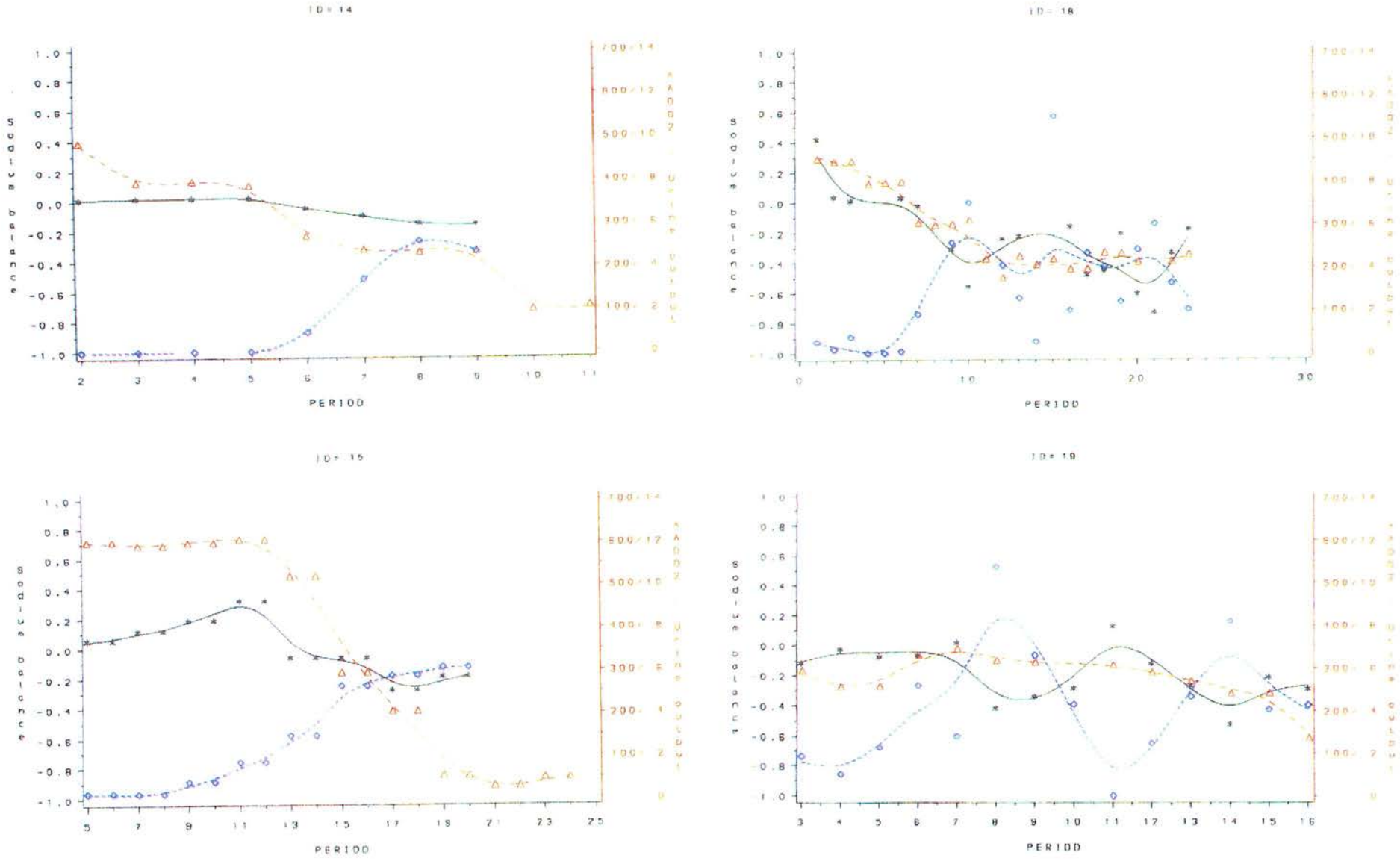


Fig 8.16

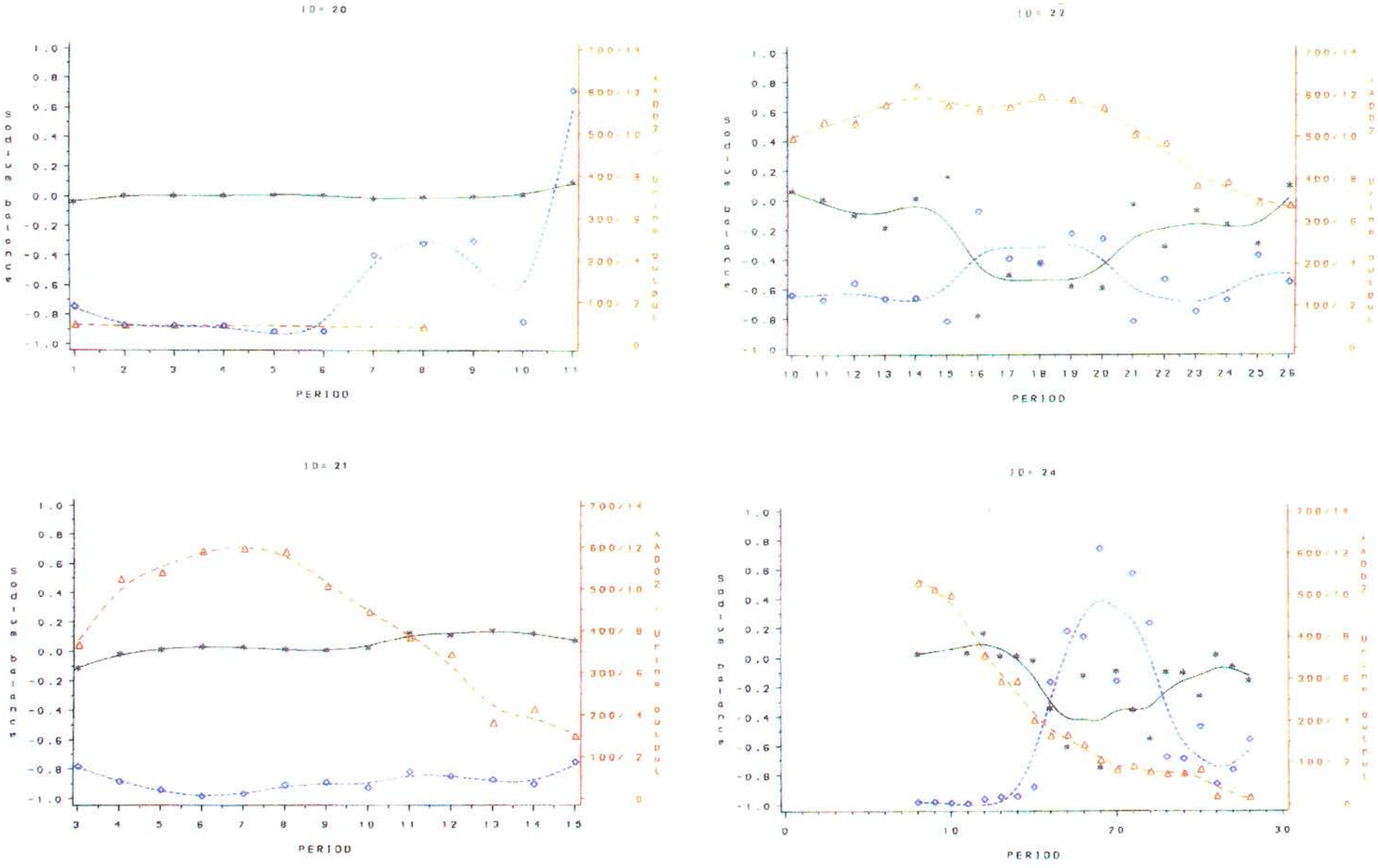


Fig 8.17

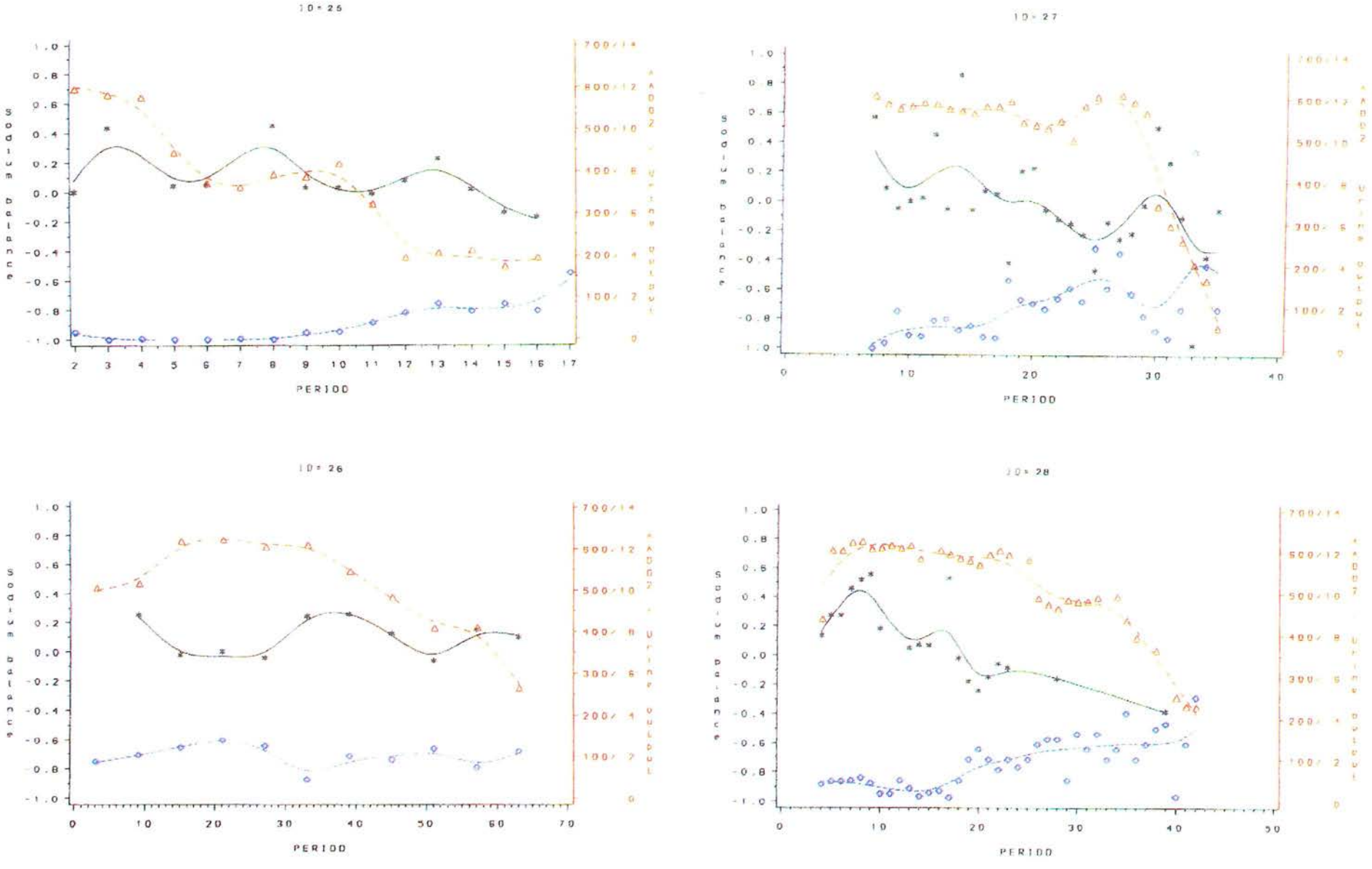
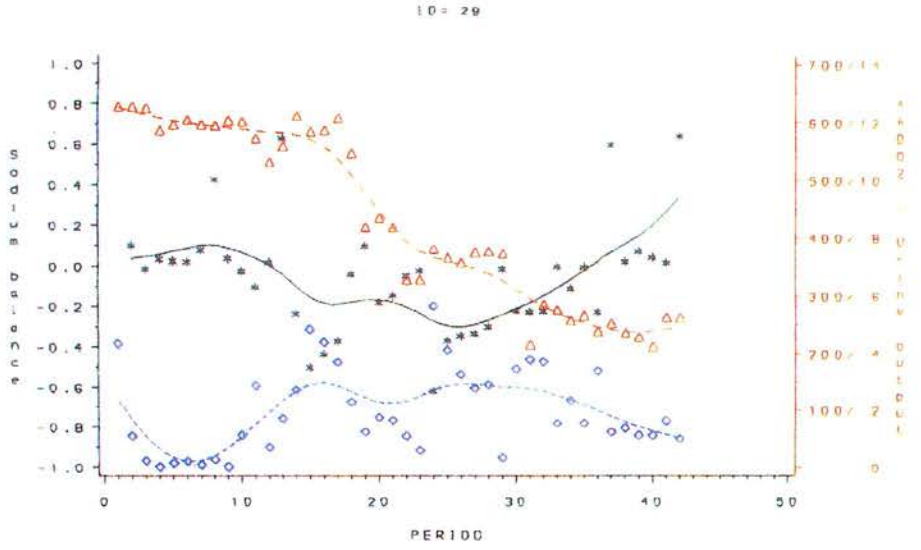
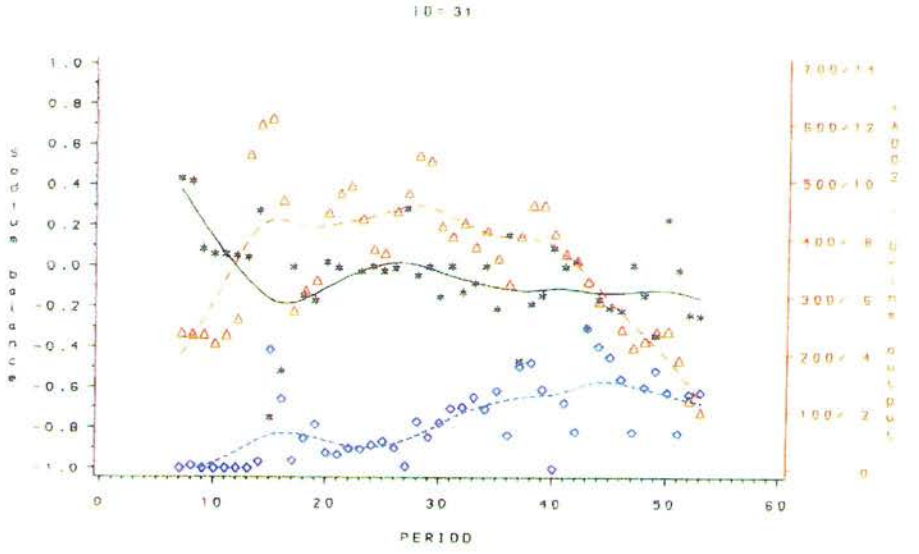
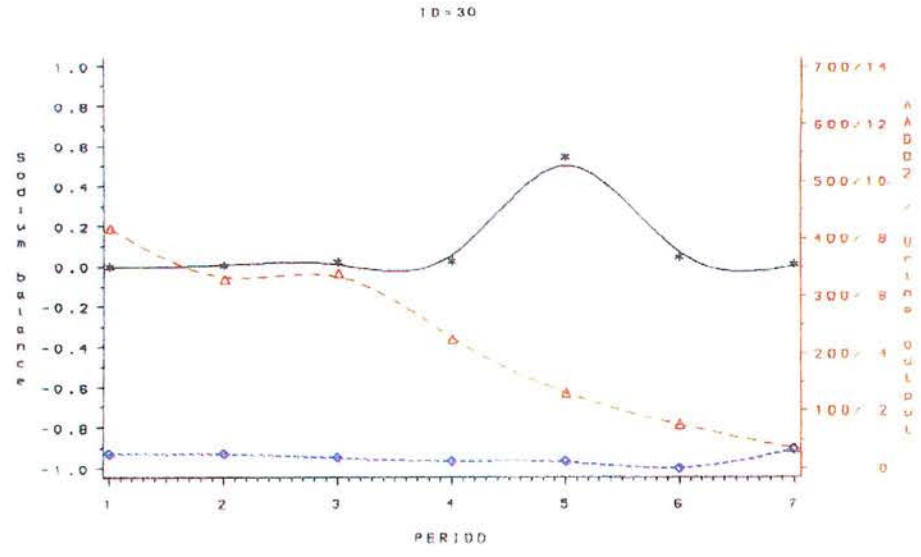


Fig 8.18







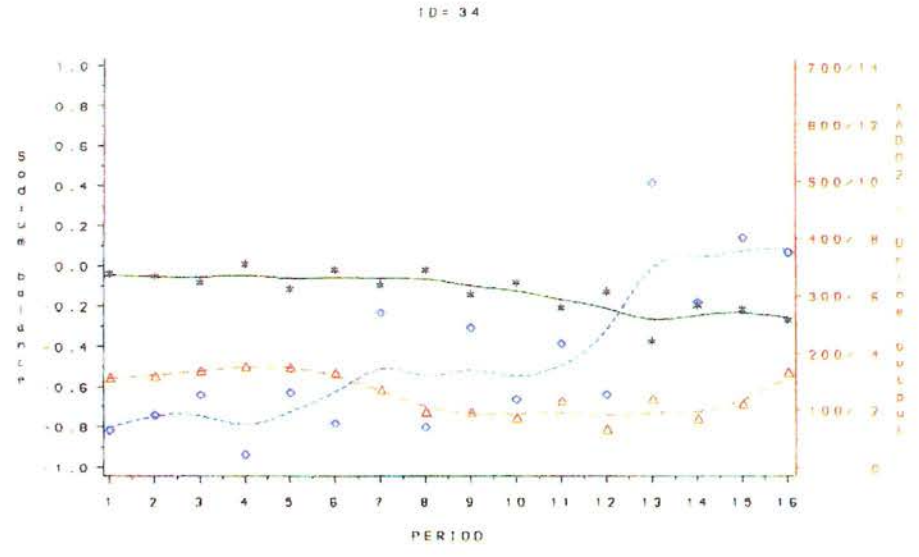


Table 8.11

Sodium balance, $AaDO_2$ and parameters of renal function by respiratory phases, presented as mean (SD) with estimated contrasts as determined by multivariate analysis of variance.

*** p<0.01; comparison was made using multivariate analysis of variance having allowed for between baby diffferences.**

	deteriorating	improving	estimated contrast
$AaDO_2$*	430 (176)	348 (189)	56
sodium intake	0.16 (0.22)	0.17 (0.14)	0.0017
sodium balance*	1.42 (3.97)	- 1.99 (3.92)	1.92
urine flow rate*	1.2 (1.36)	2.8 (2.15)	-0.86
Ccr*	0.24 (0.25)	0.47 (0.27)	-0.09
Cosm*	0.017 (0.03)	0.048 (0.04)	-0.01
CH_2O	- 0.001 (0.01)	- 0.003 (0.02)	0.00013
FeNa*	4.32 (5.11)	5.67 (4.13)	-0.88
plasma sodium	139 (6.3)	140 (6.5)	-0.59
plasma creatinine	112 (40)	110 (31)	-3.08
plasma osmolality	291 (21)	294 (20)	-3.05
urine osmolality*	359 (155)	364 (131)	17.93
fluid intake*	93 (42)	106 (38)	-6.11

($AaDO_2$, alveolar arterial oxygen gradient in torr; sodium intake, mmol kg^{-1} day^{-1}; sodium balance, mmol kg^{-1} day^{-1}; urine flow rate, ml kg^{-1} h^{-1}; Ccr, creatinine clearance in ml min^{-1} kg^{-1}; Cosm, osmolar clearance in ml min^{-1} kg^{-1}; CH_2O, free water clearance in ml min^{-1} kg^{-1}; plasma sodium, mmol l^{-1}; plasma creatinine, umol l^{-1}; plasma osmolality, mosm l^{-1}; urine osmolality, mosm l^{-1}; fluid intake, ml kg^{-1} day^{-1}.)

9

GLUCOSE

Hyperglycaemia is a not uncommon occurence among preterm infants receiving intravenous glucose infusions [Dweck & Cassady 1974]. The hazards of hyperglycaemia include hyperosmolality and, it is also generally believed, an osmotic diuresis [Miranda & Dweck 1977]. Hyperosmolality may lead to the adverse neurological consequences of intracellular acidosis, disruption of the blood brain barrier, potentiation of bilirubin toxicity and

intracranial haemorrhage [Finberg 1967; Luttrell & Finberg 1959; Rapoport et al 1972]. In view of the possible neurological consequences of hyperosmolality it cannot be considered ethically acceptable to expose an infant to hyperglycaemia deliberately. The only legitimate manner in which to study hyperglycaemia in the human neonate is to observe prospectively the occurrence of hyperglycaemia during the course of routine clinical management.

Methods

The renal effects of hyperglycaemia were assessed in a group of preterm infants who developed hyperglycaemia during the course of routine clinical care. Each baby formed part of the larger study of renal function in the first week of life in preterm infants. The infants in this larger study underwent continuous collection of urine in four hourly time blocks and serial sampling of blood for biochemical assay including glucose assay, as described in chapter 3 - Methods.

Hyperglycaemia was defined for the purposes of this study as a blood glucose of or exceeding 10 mmol l^{-1}. Elevated blood glucose levels were, in each case, confirmed on repeat assay. Those infants who developed hyperglycaemia were subjected to further analysis. Parameters of renal

function during hyperglycaemia were compared with periods of normoglycaemia in the same infants.

No infant was receiving enteral feeds and intravenous infusion volumes were noted as described in chapter 3 - Methods. No baby received treatment with insulin and the hyperglycaemia was treated by a reduction in glucose infusion rate whilst maintaining a constant fluid intake. No attempt was made to influence clinical management.

Glucose infusion rates were calculated from a knowledge of dextrose concentration in the fluid administered. Excretion rates were calculated as the product of urine concentration and urine flow rate; filtered loads as the product of plasma concentration and creatinine clearance rate and fractional excretion as excretion rate divided by filtration rate.

Glomerular filtration rate was equated with creatinine clearance and calculated as creatinine excretion rate divided by plasma concentration. Osmolar clearance was calculated as osmolar excretion rate divided by plasma osmolality; free water clearance as urine flow rate minus osmolar clearance; tubular reabsorption of glucose as filtered glucose minus excreted glucose. Data are expressed per kilogram body weight.

Multivariate analysis of variance, allowing for between baby differences and gestational age, was used to compare parameters of renal function during the periods of hyperglycaemia with periods of normoglycaemia.

Results

Fourteen of the 34 babies studied developed hyperglycaemia (defined as a blood glucose exceeding 10 mmol l^{-1}) during 21 four hourly periods over the course of this study. In these same infants, normoglycaemia was observed during 19 four hour periods, on the same days of life. Birth weights, in these 14 infants, ranged from 680 g to 1618 g (median 1006 g) and gestational ages from 25 to 32 weeks (median 27).

The mean blood glucose during the hyperglycaemic periods was 15.8 mmol l^{-1} (median 13.7, range 10.3-26.0); mean urinary glucose 16.9 mmol l^{-1} (median 14.9, range 0.2-52.0); the glucose infusion rate averaged 7.7 mg kg^{-1} min^{-1} (median 7.7, range 1.17-17.6).

Tables 9.1 - 9.4 show the clinical data, parameters of renal function, sodium excretion and water and solute excretion during the periods of normoglycaemia and hyperglycaemia. Values are presented as means and standard deviations; comparisons were made using multivariate

analysis of variance allowing for gestational age and between baby differences.

During hyperglycaemia the infants had, as expected, a significantly higher filtered glucose load and urinary glucose concentration. Plasma sodium concentration and filtered sodium load did not differ during hyperglycaemia and normoglycaemia, but fractional sodium excretion and sodium excretion were significantly lower during hyperglycaemia.

There was no significant increase in urine flow rate, ratio of urine output to fluid intake, fractional urine flow, osmolar excretion, osmolar clearance and free water clearance during periods of hyperglycaemia. Plasma osmolality was higher during hyperglycaemia but the difference did not reach significance.

Discussion

A limitation of this study is the uncertainty of the precise duration of hyperglycaemia. Nevertheless the approach used here is justified in view of the inacceptability of deliberately subjecting an infant to hyperglycaemia and the arguments presented above; in addition the occurence of hyperglycaemia and glycosuria are both clearly demonstrated.

The variability of glucose tolerance in such a population is exemplified by the similarity of glucose infusion rates during normoglycaemia and hyperglycaemia and by the wide range of glucose infusion rates over which hyperglycaemia occurred (1.17 - 17.6 mg kg^{-1} min^{-1}).

Immature infants are prone to hyperglycaemia. Contributory factors are believed to be a smaller tissue pool of fat and skeletal muscle for glucose disposal and persistent endogenous glucose production. Newborn lambs [Cowett et al 1978] and preterm rhesus primates [Sherwood et al 1977] have been shown to maintain endogenous glucose production in the presence of hyperglycaemia. Critically ill infants are more prone to develop glucose intolerance and hyperglycaemia [Lilien et al 1979]. The aetiology of hyperglycaemia in immature, stressed infants is not due to absolute hypoinsulinaemia [Lilien et al 1979], but high circulating levels of insulin suggest it may be the result of end organ unresponsiveness.

Although Bier et al [1977] showed that mean endogenous glucose production in a group of preterm infants was 5.46 mg kg^{-1} min^{-1} this measure has little practical application as both glucose needs and glucose tolerance in the vulnerable preterm infant are so variable.

Creatinine clearance remained unchanged during hyperglycaemia. Creatinine clearance has been shown to increase during the infusion of hypertonic glucose infusions in infants [Brodehl et al 1972]; however considerably higher blood glucose levels were attained than in the study reported here. Stonestreet et al [1980], studying low birth weight infants also reported no significant increase in glomerular filtration rate.

Tubular reabsorption of glucose increased during hyperglycaemia but percentage tubular reabsorption remained unchanged suggesting that this degree of hyperglycaemia did not saturate the proximal tubular glucose reabsorptive sites.

Fractional sodium excretion and urinary sodium excretion decreased during hyperglycaemia. This is difficult to understand. Baker & Kleinman [1974] showed that newborn puppies excreted more sodium during glucose loading due to inhibition of proximal tubular sodium reabsorption. However they also found a greater sensitivity of the neonatal proximal tubule to the osmotic effect of glucose - an observation at variance with the results presented here. Interestingly these workers showed that glomerular blood flow, as measured by radioactive microspheres, was redistributed towards inner cortical nephrons during glucose loading in puppies but not in adult

dogs. The intrarenal circulation of the neonate is labile and subject to redistribution secondary to a number of stimuli [Aperia et al 1977]. The inner cortical nephrons are more mature than the outer nephrons [Potter 1965]; they therefore might be expected to have a greater capacity for sodium reabsorption and hence provide an explanation for the decreased sodium excretion in the study reported here.

Of particular interest is that no evidence of an osmotic diuresis was found. Urine flow rate, fractional urine flow and the ratio of fluid intake to urine output remained unchanged. Though this has been reported by other workers [Stonestreet et al 1980 ; Cowett et al 1979], osmotic diuresis is still cited as a common complication of hyperglycaemia in preterm neonates receiving standard clinical care [Miranda & Dweck 1977]. However it would seem that, unlike the situation in older infants, the immature kidney appears unable to hyperfiltrate in the presence of hyperglycaemia.

The danger of hyperglycaemia, to the immature infant, over the ranges described here, thus lies in the possibilty of associated hyperosmolality and not with the development of an osmotic diuresis.

Conclusions

1. Hyperglycaemia, with blood glucose concentrations between 10 - 26 mmol l^{-1}, occurred at glucose infusion rates ranging from 1.17 - 17.6 mg kg^{-1} min^{-1}, in a group of neonates between 25 - 32 weeks gestational age.

2. This degree of hyperglycaemia did not result in an osmotic diuresis.

3. This degree of hyperglycaemia was associated with a significant decrease in fractional sodium excretion and urinary sodium loss.

Hypothesis

In the extremely preterm infant, hyperglycaemia may result in a redistribution of intrarenal blood flow to the salt retaining inner cortical nephrons.

Table 9.1

Clinical data during periods of normoglycaemia and hyperglycaemia.

	blood glucose <10 mmol l^{-1}	blood glucose >10 mmol l^{-1}	F	sig. of F
bgluc	5.6 (2.1)	15.8 (4.7)	56.8	<0.001
posm	289 (18.3)	299 (13.5)	0.76	NS
pcr	101 (34.8)	110 (21.1)	0.08	NS
pna	142 (6.8)	141 (5.5)	0.90	NS
ugluc	9.2 (11.8)	16.9 (14.3)	7.22	0.01
uosm	360 (123)	352 (84)	0.46	NS
ucr	1497 (1116)	1496 (677)	0.12	NS
una	97 (40)	84 (37)	6.19	0.02

[Values are presented as mean (standard deviation); bgluc, blood glucose in mmol l^{-1}; posm, plasma osmolality in mosm l^{-1}; pcr, plasma creatinine in mmol l^{-1}; pna, plasma sodium in mmol l^{-1}; ugluc, urinary glucose in mmol l^{-1}; uosm, urinary osmolality in mosm l^{-1}; ucr, urinary creatinine in mmol l^{-1}; una, urinary sodium in mmol l^{-1}]

Table 9.2

Parameters of renal function during periods of normoglycaemia and hyperglycaemia.

	blood glucose <10 mmol l^{-1}	blood glucose >10 mmol l^{-1}	F	sig. of F
ccr	0.599 (0.29)	0.446 (0.31)	1.22	NS
fg	0.0035 (0.002)	0.007 (0.006)	10.07	<0.01
trg	0.003 (0.002)	0.007 (0.006)	9.08	<0.01
ptrg	88 (13.2)	92 (7.7)	0.8	NS
glucin	7.9 (2.8)	7.7 (3.4)	0.09	NS
glucexc	0.027 (0.035)	0.033 (0.037)	0.87	NS

[Values are presented as mean (standard deviation); ccr, creatinine clearance in ml min^{-1} kg^{-1}; fg, filtered glucose in mmol kg^{-1} min-1; trg, tubular reabsorption of glucose in mmol kg^{-1} min^{-1}; ptrg, percentage tubular reabsorption of glucose; glucin, glucose infusion rate in mg kg^{-1} min^{-1}; glucexc, glucose excretion in mmol kg^{-1} h^{-1}]

Table 9.3

Parameters of renal function during periods of normoglycaemia and hyperglycaemia.

	blood glucose <10 mmol l^{-1}	blood glucose >10 mmol l^{-1}	F	sig. of F
fna	0.088 (0.04)	0.063 (0.04)	2.22	NS
fena	6.4 (4.1)	5.3 (3.7)	4.57	0.04
naexc	0.33 (0.26)	0.19 (0.17)	4.53	0.04

[Values are presented as mean (standard deviation); fna, filtered sodium in mmol kg^{-1} min^{-1}; fena, fractional sodium excretion; naexc, sodium excretion in mmol kg^{-1} h^{-1}]

Table 9.4

Parameters of renal function during periods of normoglycaemia and hyperglycaemia.

	blood glucose <10 mmol l^{-1}	blood glucose >10 mmol l^{-1}	F	sig. of F
outin	0.67 (0.38)	0.53 (0.39)	0.92	NS
uv	3.2 (1.9)	2.3 (1.9)	1.3	NS
Feuv	8.6 (3.6)	8.6 (4.1)	0.01	NS
Cosm	0.064 (0.044)	0.046 (0.04)	1.01	NS
CH2O	-0.0106 (0.025)	-0.0079 (0.019)	0.37	NS
osmexc	1.12 (0.8)	0.84 (0.75)	0.75	NS

[Values are presented as mean (standard deviation); outin, ratio of fluid intake to urine output; uv, urine flow rate in ml kg^{-1} h^{-1}; Feuv, fractional urine flow; Cosm, osmolar clearance in ml min^{-1} kg^{-1}; CH_2O, free water clearance in ml min^{-1} kg^{-1}; osmexc, osmolar excretion in mosm kg^{-1} h^{-1}]

10

SERUM BETA-2-MICROGLOBULIN

The assessment of glomerular function in the preterm neonate is difficult. Clearance studies in this age group are often imprecise given the problems of accurate urine collection and incomplete bladder emptying; continuous infusion techniques are lengthy. A useful but approximate estimate of glomerular filtration rate (GFR) may be obtained by measuring the serum level of a constantly produced endogenous substance. In clinical practice,

despite the limitations afforded by tubular secretion, dependence on muscle mass and diminished production in patients with renal failure, plasma creatinine (PCr) is widely used as a screening measure of GFR. There are however added problems in the use of PCr in the neonate; PCr in newborns reflects not only muscle mass and renal function but is initially influenced by the maternal creatinine level and then falls rapidly during the first days of life [Trompeter 1983], making the interpretation of changes difficult.

Serum beta-2-microglobulin (SB2MG) is a low molecular weight protein (11,800 daltons). It is produced by almost all nucleated human cells and almost completely filtered by the normal glomerulus. As excretion of SB2MG is virtually entirely renal, SB2MG has been proposed as a screening measure of GFR. The purposes of this study were to assess normal values for SB2MG in preterm infants, to examine the influence of gestational and postnatal age and the relationship with PCr and endogenous creatinine clearance.

Materials and methods

SB2MG and PCr were measured in well babies during the first sixteen days of life. Infants were considered "well" if breathing spontaneously in air, receiving enteral feeds and on no antibiotic or diuretic therapy. The relationships

between SB2MG and PCr and gestational age and postnatal age were initially explored using linear regression and these plots are presented for visual inspection. As repeated measures were made of SB2MG and PCr in the same infants, significance testing using simple linear regression would be inappropriate [O'Brien Smith 1987]; these relationships were therefore tested using multivariate analysis of variance. Final analysis utilised multiple linear regression.

SB2MG was also measured together with endogenous creatinine clearance, using timed urine collections, on 26 days in 11 infants receiving intensive care; these infants formed part of the group in whom renal function was studied in the first week of life as descibed in chapter 3 - Methods. Analysis was similarly using linear regression followed by multivariate analysis.

Assays of SB2MG were performed using the Enzygnost-b2-Microglobulin reagents from Behringwerke A.G., W. Germany (supplied by Hoechst UK Ltd., Hounslow). Samples were assayed in duplicate.

Results

The between-batch coefficient of variation for SB2MG assay was 6.74% (mean SB2MG=8.204 mg l^{-1}, SD=0.553) and

within-batch coefficient of variation 5.8% (mean SB2MG=3.9 mg l^{-1}, SD=0.43).

SB2MG and PCr were measured on 59 occasions in 30 well babies of mean gestational age 31 weeks (median 31, range 24-34) and mean birth weight 1.4 kg (median 1.4, range 0.566 - 2.288) during the first 16 days of life. SB2MG was measured together with endogenous creatinine clearance on 26 days in 11 infants receiving intensive care. These infants were of mean gestational age 28 weeks (median 28, range 25 - 31) and mean birth weight 1.02 kg (median 0.980, range 0.68 - 1.37). The mean period of continuous urine collection was 1200 minutes (median 1200, range 210 - 1800).

The median level of SB2MG was 3.26 mg l^{-1} (mean 3.44, 95% confidence interval 3.12 - 3.76) in well babies of mean postconceptional age 217 days (median 224, range 182 - 240).

In the group of well babies, SB2MG showed a negative correlation with gestational age (Fig 10.1); multivariate analysis, allowing for between baby differences, showed this to be significant (F=3.1, p=0.002). SB2MG was not influenced by postnatal age (Fig 10.2) (F=2.1, p=0.16). PCr showed no correlation with gestational age (Fig 10.3)

(F=1.19, p=0.32) and a significant negative correlation with postnatal age (Fig 10.4) (F=7, p=0.01).

Multiple linear regression was used to construct the following equation predicting SB2MG from gestational and postnatal age:

SB2MG (mg l^{-1}) = 9.28 - 0.05 PNA (days)- 0.018 GA (weeks)

SE of estimate = 1.16

A negative correlation was suggested between creatinine clearance and SB2MG (Fig 10.5). However multivariate analysis of variance did not confirm this impression (F=0.64, p=0.4) nor did logarithmic transformation change this relationship.

Similarly multivariate analysis of variance did not confirm a relationship between creatinine clearance and either plasma creatinine (F=0.22, p=0.6) or the reciprocal of plasma creatinine (F=0.07, p=0.8).

Discussion

Potentially adverse influences on renal function are numerous in the preterm baby. In part because of the difficulties in monitoring basic parameters such as urine flow rate and changes in weight, there is often a delay in

recognising renal impairment until considerable derangement in fluid and electrolyte balance occurs or until the consequences of chronic renal failure are manifest.

Despite recognised limitations [Brezis et al 1986] PCr is widely used as a screening measure of GFR. However in the newborn baby the use of PCr in this manner is further compounded by the fact that the neonatal level is initially dependent on the maternal level and thereafter changes rapidly [Trompeter et al 1983] with postnatal age, a feature confirmed in our study. The requirement to excrete the maternally acquired creatinine load probably accounts for part of the fall in PCr with postnatal age. That this change in PCr is at least in part independent of changes in GFR is borne out by the lack of correlation between creatinine clearance and PCr or the reciprocal of PCr. Within the limits of the 16 day postnatal period during which these measurements were made, PCr was not significantly influenced by gestational age.

The relationship between SB2MG, PCr and GFR at various ages has been investigated by several groups. As excretion of SB2MG is virtually entirely renal there is good negative correlation between SB2MG and GFR [Brocklebank et al 1983]. This relationship has been shown to be significantly better than between PCr corrected for height and EDTA clearance [Van Acker et al 1984]. In a previous study the

best fit was obtained when log SB2MG values were correlated with log creatinine clearance [Vincent et al 1980]. In the study reported here, analysis of variance allowing for the appreciable between baby differences, did not show a significant relationship between SB2MG and creatinine clearance.

Other workers have shown the predictive value of SB2MG to be superior to that of PCr especially when glomerular filtration rate is moderately impaired [Wibell 1978; Van Acker et al 1984]. During the study period reported here SB2M remained relatively stable at a level influenced by gestational age, in contrast to PCr. This would suggest that SB2MG might provide a more sensitive index of renal impairment.

There are limited data regarding normal values for SB2MG in neonates. Van Oort et al [1980] report a mean value of 3.54 mg l^{-1} in fourteen well babies of unspecified gestational age in the first week of life and 3.39 mg l^{-1} in nine babies aged 8 to 30 days; Engle and Arant [1983] report a mean of 5.89 mg l^{-1} in nine babies of conceptional age 26 to 30 weeks, falling to 3.56 mg l^{-1} at a conceptional age of 34 to 37 weeks (thirteen babies).

The study reported here, like those of other workers [Engle and Arant 1983; Wibell 1976; van Oort et al 1980],

has shown a negative correlation between SB2MG and gestational age. This decline with age continues, reaching adult values of around 2 mg l^{-1} after the first year [van Oort et al 1980]. Such a decline is consistent with the known rise in GFR with age. Aperia and Broberger [1979] are alone in reporting an increase in SB2MG with increasing conceptional age; their study is however open to criticism, involving as it did, acute volume loading of the infants, a manoeuvre known to influence GFR [Wolgast et al 1983].

From the data presented here, it is not possible to predict absolute GFR from a knowledge of SB2MG. However, it has been shown that, unlike PCr, the level of SB2MG remains stable in the first two weeks of life at an initial level determined by gestational age. For this reason it is suggested that, in the neonate, day to day variations in SB2MG may provide a more sensitive screening measure of renal impairment.

Conclusions

1. The mean concentration of SB2MG, measured in 30 well babies of 30 weeks mean gestational age, in the first 16 days of life, was 3.44 mg l^{-1}.

2. SB2MG fell significantly with gestational age but was stable within the first 16 days of life.

3. In the neonate, day to day variations in SB2MG may provide a more sensitive screening measure of renal impairment.

Figures 10.1 - 10.2

Serum beta-2-microglobulin by gestational age and postnatal age.

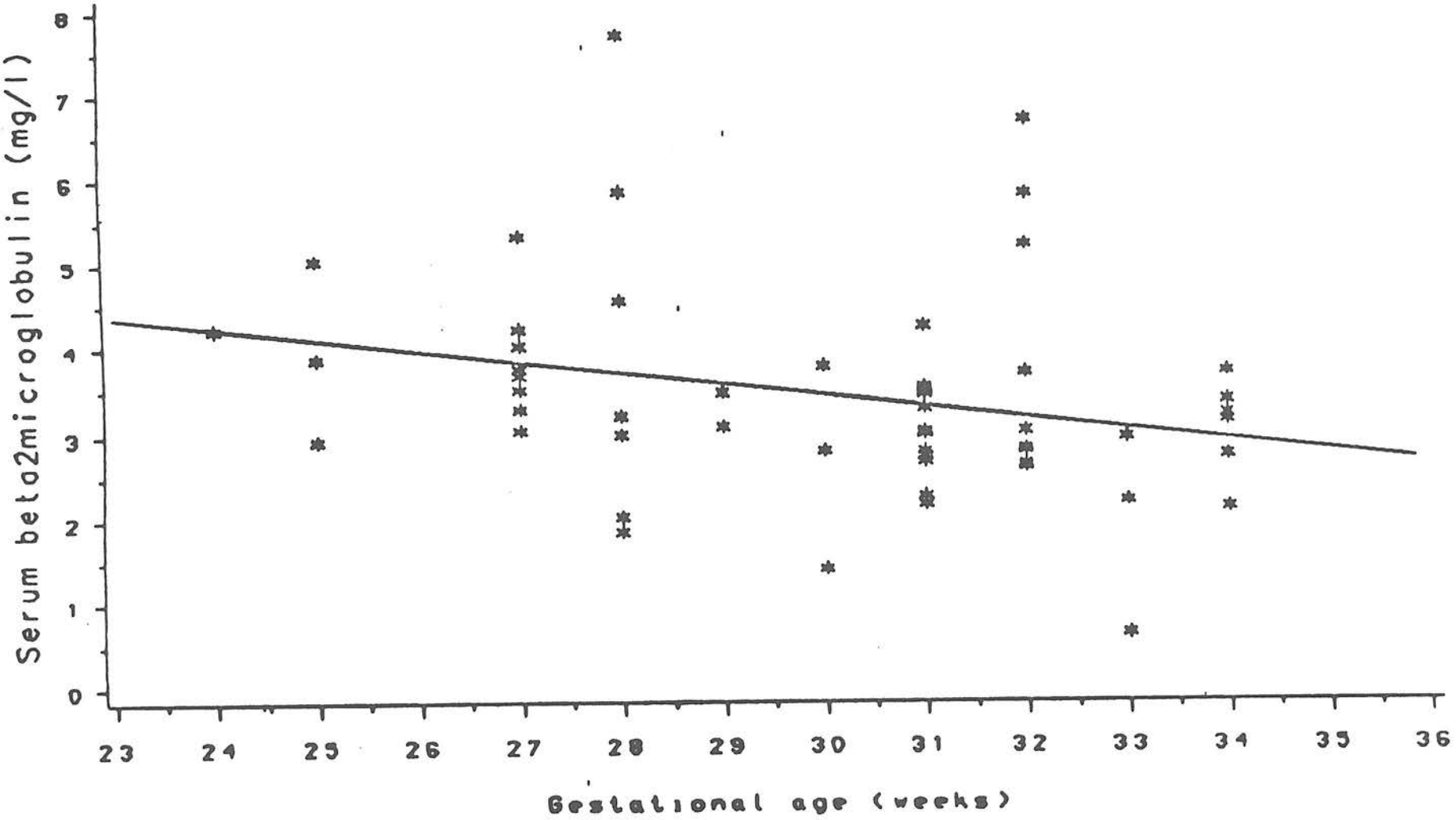

Serum beta2microglobulin (mg/l)
0
1
2
3
4
5
6
7
8
23
24
25
26
27
28
29
30
31
32
33
34
35
36
Gestational age (weeks)

Fig. 10.1

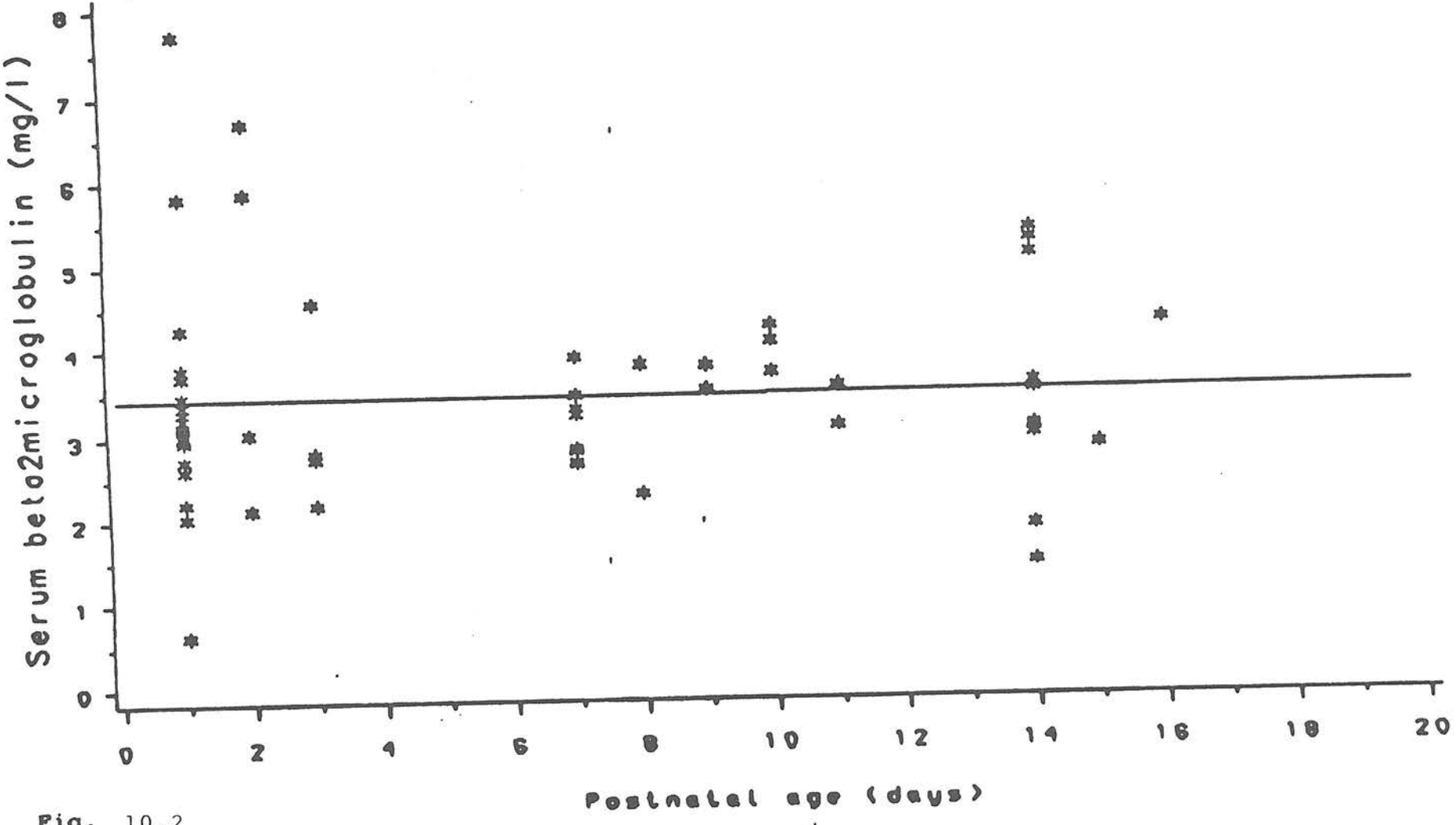

Serum beta2microglobulin (mg/l)
0
1
2
3
4
5
6
7
8
0
2
4
6
8
10
12
14
16
18
20
Postnatal age (days)

Fig. 10.2

Figures 10.3 - 10.4

Plasma creatinine by gestational age and postnatal age.

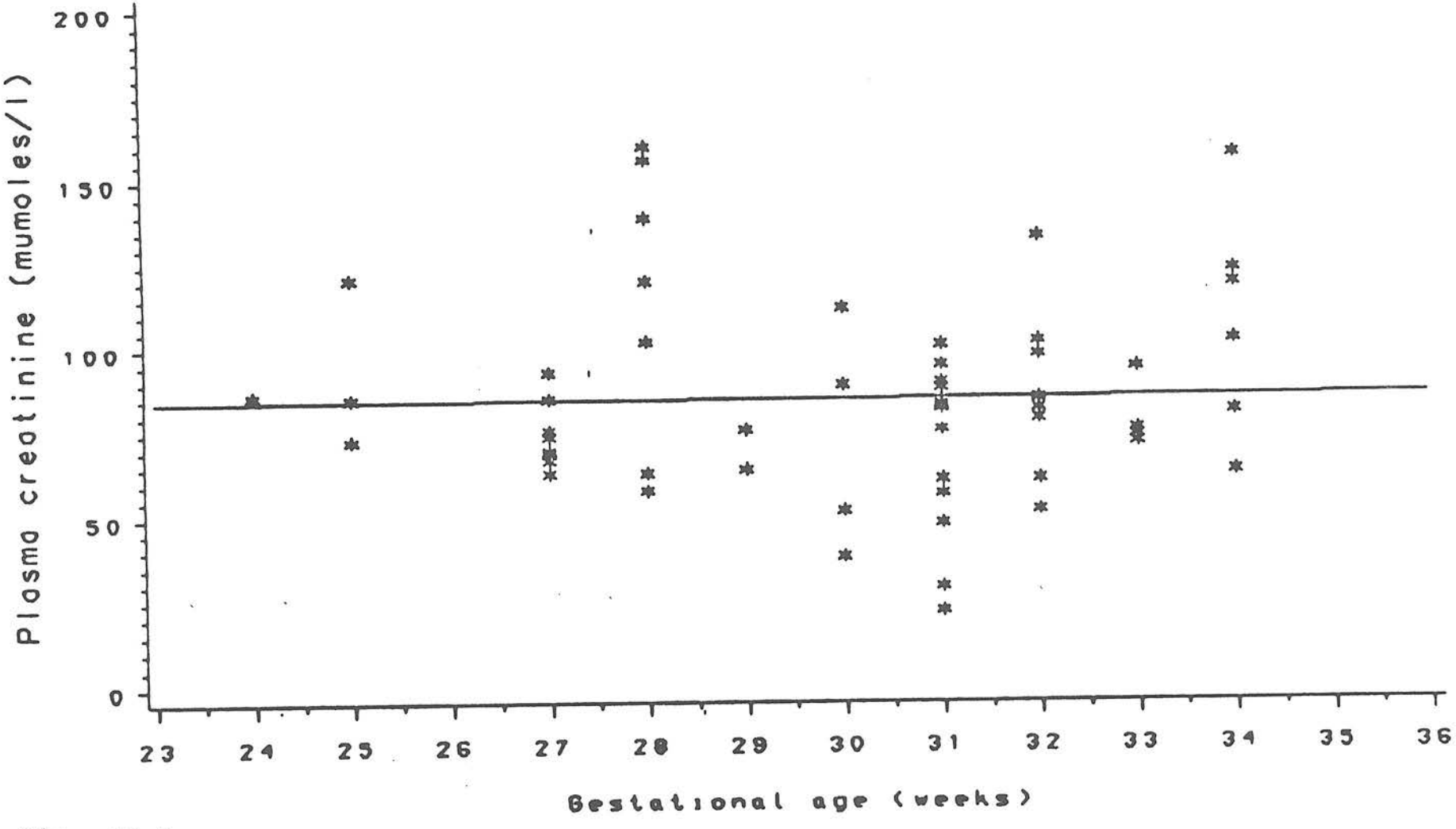

Plasma creatinine (mumoles/l)
200
150
100
50
0
23
24
25
26
27
28
29
30
31
32
33
34
35
36
Gestational age (weeks)

Fig. 10.3

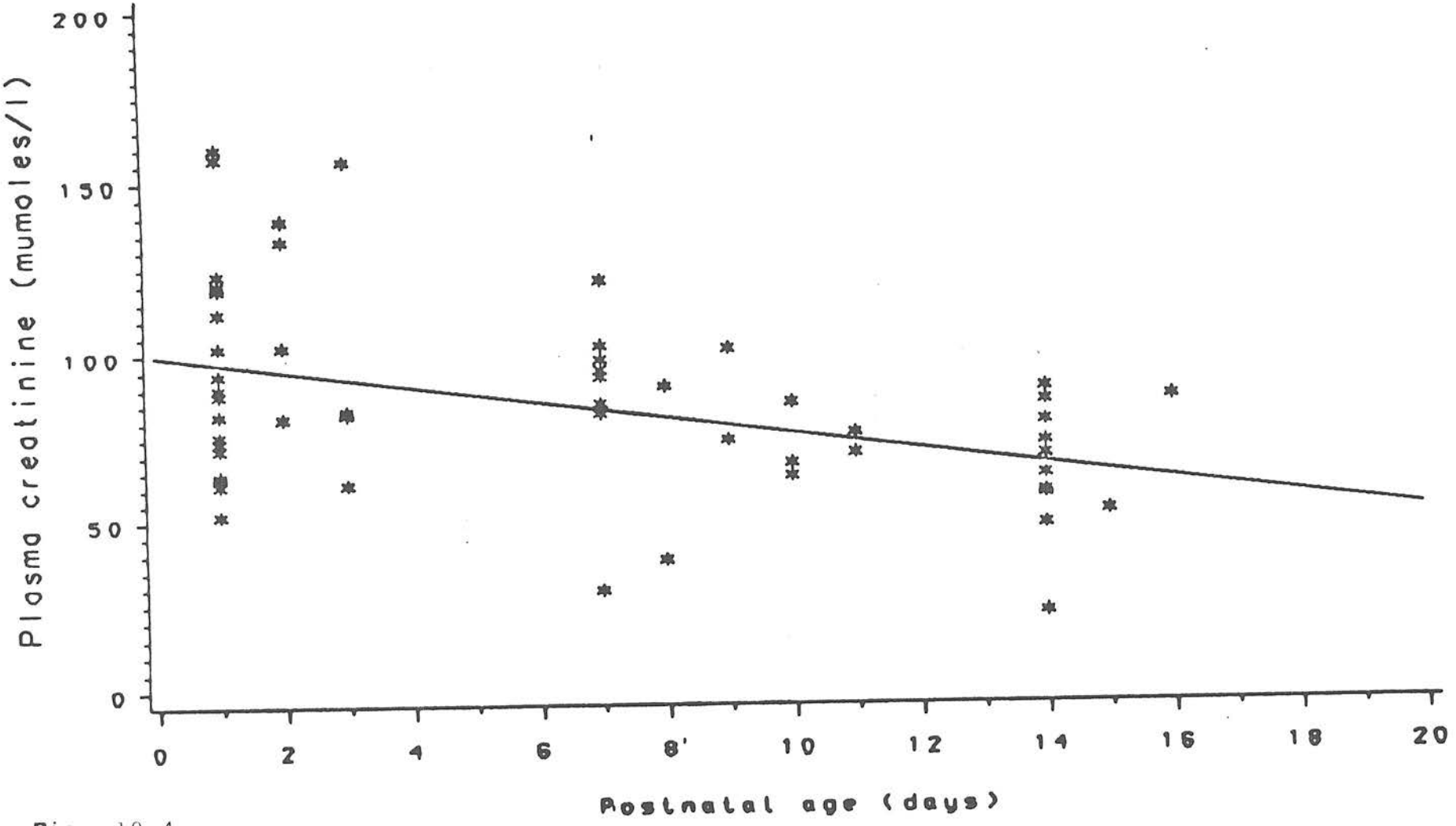

Plasma creatinine (mumoles/l)
200
150
100
50
0
0
2
4
6
8'
10
12
14
16
18
20
Postnatal age (days)

Fig. 10.4

Figure 10.5

Creatinine clearance by serum beta-2-microglobulin.

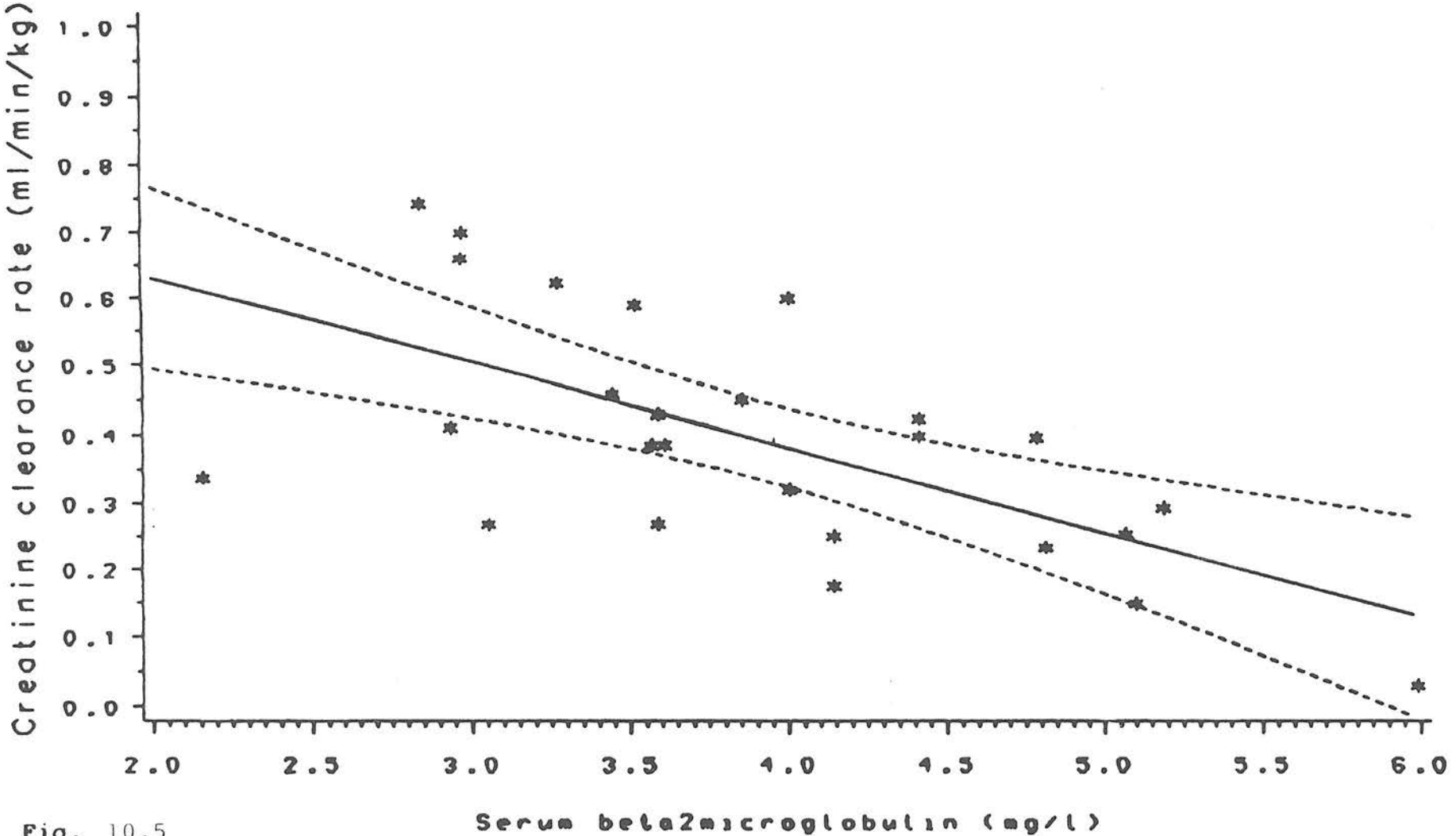

Creatinine clearance rate (ml/min/kg)
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
Serum beta2microglobulin (mg/l)

Fig. 10.5

11

ACUTE RENAL FAILURE

With the increased intensity of care offered to neonates and with constantly improving continuous monitoring technology it is now not an infrequent occurrence to recognise a neonate with renal impairment. Acute renal failure (ARF) in its broadest terms, may be defined as a sudden reduction in renal function to a level insufficient to maintain homeostasis [Barratt 1987]. It is characterised by a sudden decrease in glomerular filtration

rate (GFR) which leads to disturbances in water, acid-base and electrolyte homeostasis and to the retention of nitrogenous waste products. In the neonate, as in other age groups, renal failure is divided into three categories - prerenal, intrinsic and postrenal failure. A diagnosis of prerenal failure is usually made if an oliguric infant responds to a fluid challenge with an increase in urine output. A diagnosis of postrenal failure is made if there is evidence of obstruction to urine flow - usually readily recognisable on ultrasound scanning.

However the diagnosis of intrinsic renal failure in the neonate and in particular the preterm neonate, is difficult [Stapleton et al 1987]; there are no accepted diagnostic criteria. There is limited information relating to incidence and outcome but survivors may sustain residual renal damage [Anand et al 1978; Alexander & Hill 1978]. An evaluation of the incidence of ARF in the sick neonatal population, based on diagnostic criteria arbitrarily extrapolated from older populations would be inappropriate, given the relative immaturity of renal function. For this reason a prospective survey of 388 consecutive admissions to a regional neonatal referral unit was carried out to determine the incidence of renal impairment suggestive of ARF and the most useful diagnostic indices.

Methods

Between March and December 1985 388 infants were admitted to the Regional Neonatal Intensive Care Unit, Liverpool Maternity Hospital. A description of this tertiary referral centre, population characteristics and standard methods of management are provided in chapter 3 - Methods.

As there are no accepted diagnostic criteria for ARF in the neonate the initial selection of infants with evidence of renal impairment was based on the arbitrarily selected criteria listed in Table 11.1. Major criteria were a plasma creatinine (PCr) rising persistently over a minimum of two days, anuria or oligura (urine flow rate less than 1.0 ml kg^{-1} h^{-1}) for a minimum 8 hours duration and a serum potassium exceeding 7.5 mmol l^{-1}. Minor criteria were an unexplained metabolic acidosis (pH < 7.25, base deficit > 10 mmol l^{-1}) and haematuria. All selected infants fulfilled a minimum of one major and one minor criterion, but the majority fulfilled several criteria.

In each case selection was made after normalization and stabilization of blood pressure. Careful attention was paid to maintenance of peripheral perfusion and hydration. An ultrasound scan of the renal tract was performed to rule out obstructive causes. Infants who were either anuric or

oliguric received a fluid challenge of 10 - 20 ml kg^{-1} of dextrose together with frusemide, 1 mg kg^{-1}, intravenously. Infants who responded to such a fluid load with an increase in urine output were considered to be in prerenal failure.

The following perinatal details were recorded: presence of perinatal asphyxia (1 minute Apgar score <3); antepartum haemorrhage; maternal pre eclampsia. A record was made of the major underlying diagnosis in each case together with birthweight, gestational age and postnatal age at the time of diagnosis. Measurement of urine and plasma creatinine, urea, sodium and potassium were made at the time of diagnosis and prior to any fluid challenge. Fractional sodium excretion (FeNa), renal failure index (RFI) and urine to plasma creatinine ratio (UCr/PCr) were calculated at the time of diagnosis prior to any fluid challenge. The formulae may be found in chapter 3 - Methods.

Results

Twenty four of 388 (6.2%) consecutive admissions developed evidence of renal impairment suggestive of intrinsic ARF based on the criteria listed above. Eleven infants were anuric at the time of diagnosis and 10 were oliguric; 3 had a urine flow rate in excess of 1 ml kg^{-1} h^{-1}. Urine flow rate in those not anuric ranged from 0.02 -

3 ml kg^{-1} h^{-1} (mean 0.71, median 0.12). Eighteen infants died (75% mortality) of whom 2 had ventilation electively discontinued. All 3 infants with non oliguric renal failure died.

The range of primary diagnoses is listed in Table 11.2. Septicaemia is the major contributor (33%). All the infants in this category who died weighed less than 1500 g. Four babies suffered severe perinatal asphyxia (17%); all were over 35 weeks gestation and all were outborn. One full term infant had hypoplastic left heart syndrome and ventilation was electively discontinued. Gestational age excluding these five mature infants ranged from 25 - 32 weeks (mean 26.5, median 28). Conservative management was employed for each of the 6 survivors. No baby received peritoneal dialysis.

Three infants, initially selected on the basis of oliguria, showed improved urine output after a fluid load; indices measured prior to the fluid load are listed in Table 11.3. These infants were considered to have been in prerenal failure.

Sixteen babies of the 24 babies presented in the first 48 hours of life. Among these there was a history of antepartum haemorrhage in 8 and preeclamptic toxaemia in 4; 4 had suffered severe perinatal asphyxia; 2 had received

indomethacin within the first 4 postnatal hours; 1 was born to a mother suffering preeclamptic toxaemia, disseminated intravascular coagulation and ARF and 1 following severe antepartum haemorrhage; 2 had severe hyaline membrane disease; the remaining diagnoses were rhesus hydrops, massive intraabdominal haemorrhage, septicaemia, hypoplastic left heart syndrome and massive intracerebral haemorrhage; the aetiology in the remaining baby, who was outborn, was uncertain but possibly involved unrecognised perinatal asphyxia.

Plasma creatinine, in case infants at the time of diagnosis, ranged from 96 - 246 umol l^{-1} (mean 155, median 155). Fifteen of the 24 infants had PCr values at the time of diagnosis outwith the 5% tolerance limits for post conceptional age based on the data of Trompeter et al [1983]. Fractional sodium excretion (FeNa, %) urine to plasma creatinine ratio (UCr/PCr), urinary sodium concentration (UNa, mmol l^{-1}), urine flow rate (UV, ml kg^{-1} h^{-1}) and renal failure index (RFI) for oliguric cases, non oliguric cases and the three babies with prerenal oliguria are presented in Table 11.3.

Discussion

Little emphasis is placed on the recognition and management of renal impairment in the sick newborn baby. Standard textbooks of neonatal medicine deal with the subject in a perfunctory manner, if at all. Yet the incidence of the problem would appear to be high. Norman and Asadi [1979] reported a 6% incidence of ARF in a series of 314 consecutive admissions to a neonatal intensive care unit, a figure comparable to that reported here of 6.2%. The mortality of ARF in the neonate is considerable. Previous reports quote mortalities of 45% [Norman & Asadi 1979], 60% [Ellis & Arnold 1982] and 50% [Mathew et al 1980]. Each of these studies related to infants of mean gestational age 34 - 35 weeks. The mortality in our series is 75% in a population with a mean gestational age of 30 weeks. The high mortality is probably due to a combination of difficulty and therefore delay in diagnosis, the technical problems of treatment in babies many of whom are of very low birth weight and because ARF usually occurs in severely ill infants with multisystem impairment.

Only 3 cases of prerenal failure were identified. This is in contrast to the findings of Norman and Asadi [1979] that 72% of oliguric infants responded to a trial of volume expansion with a sustained increase in urine output.

This may reflect the improved appreciation in recent years of the high insensible water losses of the very low birth weight infant which may be as high as 6-7 ml kg^{-1} h^{-1} in less than 1000 g infants nursed under radiant warmers [Baumgart 1982]. As in previous series septicaemia is the major underlying cause. Two infants were infected with s. aureus, one with s. epidermidis and four with gram negative organisms. The pathophysiology of the development of ARF in overwhelming sepsis is controversial but may reflect shock, intravascular coagulation and endotoxaemia.

In contrast to previous reports none of the 24 infants had underlying urinary tract malformations, nor were there any cases of post renal failure. This may in part be attributable to the increase in antenatal ultrasound scanning allowing early identification and appropriate management before the onset of renal impairment. Additionally such infants often present following discharge from the maternity hospital leading to their admission directly to a renal or neonatal surgical unit.

Two babies developed renal impairment that was attributable to the use of indomethacin. This is a well recognised hazard of indomethacin therapy [Catterton et al 1980; Halliday et al 1979]. Elevation of plasma creatinine, reduction in glomerular filtration rate and fall in urine flow rate have all been described and would appear to

result from the decrease in renal blood flow induced by indomethacin inhibition of prostaglandin synthetase. A contraindication to indomethacin therapy is evidence of preexisting renal impairment; neither of these two infants had any such evidence at the time of treatment but both were treated within 4 hours of birth. These observations lend weight to the argument that the "prophylactic" administration of indomethacin cannot be recommended, particularly within the first few hours of life during which time major redistribution of regional blood flow is taking place.

No evidence of renal impairment secondary to tolazoline administration was seen. Tolazoline has both pulmonary and systemic vasodilatory activity and it is likely that failure to maintain blood pressure adequately with concurrent colloid infusion during tolazoline treatment was responsible for the association with ARF previously described [Trompeter et al 1981].

Three babies developed renal impairment in association with the hypoxia of severe hyaline membrane disease; two died, both as a primary consequence of the respiratory illness.

The lack of renal functional impairment in this population arising as a consequence of primary infection of

the urinary tract is striking. None of the infants in this series had infected urine.

Perinatal events may influence the development of renal impairment. Of the 16 cases identified in the first 48 hours of life, 8 had a history of antepartum haemorrhage, though in only 1 did the renal impairment appear directly attributable to the haemorrhage. One infant with haematuria and intractable oliguria who was also hypertensive, was delivered of a mother who had herself developed ARF and disseminated intravascular coagulation secondary to pre eclamptic toxaemia. Little is known of renal function in infants born to pre eclamptic mothers though such infants have been described as having a significantly higher mean blood pressure in the first 20 minutes of life than a control group [Miller et al 1983].

Of indicators of renal impairment, changes in plasma creatinine and urine flow rate are at present used most frequently by the neonatal clinician but there are unfortunately problems in the interpretation of both these parameters in the newborn baby. The neonatal plasma creatinine level is initially dependent on the maternal level and changes rapidly during the first week of life. A sustained rise in plasma creatinine is indicative of a fall in glomerular filtration rate, but glomerular filtration rate is also changing at a rate dependent on both

gestational and postnatal age [Trompeter et al 1983]. Standard laboratory methods of plasma creatinine measurement may include the assay of non creatinine chromogens, the presence of which are significant when small changes are being considered.

Oliguria resistant to volume repletion is generally considered indicative of intrinsic renal failure but normal values for urine flow rate in preterm infants are poorly documented [Jones et al 1972]. 7% of infants fail to void during the first 24 hours of life [Kramer & Sherry 1951] and neonates do not empty their bladders completely on voiding [Osborne 1977] rendering external urine collections of short duration inaccurate. There is also the question of what constitutes oliguria in the preterm infant. Solute retention might be expected to occur at a urine flow rate of less than 1 ml kg^{-1} h^{-1} in the presence of an average renal solute load of 15 mosm kg body $weight^{-1}$ day^{-1} and an average maximum urinary concentration of 500 - 700 mosm kg $water^{-1}$ [Edelmann et al 1960] but babies in their first day of life have considerably smaller solute loads and a more appropriate figure may be 0.5 ml kg^{-1} h^{-1}.

Three babies had urine flow rates in excess of 1 ml kg^{-1} h^{-1}. All 3 were very oedematous and had haematuria; 2 were hyperkalaemic and of these 1 had a severe metabolic acidosis; only 1 had a raised plasma creatinine. Grylack et

al [1982] described the occurrence of non oliguric ARF in the newborn but their conclusions are less than convincing based as they are on an acceptance of a raised BUN as sufficient evidence of renal impairment. Non oliguric renal failure is believed to result from lesser degrees of tubular insult and to have a more favourable prognosis [Chevalier et al 1984]. However, in the present study, all 3 infants with non-oliguric ARF died. It is likely that with improved methods of monitoring renal function in extremely tiny babies the incidence of such lesser degrees of renal insufficiency will be found to have been underestimated.

Thirteen of the 24 infants had a serum urea within the normal range at the time of diagnosis. Measurement of serum urea is probably of little value in the newborn influenced as it is by numerous non renal factors. Misleading elevations in the presence of normal renal function may be seen in catabolic states such as sepsis and trauma and in the presence of sequestered blood, areas of tissue necrosis and haemoconcentration. Conversely, the higher anabolic state of the healthy newborn suggests that relatively smaller increments in plasma urea may reflect renal impairment.

In prerenal failure avid reabsorption of sodium and water results in urine of low sodium content and high

UCr/PCr while in established acute tubular necrosis the inability to conserve sodium and water results in urine of high sodium content and low UCr/PCr. These observations form the basis for the use of FeNa and RFI in differentiating prerenal from renal failure in older children and adults and such criteria have been applied to the neonate [Anand 1982; Aschinberg et al 1977; Engle 1986; Stapleton et al 1987].

Mathew et al [1980], in a study involving neonates of predominantly greater than 32 weeks gestation, suggest that a FeNa of 2.5% or greater is suggestive of renal as opposed to prerenal failure. A cut off FeNa of 3% has also been suggested [Norman & Asadi 1979], but in their study of 20 infants with ARF, only 7 were of less than 35 weeks gestation. Clinically well neonates of low gestational age may have FeNa values of up to 6% [Siegel & Oh 1976].

Similarly several authors suggest that a RFI of greater than 2.5 [Ellis & Arnold 1982; Mathew et al 1980], UCr/PCr of less than 20 and a urinary sodium concentration exceeding 40 mmol l^{-1} [Medani et al 1979] are indicative of intrinsic renal failure.

In the present study all three infants with prerenal oliguria had values for FeNa of less than 2.5%, a renal

failure index of less than 2.5 and UCr/PCr exceeding 20 but urinary sodium excretion was high.

These parameters were measured in 7 of the 10 babies with volume repletion resistant oliguria (Table 11.3). In this group urinary sodium is uniformly greater than 40 mmol l^{-1} but examination of FeNa, UCr/PCr and RFI appears to distinguish two subgroups with demarcation values of approximately 3%, 20 and 5.5 respectively. Three of the 6 survivors came from the subgroup with low FeNa, high UCr/PCr and low RFI, values which might be interpreted as suggestive of volume responsive prerenal oliguria; patient 2, who received indomethacin within the first four hours of life, patient 3, a 30 week rhesus hydrops, and patient 4, with severe hyaline membrane disease. The fatality, patient 1, had a pseudomonas septicaemia.

It is possible that the intractable oliguria in these infants with relative preservation of tubular concentrating ability reflects a decrease in GFR perhaps brought about by intense renal vasoconstriction, as has been suggested as occurring in infants with severe hyaline membrane disease, without intrinsic renal damage. Certainly low FeNa values have been described in clinical settings associated with marked glomerular hypoperfusion and avid renal tubular sodium reabsorption [Zarich et al 1985] such as congestive cardiac failure, with altered intrarenal haemodynamics such

as caused by indomethacin and following acute intra or extrarenal obstruction such as caused by haemoglobin and myoglobinuria.

In summary intrinsic renal impairment in the neonate is most likely to be seen after severe perinatal asphyxia in mature infants and in overwhelming septicaemia. Indomethacin therapy poses a particular hazard. Difficulties lie in detecting intermediate forms of damage. It is suggested that to the accepted spectrum of prerenal failure or hypoperfusion states, medullary ischemia and cortical ischemia be added oliguria resistant to volume repletion with intact tubular function.

Assessment of renal function is likely to be misleading if based on either changes in urine flow rate or on calculated indices of function in isolation. Healthy preterm neonates may have a high urinary sodium concentration and fractional sodium excretion and given both the problems in interpreting urine flow rates discussed above and the not insignificant difficulty in accurately collecting urine from neonates, meticulous attention to fluid balance and body weight remains the cornerstone of management. Early diagnosis at present depends on recognition of failure to achieve the normal postnatal fall in plasma creatinine.

Conclusions

1. The incidence of acute renal failure, assessed prospectively in 388 consecutive admissions to a regional tertiary neonatal referral centre, was 6.2% (24).

2. Overwhelming septicaemia was the commonest underlying cause, occurring in 8 infants (33%). Perinatal asphyxia was the commonest cause in mature infants.

3. There was a 75% mortality.

4. Eleven babies presented anuric, 10 oliguric and 3 were non-oliguric. The incidence of non-oliguric renal failure may have been underestimated.

5. In the differentiation of prerenal from renal failure in the oliguric infant, a urinary sodium concentration exceeding 40 mmol l^{-1} is highly sensitive but of poor specificity; a FeNa exceeding 3% is poorly sensitive but highly specific.

6. The most useful screening measure would appear to be failure to achieve the normal postnatal fall in plasma creatinine.

Table 11.1

Selection criteria for infants with renal impairment

Major criteria	
Rising plasma creatinine	persistently rising over a minimum of two days; the rise outwith the 95% tolerance limits for the assay in our laboratory.
Anuria or oliguria	oliguria - < 1 ml kg^{-1} h^{-1}; present for a minimum of 8 hours.
Hyperkalaemia	unhaemolysed sample; confirmed on repeat testing; >7.5 mmol l^{-1}
Minor criteria	
Metabolic acidosis	pH < 7.25; base deficit > 10 mmol l^{-1}; otherwise unexplained.
Haematuria	

Table 11.2

Renal impairment - primary diagnoses

	number of babies (%)	deaths
septicaemia	8 (33)	7
perinatal asphyxia	4 (17)	3
severe HMD	3 (12.5)	2
massive haemorrhage	4 (17)	4
indomethacin	2 (8)	1
rhesus hydrops	1 }	0
maternal PET/DIC/ARF	1 } (12.5)	0
hypoplastic LHS	1 }	1
total	24	18

Table 11.3

Parameters of renal function in infants with evidence of renal impairment. (For explanation of abbreviations see text.)

patient	FeNa	UCr/PCr	UNa	Uv	RFI
(oliguric)					
1	2.77	22	114	0.5	5.2
2	0.75	51	48	0.12	0.9
3	0.9	35	43	0.02	1.2
4	1.5	20.7	44	0.05	2.1
5	5.48	17	131	0.05	7.7
6	11.5	6.6	100	0.55	15.2
7	64.5	1.36	136	0.1	100
(non oliguric)					
8	44	2.4	160	2.6	66.7
9	2.6	21	75	3	3.6
(prerenal)					
10	0.9	29.9	44	0.2	1.5
11	1.4	38.4	74	0.2	1.9
12	0.8	22.2	22	0.15	1.0

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CONCLUDING REMARKS

Justification for the approach adopted.

A possible criticism of this study is that observations have been made and conclusions drawn from an essentially unselected group of infants with differing clinical characteristics. Nevertheless this approach can be justified in that it is also true that these infants form a clearly definable group, that of the infant of less than 34 weeks gestation with respiratory distress syndrome. Such infants form the major work load of neonatal intensive care units and a reluctance to study them directly because of the difficulties of controlling the number of clinical variables involved has resulted in the equally questionable application of data extrapolated from clinically different populations.

Duration of observations.

The infants were studied for differing lengths of time. Though not ideal, that this was unavoidable is a reflection of the practical difficulties involved. One in three admissions to this neonatal unit of babies of less than 1500 g birthweight were outborn, thus limiting the number it was possible to study from birth; only males were studied because of the need for accurate urine collection;

the study was conducted during a full time clinical appointment and could not therefore be supervised as closely as desired - this meant again for example that babies could not always be studied from birth and that breakdown of the skin of the perineum or leakage of urine from the collecting system meant ending that particular study; only one set of collecting apparatus was available allowing only one baby to be studied at any given time; the death of an infant obviously terminated a study as did the introduction of enteral feeds, loss of intraarterial access and transfer back to the referring hospital.

Statistical approach

A more useful approach than refusing to study clinically complicated subjects is to choose the method of statistical analysis with care. This underlies the use of multivariate analysis of variance in this study. The use of multivariate analysis of variance is essential when dealing with several interrelated variables [Hand & Taylor 1987]. Controlling for potentially confounding variables as done in this study may have weakened the chances of detecting an important relationship but it will also have minimised the chances of claiming significance when in fact none exists. For a small study this is an important consideration. It is

fair to say therefore, that the conclusions from this study are robust enough to merit further, controlled studies in selected groups of infants.

Glomerular filtration rate

Endogenous creatinine clearance was chosen as the method for measuring glomerular filtration rate as this would be readily applicable in a clinical setting. Two potential problems, that of extrarenal clearance and tubular secretion of creatinine were unlikely to be of relevance in the preterm neonate; a third, that of the presence of non-creatinine chromogens in plasma would appear from the literature to be minimised by the use of a kinetic reaction rate method of analysis [Schwartz et al 1987]. The Beckman autoanalyser used in this study utilises such a method [Hicks et al, 1979; Cottrell & Frings, 1979] and is also in wide use in hospital laboratories. Since the work and analysis for this study were completed it has become apparent that the presence of non-creatinine chromogens may be more of a problem in the preterm neonate than hitherto appreciated (Coulthard MG, personal communication of unpublished observations). Virtually all of the relevant literature should therefore be regarded with caution and in future studies a method of

creatinine assay not subject to interference, such as high pressure liquid chromatography (HPLC) or dilution mass spectroscopy, should be used. As far as this study is concerned, the same considerations apply to absolute measures of creatinine clearance. They do not however detract from the observation that following approximate correction for the presence of non-creatinine chromogens, creatinine clearance in this group of infants with respiratory disease was similar to comparable published measurements made in well infants.

Creatinine excretion.

Non-creatinine chromogens do not cause interference in urine samples and the measurements of creatinine excretion rate are thus reliable. A particular strength of the study is that accurate, timed urine collections were made over prolonged periods, thus minimising the problem of incomplete and variable voiding. The conclusion that creatinine excretion per unit weight increases between 25-34 weeks gestation, a conclusion that is at variance with certain published opinion, is strengthened by the meta-analysis incorporating data from the literature. Estimates of muscle mass derived from creatinine excretion rate are shown to be in close agreement with anatomical measures.

Serial measurements of body composition are poorly conducted in most newborn populations despite the fact that graduates from intensive care are liable to impaired growth for a variety of reasons. This simple method for estimating muscle mass should have useful application in clinical management.

Urine flow rate.

Urine flow rate on the first day of life was very often less than 1 ml kg^{-1} h^{-1} and was insufficient given the frequent concurrence of of inappropriate weight gain. The babies in this study often developed an inappropriate expansion of the extracellular space as shown by early weight gain, positive sodium balance and a normal plasma sodium concentration. A poor urine output is frequently missed in clinical practice because it is not monitored adequately. Equally, that a given urine output is insufficient is often not appreciated because babies are not weighed frequently enough and weights are not obtained net of attachments such as electrodes, endotracheal tubes and cannulae. Suggested explanations for the low first day urine flow rate have been that a urine output of less than 1 ml kg^{-1} h^{-1} is adequate given the low first day solute load, that it reflects the high circulating level of ADH

known to occur around the time of birth or that it reflects transiently impaired renal function. An alternative explanation is suggested by the observations of this study; namely that it is a response to an excessive salt intake. This hypothesis might be tested by comparing first day urine output in matched groups receiving different amounts of sodium.

The frequent observation of hyperosmolality should cause concern. Values around 300 mosm l^{-1} were often seen and would be more than sufficient to provoke the release of ADH and further impair water excretion.

Sodium.

It is not acceptable to regard the handling of sodium in the preterm baby as simply a function of immaturity. Changes in the handling of sodium are crucial to postnatal adaptation. The known contraction in extracellular fluid volume that occurs following birth must be accompanied by a loss of sodium; this study has shown the importance of considering the immediate postnatal period, during which cardiopulmonary adapation occurs, separately from subsequent periods when the problems of prematurity may be considered in relative isolation; the trigger transiently

imposing sodium loss onto the normal response of the growing organism to retain sodium is not known. The observations of this study suggest that the trigger is some function of cardiopulmonary adaptation. Studies are currently in progress to explore this further.

Glucose.

The inadvisability of extrapolation of data from other age groups is underlined by the observation that hyperglycaemia of the degree seen in this study did not lead to an osmotic diuresis. This has also been noted by other workers [Coulthard MG, unpublished observations] but needs to be more widely recognised as advice to increase fluid intake in the presence of hyperglycaemia and glycosuria is often found in textbooks of neonatology. The finding in this study that hyperglycaemia was associated with sodium retention and the hypothesis that this may be the result of a redistribution of blood flow during hyperglycaemia to the salt retaining inner cortical nephrons requires further evaluation. A direct, controlled study would not however be possible because it would be unethical to deliberately subject preterm babies to hyperglycaemia.

Beta-2-microglobulin/acute renal failure.

Renal failure would appear to be as common in the newborn population as previously reported, though the peak occurrence has shifted to infants of greater immaturity. A major problem remains that of diagnosis and definition. That this should be so is not surprising given the limited knowledge of normal renal function. Changes in plasma creatinine may be of more value when it is possible to measure true creatinine readily though the normal physiological changes in the immediate postnatal period will always adversely affect sensitivity and specificity. Monitoring serum beta-2-microglobulin may be a more useful approach. Senstive markers of tubular damage are also required to allow evaluation of, for example, damage following asphyxial insult or exposure to nephrotoxic agents. The measurement of urinary beta-2-microglobulin in this study was not found to be helpful because the accuracy of the assay was dependent on immediate correction of urinary pH and therefore affected by any delay in voiding. More studies of alternative urinary markers such as N-acetyl-glucosamine (NAG) isoenzymes may prove of value.

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APPENDIX

Publications arising from this thesis.

1. **Modi N.** Development of renal function. Br Med Bull 1988 44:935-956.

2. **Modi N.** Treatment of renal failure in neonates. Arch Dis Child 1989 64:630.

3. **Modi N,** Hutton JL. Urinary creatinine excretion in the newborn. Arch Dis Child 1989 64:304-305.

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