THE MAINTENANCE OF STABILITY IN THE NEWLY BORN*

1. CHEMICAL EXCHANGE

BY

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Sir Leonard Parsons was a very good friend to me. I met him first in the uneasy days just before the last world war, through an old colleague of mine who had gone to work in his department. He welcomed the idea that we should begin some joint work there and fostered my newly born interest in infant physiology till it was old enough to look after itself. I remember many stimulating visits to the Children's Hospital to discuss our results and Sir Leonard's leisured kindness on every occasion, in spite of all the administrative tasks which were pressing upon him at that time. We met again in very much happier circumstances at the British/Swiss Medical Congress which was held in Basel in 1946, and there his presence of mind may have been the means of saving my life. We had been talking about undernourished children in Germany, where my colleagues and I had been working, and I was so absorbed by listening to what he had to say about the clinical aspects of undernutrition in children one lovely September day outside 'Les Trois Rois' that I should certainly have been run over had he not pulled me back in time.

It was therefore a great privilege and also a pleasure to be invited to give these lectures, for it allows me an opportunity of helping to commemorate the man we all admire and to whom I owe so much.

The composition of the body, as revealed by chemical analysis, remains remarkably constant from hour to hour and from day to day. The efficiency of adults depends upon this, or in other words upon the maintenance of stability outside and inside the cells. This does not imply stasis, as the word homoeostasis might suggest, or indeed any constancy among the individual molecules, for each and every component of the body is in a state of intensely rapid flux. Few of the molecules in my plasma, for instance, were there a few minutes ago, yet its volume and temperature have altered very little in the last four or five hours, and the concentrations of glucose, sodium and potassium in it were much the same this morning as they were the day before yesterday. There is no need to multiply examples of this overall stability in adult life, for it has been implicit in the whole of physiology since the time of Claude Bernard (1865). Various aspects of it have been presented recently and very readably from different points of view by Hubble (1957), McIntosh (1957) and Pickering (1958). It is enough for the moment to emphasize that this overall stability is the result of a great number of the physical and chemical characteristics of the body being maintained in so-called 'steady states'. The internal temperature, the blood pressure, the volume of the plasma, its *p*H, the concentration of sugar, sodium and potassium in it, and in the cells, are all good examples. There are almost no limits to the number of these 'steady states' within the body.

When an adult is living in the physiological environment for which he was evolved, the stresses and strains of its daily life are rarely enough to break down the mechanisms which maintain the steady states, but a high altitude will do it and so will a very hot climate or too little drinking water, and so will disease. Most of the infections, for instance, alter the setting of some of the thermal regulating mechanisms, which then allow the temperature of the body to rise and maintain it in an abnormal steady state (Pickering, 1958). Nephrosis again raises the volume of extracellular fluid in the body by altering the setting of the controls and, so long as the nephrosis persists, the abnormal and disabling steady state persists also.

The newborn animal resembles its parents in that it has the same temperature at birth, the same

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general make-up and the same osmolar concentrations of electrolytes in its plasma, but in other respects its composition is not altogether the same. There is relatively more fluid outside its cells, for example (Flexner, Wilde, Proctor, Cowie, Vosburgh and Hellman, 1947; Friis-Hansen, 1954), and correspondingly more sodium and chloride in its body (Stapleton, 1958), for these are the main ions in extracellular fluid, and there are many less striking differences in chemical composition. There is, for example, a higher concentration of inorganic phosphate in the plasma (Murtagh, Videla, Marenzi and Braegger, 1957) and there may be a higher concentration of potassium (Widdowson and McCance, 1956). Some of the 'steady states', in other words, so highly characteristic of the adult, may not necessarily be the same in the newborn animal.

Birth is generally regarded as a physiological upheaval, and so it is, but mainly for what may be described as the supply services and sewage departments, and a successful entry into the new world should involve no major loss of internal stability. The great reorganizations in the vascular, pulmonary and digestive systems are all directed towards maintaining the services and steady states which had been in existence before.

It is not generally realized to what extent the foetus, with its 'adnexa', maintains its own steady states and internal stability. The foetus creates and maintains its own large volumes of extracellular fluids and then gradually reduces them in that part of itself destined to become the newborn animal. Work of our own has shown that birth makes no break in this process. The creation and functional efficiency of other foetal fluids are also the work of the foetus. The maintenance and composition of the allantoic and amniotic fluids, for instance, are the work of its kidney (Ahlfeld, 1906; Makepeace, Fremont-Smith, Dailey and Carroll, 1931; Bates, 1933; Potter, 1952; Baird, 1957; Davies and Routh, 1957; Alexander, Nixon, Widdas and Wohlzogen, 1958a, b) and of the membranes themselves (Dickerson and McCance, 1957; McCance and Dickerson, 1957; Jeffcoate and Scott, 1959), but unfortunately we know very little about all this at present. The high concentration of amino acids in foetal plasma, and of certain vitamins (Baker, Ziffer, Pasher and Sobotka, 1958), the accumulation of immune bodies (Brambell, 1954), and variations in placental blood flow (Nyberg and Westin, 1957; Westin, 1957) must be regarded as regulations of the foetus for its own welfare, and many of these foetal steady states are carried forward for weeks or months by the newborn animal. Some, the high concentrations of fructose, for example (Goodwin, 1957), and of creatinine (Zweymüller, Widdowson and McCance, 1959) in the plasma of some ungulate foetuses are not, and some of the changes which do take place in the infantile steady states are part, specifically, of the physiology of the newly born (Bangham, Ingram, Roy, Shillam and Terry, 1958; McCance and Widdowson, 1959a).

The chemical stability of the body in the newly born depends mainly upon the same organs as in later life. As in adults, moreover, cells all over the body may participate in maintaining the stability of the internal environment by sacrificing some of their own (Schwartz, Jenson and Relman, 1954; Leaf and Newburgh, 1955; Elkinton and Danowski, 1955), and the stability of the internal environment can be destroyed with fatal results if the cells are not able to maintain themselves in a state of functional efficiency. Nevertheless the newborn animal is not just a little adult. Its stability may be threatened or upheld in ways without counterpart in adults. Some of these are important practically, all theoretically.

The object of these lectures is to examine a few of these stabilizing mechanisms and steady states; why some of them are particularly vulnerable in the first few days of life and what happens if they fail. Comparison with adults will be necessary and also a study of several species, for only thus is it possible to grasp the complexities of the subject and arrive at any useful generalizations. Our knowledge is not great enough to solve any of these problems satisfactorily, even those on which most work has been done. Nevertheless, enough is known to demonstrate its importance and the desirability of extending this knowledge.

The Arterial Tension of Oxygen

Acute deprivation of oxygen constitutes an immediate hazard to every steady state within the body, and indeed to life itself, but adults and newborns react to it rather differently. Elderly people may never recover their mental poise after what may seem to the onlooker to have been a trifling incident, such as a minor anaesthetic (Bedford, 1957; Bourne, 1957). If the lack of oxygen has encouraged overbreathing in an atmosphere containing little or no carbon dioxide the respiratory alkalosis thus created may have contributed to the results, for this has been shown to reduce cerebral blood flow (Kety, 1950).

When adult dogs are placed in nitrogen, or the air surrounding them is suddenly decompressed, their blood pressure, their respiration rate and consequently the *p*H of their blood all rise within the first minute, but by about the second or third minute

their blood pressure has begun to fall rapidly, and respiration may cease. The *p*H of the blood falls as death approaches, but remains within normal limits, and is usually not far from its initial level at the end. When puppies are suddenly deprived of oxygen, their blood pressure, respiration rate and blood *p*H do not rise, but all fall progressively. Respiratory efforts may be made for 16-20 minutes and the heart may go on beating feebly for twice this time. Anoxia raises the cardiac output to about four times its previous level in adult sheep, whereas it leaves it unchanged in the newborn lamb (Cross, Dawes and Mott, 1958a, 1959). Puppies have recovered after 26 minutes without oxygen when their blood pressure had fallen to 5·2/3·7 mm. Hg and the *p*H of their blood to 6·5 (Swann and Brucer, 1949; Swann, 1953; Swann, Brucer and King, 1953; Swann, Christian and Hamilton, 1954); puppies' brains are also very tolerant of anoxaemia (Kabat, 1940), and some primitive respiratory centre can continue to initiate gasps for many minutes even when the heads of many newborn animals are removed from their bodies and placed in nitrogen, but this ability fades away as the animals grow (Selle, 1941; Thoms and Hiestand, 1947).

Prolonged survival of this kind, relative to that of an adult, and a useful life thereafter, seem to depend on the ability of the newborn animal to make extensive use of anaerobic glycolysis to provide the energy required to maintain its life processes and in particular to synthesize the high energy phosphate bonds which maintain the proper structure and function of its brain (Stone, Marshall and Nims, 1941; Fazekas and Himwich, 1941; Fazekas, Alexander and Himwich, 1941; Čapek, Hahn, Křecek and Martínek, 1956). If glycolysis is prevented by iodoacetate or fluoride, newborn rats die in a few minutes in nitrogen, although they can still live on for 50 minutes in oxygen, presumably by utilizing their available carbohydrate in other ways, as will later be discussed (Fazekas and Himwich, 1941; Conference, 1958). The effects of anoxia on the brain can be mitigated by an adequate supply of circulating glucose or made worse by hypoglycaemia and insulin (Himwich, Fazekas and Alexander, 1941; Himwich, Bernstein, Herrlich, Chesler and Fazekas, 1942; Gellhorn and Kessler, 1942). It is possible, however, that the quantity of glycogen available to the heart muscle may sometimes set the seal on the survival time (Dawes, Mott and Shelley, 1959). As might have been anticipated, this resistance to oxygen deprivation has been shown to vary with the species and the maturity of the animal at birth, but particularly with the state of development of the brain at this time. Guinea-pigs, for example, which are highly developed at birth, succumb much more quickly than rats in a reduced supply of oxygen (Fazekas *et al.*, 1941), and the brain seems to be the most vulnerable organ, even in the undeveloped rat (Adolph, 1948; Čapek *et al.*, 1956; Conference, 1958).

The transition from uterine to atmospheric respiration does not always go as smoothly as one could wish (Editorial, 1957a, b; Turnbull and Baird, 1957), and some investigators have taken a very serious view of respiratory failure and oxygen deficiencies in the newborn baby (Darke, 1944; Preston, 1945; Evans, 1948; Bernstein, 1958). Others admittedly have not (Campbell, Cheeseman and Kilpatrick, 1950; Usdin and Weil, 1952; Apgar, Girdany, McIntosh and Taylor, 1955) and the resistance of newborn animals to a shortage of oxygen is undeniably great (Adolph, 1948; Smith, 1959; Swann *et al.*, 1954), partly perhaps because they do not as a rule over-ventilate (Cross, Tizard and Trythall, 1955), and also because they can make such good use of anaerobic glycolysis to supply all their physiological needs (Dawes, Mott and Shelley, 1958). Signs of anaerobic metabolism may be found after normal birth, even in man (Gonzales and Gardner, 1957). Kittens and rats have been delivered in good shape after their mother had died of anoxaemia (Fazekas *et al.*, 1941), and it is common knowledge how difficult it is to drown these animals. The whole matter has been the subject of experiment since the time of Boyle (1672), and there are many records of healthy infants being born alive up to 20 minutes after the death of their mothers (Harvey, 1651; Hellman, 1953). The case recorded by Bullough (1958) shows what a newborn infant can withstand in the way of asphyxia and still survive to win a baby competition nine months later.

In spite of this tolerance, if an infant is born in an advanced stage of asphyxia and if respiration does not begin when the cord is cut (perhaps because of the asphyxia), an acute emergency may develop in a few moments. The crisis may appear later in a more chronic form, particularly in premature infants, as part of the so-called 'respiratory distress syndrome'. Whatever the cause, the primary and secondary changes in the chemistry of the internal environment are now becoming clear, and are common to all species (Dawes and Mott, 1959). The failure of the supply of oxygen may not be so immediately fatal to the newborn baby as it would be to an adult because of the ability of the newly born to make good for a time with anaerobic glycolysis, but this results in the accumulation of lactic and to some extent other non-volatile acids in

the body. The stabilizing systems in the plasma and cells respond to this, and mitigate the effects, but the *p*H falls and the available 'buffer base' is reduced. If CO_2 can be eliminated there is a fall in the plasma bicarbonate. In human infants the plasma bicarbonate is normally lower than the values accepted as normal for adults (Reardon, Baumann and Haddad, 1954), but in line with those found in late pregnancy (Goodland, Reynolds and Pommerenke, 1954), with which the foetal bicarbonate has been in equilibrium *in utero* (Weisbrot, James, Prince, Holaday and Apgar, 1958). In respiratory failure, however, the elimination of CO_2 is interfered with to the same extent as the delivery of oxygen. Consequently the pressure of CO_2 rises, and this intensifies the acidosis, but as the compensation for it is a rise in the plasma bicarbonate it is impossible to interpret single determinations of plasma bicarbonate, and a figure quite normal for a pregnant or non-pregnant adult might be found in the presence of a serious fall of plasma *p*H, much too high a pressure of CO_2 and a much reduced buffer base (Singer and Hastings, 1948).

The incidence of asphyxia in full term infants has been investigated by Miller, Behrle, Smull and Blim (1957), and more recently by James, Weisbrot, Prince, Holaday and Apgar (1958) and James (1958). These investigators have employed very beautiful and delicate techniques to follow the chemical changes in the serum for the first hours or days of life. An abstract of their findings has been given in Table 1 and their results are very well worth thought-

TABLE 1
RECOVERY FROM NEONATAL ASPHYXIA IN 'NORMAL' BABIES

	*p*H	P CO_2 mm. Hg	Plasma Bicarbonate mEq./l.	Buffer Base mEq./l
Birth ..	7·23	58	25	41
1 hr. ..	7·30	39	21	42
3 hr. ..	7·34	38	22	44
24 hr. ..	7·41	34	21	45

ful consideration. Firstly, these workers have found that, although there are great individual variations, which make it difficult to generalize, few infants are delivered without some signs of asphyxia. This may be partly the natural course of events, but there are strong reasons for believing that much of it is man-made and preventable. Few babies are born today as nature intended them to be. Anaesthetics are given to the mother which are known to reduce the blood pressure and to prolong the dangerous second stage of labour. If they are volatile anaesthetics the methods of administration may interfere with maternal gas exchange in the lungs and give rise to some deficiency of maternal oxygenation. Women are frequently delivered lying on their backs which must interfere with the venous return from the uterus and lower limbs, and drugs are used which depress the respiratory centres in the infant and make resuscitation more difficult (James *et al.*, 1958; Shields and Taylor, 1957; Henderson, Mosher and Bittrich, 1957). Secondly, changes in the tensions of oxygen and CO_2 and signs of an acidosis are not the only, or perhaps the most serious, results of asphyxia. The serum potassium may rise; this may be due to hydrogen-potassium exchange across the cell boundary, more commonly seen in reverse during potassium deficiencies, or it may be due to the acidosis preventing the cells in some part of the body maintaining the normal gradient between themselves and their surroundings (Schwarz, Cohen, Lubash and Rubin, 1959). Thirdly, in spite of all these handicaps, once respiration is established the full term infant shows great powers of recuperation, restores the chemical abnormalities in its serum to normal and establishes its own internal stability on a physiological basis.

The premature infant can do the same. Usher (1958) has followed some of these infants carefully and watched the clinical and chemical signs of asphyxia develop with the onset and progress of respiratory distress. He has emphasized the rise in the serum potassium and attributed to it the gross abnormalities he has found in the electrocardiogram, and to it also possibly the immediate cause of death. He has also succeeded in reversing some of these signs of chronic asphyxia by glucose and alkaline infusions. Similar beneficial effects on the serum potassium and the cardiogram have been obtained by the administration of bicarbonate to adults suffering from the severe acidosis of uraemia (Schwarz *et al.*, 1959).

Asphyxia therefore constitutes the first great threat to somatic stability in the newly born. Infants are very tolerant of anoxaemia and asphyxia, but both of these affect their chemical stability and, as will later be shown, their thermal balance, and everything should be done to prevent them or minimize their effects. Once respiration is established or re-established, however, the infant can safely be left to recover and maintain all the steady states which depend upon an adequate supply of oxygen (Kaiser and Goodlin, 1958).

The Level of Circulating Bilirubin

Some yellowness of the skin is so common in the days following birth and usually so transient and apparently harmless that it came to be termed

physiological jaundice of the newborn. In premature babies, however, it may be much more severe (Crosse, Meyer and Gerrard, 1955) and indeed pathological. The dangerous limits for circulating bilirubin are of the order of 20 mg./100 ml. of serum (Lucey and Dolan, 1959). This concentration is a direct threat to the stability of the internal environment, and the whys and wherefores for this are among the most interesting developments of modern paediatrics (Editorial, 1958). The pigment is always of the 'indirect' type according to the van den Bergh nomenclature. This pigment is relatively non-toxic, but it was found by Day (1954) and by Walters and Bowen (1955) that as its concentration rose the pigment interfered with the uptake of oxygen by rat brain tissue *in vitro*. Chopped tissues and homogenates were used and the inhibition was much greater in newborn than in adult preparations. The inhibition was removed by adding cytochrome or methylene blue. Zetterström and Ernster (1956) then showed on mitochondria isolated from the liver that the pigment 'uncoupled' the processes of oxidation from those of the phosphorylation of adenosine diphosphate. The evidence is, therefore, that if bilirubin accumulates to any extent the proper uptake of oxygen will cease and with it the normal production of heat so necessary to maintain the body temperature at this age. Furthermore, the metabolism which does go on will be functionally less valuable.

The pigment produced by the degradation of haemoglobin is normally prepared for excretion by the liver. The process is rather a complicated one and is illustrated diagrammatically in Fig. 1. The final step is the conjugation of the pigment with glucuronic acid and its transportation from the serum to the bile, but the evidence at present is that this can only be brought about in a certain way. Uridine triphosphate is a pyrimidine nucleotide used in many reactions in the body. These uridine compounds are involved for instance in the metabolism of galactose in the mammary gland (Malpress, 1958), and galactosaemia, the hereditary disorder of metabolism (Holzel and Komrower, 1955), is caused by a failure in the development of the enzyme in the liver which catalyses the conversion of uridine diphosphate glucose (Anderson, Kalckar and Isselbacher, 1957; Collip and Donnell, 1959) to uridine diphosphate galactose. The compound may also be involved in the transport of amino acids across the renal tubules since this is one of the mechanisms disorganized in galactosaemia (Cusworth, Dent and Flynn, 1955). In the preparation for bilirubin conjugation the uridine triphosphate combines with glucose 1 phosphate to give uridine diphosphate glucose and pyrophosphate which need not be further considered. The uridine diphosphate glucose is then oxidized by a dehydrogenase enzyme to uridine diphosphate glucuronic acid. These are the compounds from which two glucuronic acid mole-

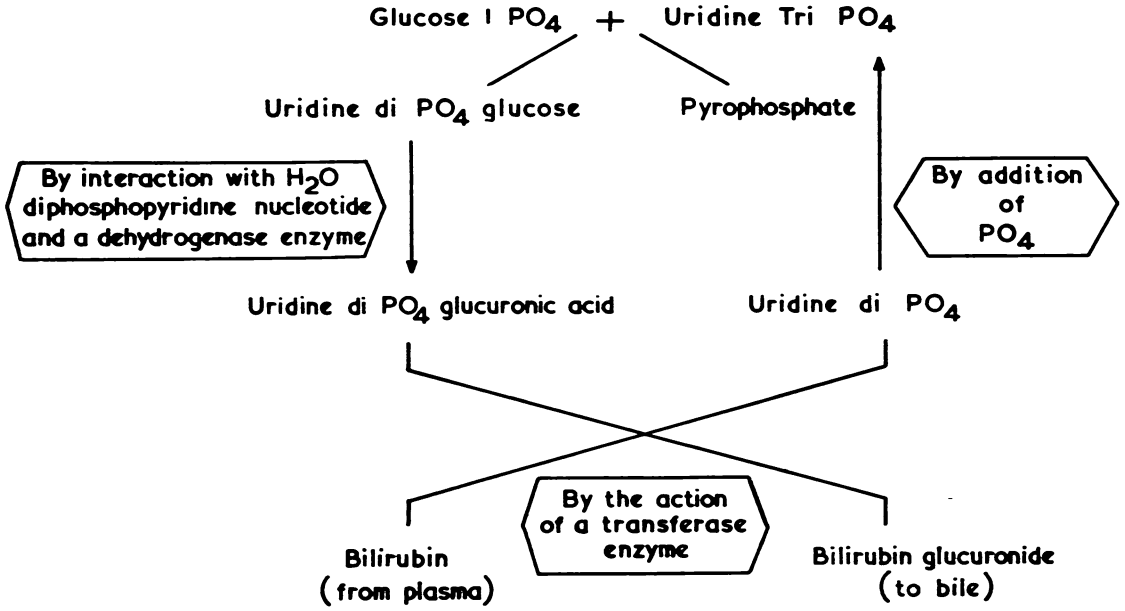

FIG. 1.—The conjugation of bilirubin with glucuronic acid in the liver cell.

cules are transferred to one bilirubin molecule and the reaction is catalysed by an enzyme which is called a transferase. The uridine diphosphate is then reconverted to uridine triphosphate by a process involving adenosine triphosphate and subsequent oxidation, and the cycle starts again. The reaction, however, goes much more slowly in the newborn animal or human infant than in adults of the same species because of the immaturity of the enzyme systems in the liver at birth (Brown and Zuelzer, 1958; Lathe, Claireaux and Norman, 1958). The activities of the dehydrogenase and of the transferase are both very small by adult standards, but they increase very rapidly (Lathe and Walker, 1957; Dutton, 1959). Bilirubin is not the only compound conjugated with glucuronic acid, and other compounds can be used to test the activity of the enzymes. Para-aminophenol has been used, and Vest (1958) used acetanilide in his work on human infants. According to him the activity increased rapidly after birth, but did not reach the adult level until the babies were about 3 months old. Evidence is strong that the enzyme systems are less developed in infants born before than at full term, which is in keeping with clinical observations all over the world on the effect of prematurity on jaundice (Shnier and Levin, 1959). Holman (1958) examined a group of white and negro premature infants in Baltimore, for instance, and found that both the incidence and the severity of the jaundice were increased by prematurity, and that it tended to be worse in the white infants than in the negro ones, probably because of the recognized racial differences between the degree of maturity of white and black infants at birth. Here then is an example of chemical stability which is threatened mainly by virtue of immaturity, and a most interesting discovery about it has recently been made by Cremer, Perryman and Richards (1958). These authors have found that the bilirubin in serum is highly photosensitive, and the levels in the body can be greatly reduced by exposing infants to sunlight or artificial light. This would appear to be the first time that light has been shown to have a stabilizing effect on the internal environment. It may have been much more important to primitive man living in equatorial Africa than to infants nowadays, but the authors suggest that treatment with light may remove the necessity for a certain number of the exchange transfusions now being carried out, admittedly with some risk (Walker and Mollison, 1957; Farquhar and Smith, 1958), as a method of treating hyperbilirubinaemia in premature infants (Editorial, 1958).

Danoff, Boyer and Holt (1958, 1959) have tried treating hyperbilirubinaemia by the administration of glucuronic acid, and have found the concentration of bilirubin in the serum to fall. Although such treatment might seem an obvious one, it does not appear to be fundamentally sound if the chain of reactions illustrated in Fig. 1 is correct, and it has been heavily criticized (Jeliu, Schmid and Gellis, 1959). Treatment of hereditary jaundice with glucuronic acid in the Gunn strain of rats also reduces the serum bilirubin, but the bilirubin is not excreted and appears to accumulate in the cells. The conclusions of Danoff *et al.* (1958, 1959) were cautious and restrained, and further experimental work on the subject will no doubt decide the issue one way or the other.

It has been recognized for some years (Allison, 1955; Bound and Telfer, 1956; Meyer and Angus, 1956; Willi, 1956) that there was some reason to suppose that the vitamin K analogues, particularly Synkavit, tended to cause a haemolytic anaemia and to increase the incidence of hyperbilirubinaemia in premature infants. This is a matter of importance because premature infants or their mothers are often given vitamin K as a protection against haemorrhagic diseases of the newly born. Synkavit is a sodium diphosphate compound of menadione, and another analogue called Hykinone, which is menadione sodium bisulphite, has now been found to be rather more dangerous than Synkavit (Lucey and Dolan, 1959). It is uncertain at present how and why exhibition of these vitamin K analogues constitutes such a risk to chemical stability. It is possible that it is due to an effect on the red blood cells and enhanced by a vitamin E deficiency (Allison, 1955). It may also be due to some unknown toxic action on the liver. Another explanation is based upon the fact that these analogues are to some extent excreted as glucuronides. This means that they must be conjugated like bilirubin. They may therefore compete with bilirubin for the transferase enzyme. If they are preferentially absorbed on to the enzyme molecule and not so easily removed, a little menadione may prevent the conjugation of a great deal of bilirubin, for this is how the sulphonamides and other compounds act upon bacteria.

Renal Function, Food and Growth

Fig. 2 shows the course of the blood urea in three species of animals during the first days of life. All were fed on mother's milk. In each of them the concentration of urea in the serum rose for a short time and then fell again to a lower level (McCance and Otley, 1951; Joppich and Wolf, 1958). It was at first supposed that the rise was an indication of functional immaturity of the kidney, and the fall due to its rapid development at this age, for the general

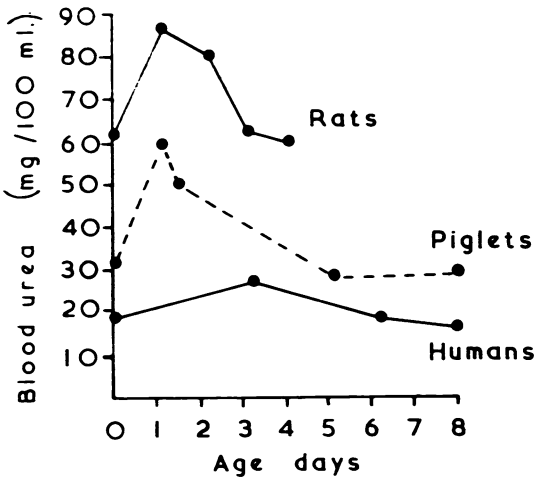

FIG. 2.—Changes in the concentration of urea in the blood during the early days of life.

work on renal function in early life seemed to suggest this. Aspects of this development have been reviewed in some detail by McCance (1950), Barnett and Vesterdal (1953), McIntosh (1957), Adolph (1957) and Vesterdal (1959), and only the general principles of infantile renal function need be considered here.

Before doing so, however, it is necessary to point out that there are certain difficulties in interpreting the results of work on the function of the kidney just after birth. These have arisen because of a natural desire to compare the findings with those in adults which were much better known. The comparison of some functions presents no difficulty. The ability to concentrate the urine for example, is among these, and some results, which were obtained by McCance and Widdowson (1954a), indicate that the kidney of the newborn does not raise the osmolar concentration of the urine to the same extent as it does in adults. When studies of glomerular filtration rates and urea clearances began to be made, however, some method of eliminating the effects of size had to be devised, for the results of these tests are given as the number of ml. of extracellular fluid passing through the glomeruli or cleared of urea per minute, and it is evident that a field mouse could never hope to compete with an elephant in this regard, although it might have a much more effective kidney. Difficulties due to size were therefore eliminated by adopting the practice used in metabolic work and expressing the results per unit of surface area. At first this seemed satisfactory to most people interested in babies, but those who worked on animals mostly expressed their results on the basis of body weight. By both methods (McCance and Young, 1940) the human newborn infant appears to have sub-normal renal function by adult standards but, whereas on the basis of surface area functions such as glomerular filtration rate rise progressively after birth and reach the adult level at about 2 years of age, on the basis of body weight they pass through a phase well above the adult level at this time of life (McCance and Widdowson, 1952). These bases of comparison cannot both be 'right' and others have been suggested from time to time. The matter has been further confused by those who have administered their test doses on one basis and compared the results on another, and the only correct and proper thing to do now is to study the renal function of the newborn and immature animal in its own right and to establish the proper normal for every age. This is gradually becoming recognized, and the paper of Edelmann, Troupkou and Barnett (1959) shows how the study of the concentrating power of the kidney in infancy is now being approached. There is, nevertheless, plenty of evidence on all bases of comparison that the kidney of the newborn animal is functionally immature. The glomerular filtration rates and urea clearance show this, and so do some of the tubular functions such as the excretion of diodone and para-amino hippuric acid, and the reabsorption of glucose. Interesting confirmation of this which does not depend upon any arbitrary basis of comparison came from the work of Rennick and Hamilton (1958) on the ability of isolated kidney slices to pick up para-amino hippurate and tetra-ethyl ammonium from the surrounding medium and concentrate them in tubule cells. The rat provides particularly good examples of renal immaturity, for just after birth its kidney varies its rates of excretion little in response to substances administered as tests. The kidneys of other species, however, have been shown to be little better. The excretion of water (McCance and Wilkinson, 1947; Heller, 1947; Ames, 1953; McCance and Widdowson, 1955; Falk, 1955; Hoy and Adolph, 1956; Adolph, 1957; Ziskind and Gellis, 1958), sodium chloride (Dean and McCance, 1949; McCance and Widdowson, 1957), and ammonium ions (Cort and McCance, 1954; Widdowson and McCance, 1958; Hatemi, 1959) have all been shown to be less efficient than the corresponding functions in adults.

Other signs of immaturity are provided by a certain lack of balance between glomerular and tubular function. Some of the excretory functions of the tubules appear to be more undeveloped than the glomerular filtration rates whereas others, such

as the reabsorption of sodium and chloride, are more highly developed. Responses, moreover, which rely upon the integration of a detector as well as the effector organ, such as the regulation of the volume and osmolar concentration of the extracellular fluids, will later be shown also to be defective, and although all newborn animals will suck milk, many will not take water by mouth till they are a certain age in response to somatic dehydration, and only 'learn' to do so as they develop (Adolph, 1957). An example of still more remote control of renal function in the newborn period is provided by those animals like the puppy, kitten and rat which can only empty their bladders during early suckling if the mother animal licks the perineum at appropriate intervals (McCance and Wilkinson, 1947; Cort and McCance, 1954). Yet the volume and composition of the body fluids remain within normal limits from birth onwards and the steady states proper to the infant are adequately maintained. The rise in the blood urea shown in Fig. 2 is trifling and its fall is not, as was originally thought, due to the rapid maturation of the urea clearance, for this takes place much too slowly. No basis of comparison can explain this discrepancy between experience and experiment, and we worried about it for years. We began to search for stabilizing mechanisms other than the kidney, and for a more constructive approach to the study of the internal stability and steady states of the developing organism.

Much of the protein nitrogen in the food of a freely growing animal is incorporated directly or indirectly into tissue protein and never appears in the form in which it is excreted by the kidney. This relieves the kidney of any such animal of much of the work which it is called upon to do in adult life. Minerals in the food are absorbed also and retained in a growing organism in the tissues and bones. Edwards (1824) fully recognized the overwhelming importance of growth in relationship to every function of the body: 'Dans la jeunesse tout paraît tendre au développement et à l'accroissement du corps.' It was emphasized by Stransky and Bálint (1920) as an aspect of renal function, but the possible implications of these wise remarks were not appreciated at the time and have only recently been demonstrated experimentally (McCance and Widdowson, 1956). Table 2 gives results which were obtained in a study of the newborn pig. Half the animals were given no food and the others were fed by hand on the kind of diet provided by the sow at this age. The intake and excretion of nitrogen was followed. Comparison of the two groups shows that nine-tenths of the protein nitrogen in the food was incorporated into the tissues and never presented

TABLE 2
NITROGEN BALANCES OF NEWBORN PIGLETS WHICH WERE 'FED' OR 'NOT FED'

	Animals Given:	
	Milk	Water
N intake (mg./kg./24 hr.) ..	3,500	0
N output (mg./kg./24 hr.) ..	350	250
N 'balance' (mg./kg./24 hr.) ..	+3,150	−250

itself to the kidney for excretion as urea. The same is true to a lesser, but still to a surprising, extent of the more slowly growing human baby aged 7 days. Immature, therefore, as the kidney of the newborn may appear to be when some such test as the urea clearance or the excretion of para-amino hippuric acid is applied to it, it is quite capable of maintaining the blood urea and creatinine within normal limits, provided growth is taking place as it should, and there is no forced degradation of tissue protein. The effect of this on the blood urea has been demonstrated by the heights to which it may rise in human infants which have survived a protracted and difficult labour (McCance and Widdowson, 1954b) or in animals kept without food in a cold environment (McCance and Widdowson, 1959b), and it could certainly be demonstrated again by giving the newborn animal some food which could not for some reason promote growth. Correspondingly, anything which can delay the breakdown of tissue protein can actually reverse the usual rise in the serum urea after birth demonstrated in Fig. 2. Glucose has been shown to do this experimentally in the starving newborn pig (McCance and Widdowson, 1956).

The stabilizing effects of growth have also been demonstrated in another way (McCance and Widdowson, 1958a). Newborn piglets were given 26 mEq./kg. body weight of potassium per 24 hours over the first 40 hours of their lives (Table 3). Some

TABLE 3
EFFECT OF GIVING KCl AND WATER OR KCl AND MILK TO NEWBORN PIGLETS

	KCl+Water	KCl+Milk
K intake (mEq./kg./24 hr. ..	26	27
K retained (mEq./kg./24 hr.)	+2·9	+10·5
Serum K (mEq./l.)	9·3	5·9
Signs of toxicity	Paralysed	None
Change in body weight (g./kg. birth weight)	−104	+103

of the piglets were given this potassium dissolved in water, others in a volume of sow's milk so adjusted that all the animals received the same amount of water as well as potassium. The animals getting the

potassium in water lost weight and did not excrete the potassium fast enough to prevent a major rise in its concentration in their sera and they became paralysed. The blood sugars also rose, which surprised us very much at the time, although the result might have been expected from the work of Silvette, Britton and Kline (1938). The other piglets gained weight, for they grew rapidly and incorporated much of the potassium into their cells. The concentrations in the sera rose relatively little, although the urine volumes were comparatively small, and the piglets appeared perfectly normal at the end.

Table 4 shows the effect of giving large but quite reasonable amounts of water unbalanced by food to newborn puppies (McCance and Widdowson, 1958b). These animals differ from piglets in that they tend to excrete water much less freely and sodium chloride more freely at this time of life. The puppies which received milk grew satisfactorily and maintained a perfectly normal internal concentration of sodium and chloride, whereas those given water only excreted a relatively small fraction of the quantity which had been administered. They gained considerable weight although they were getting no food, and their body fluids became diluted to an extent which was clearly pathological. It is probably true to say that many, if not most, of these effects were appreciated and demonstrated in rather different settings nearly 30 years ago by Kerpel-Fronius and his associates in Hungary (Kramár, 1927; Kerpel-Fronius and Leövey, 1931; Csapó and Kerpel-Fronius, 1933; Kerpel-Fronius, 1933), but the implications were missed by everyone who read the papers at the time, and by most people since.

Yet one more example of the stabilizing effects of growth is provided by a study of the metabolism of phosphate in newborn infants. Table 5 illustrates this (Widdowson and McCance, 1959). During the first 48 hours of their lives these babies were given no food, and the serum phosphorus rose somewhat and phosphorus began to be excreted. This rise appears to be due to starvation and the liberation of phosphorus from organic combination, and it is shown in a more exaggerated form in the newborn pig. By the seventh day, however, when the intake of phosphorus had been raised by mother's milk from nothing to 25 mg./kg./day and the infants were growing, so much phosphorus was being incorporated into the tissues that the serum phosphorus had fallen and virtually none was being excreted.

The capacity for growth can be saturated only by an optimum diet, and the percentage of protein, fat

TABLE 4

EFFECT OF FOOD AND GROWTH ON OSMOLAR HOMOEOSTASIS IN THE NEWBORN PUPPY

	Water Alone	Water and Milk Solids
Fluid given (ml./kg. birth weight /24 hr.)	256	256
Urine volume (ml./kg. birth weight/24 hr.)	135	37
Visible water balance (ml./kg. birth weight/24 hr.)	+121	+219
Serum Na (mEq./l.)	120	141
Serum osmolar conc. (mEq./l.)	243	310
Gain of body weight (g./kg.birth weight/24 hr.)	69	178

TABLE 5

EFFECT OF FOOD AND GROWTH ON PHOSPHORUS HOMOEOSTASIS IN NEWBORN INFANTS

	1st Day	2nd Day	7th Day
P intake (mg./kg./ 24 hr.)	0	Traces	25
P output in urine (mg./kg./24 hr.)	0·05	3·24	0·02
	At birth	At 48 hr.	7th day
Serum P (mg./100 ml.)	6·03	7·28	6·04

and carbohydrate in the mother's milk has long been known to be correlated with the growth requirements of the newborn animal (Bunge, 1898). The inorganic constituents of the diet must also be correlated with the function of the kidney and growth. The amount of calcium and phosphorus in human milk, for example, would never support the bone growth of a healthy piglet. The whole principle of feeding in the newborn period, and indeed later, must be to saturate the growth requirements of the animal in question if rapid growth is desired, but at the same time to provide the stabilizing organs with the minimum amount of work. This principle has many implications. A suitable environmental temperature, for example, may considerably reduce the requirements for food.

A good example of the necessity for integrating food and renal function is the effect of raising the intake of sodium chloride in the newborn infant or piglet by adding salt to the milk. Owing to the very large intake of fluid by the newborn animal quite a small percentage of salt in the milk can lead to the ingestion of more salt than an adult would normally take. Given the corresponding amount of water, however, an adult would excrete both without a breakdown in the stability of the body fluids. Not so the human infant. Fig. 3 shows the effect of making up the milk for three premature babies so that it contained 0·7% of sodium chloride. In each one the normal gain in weight from day to day

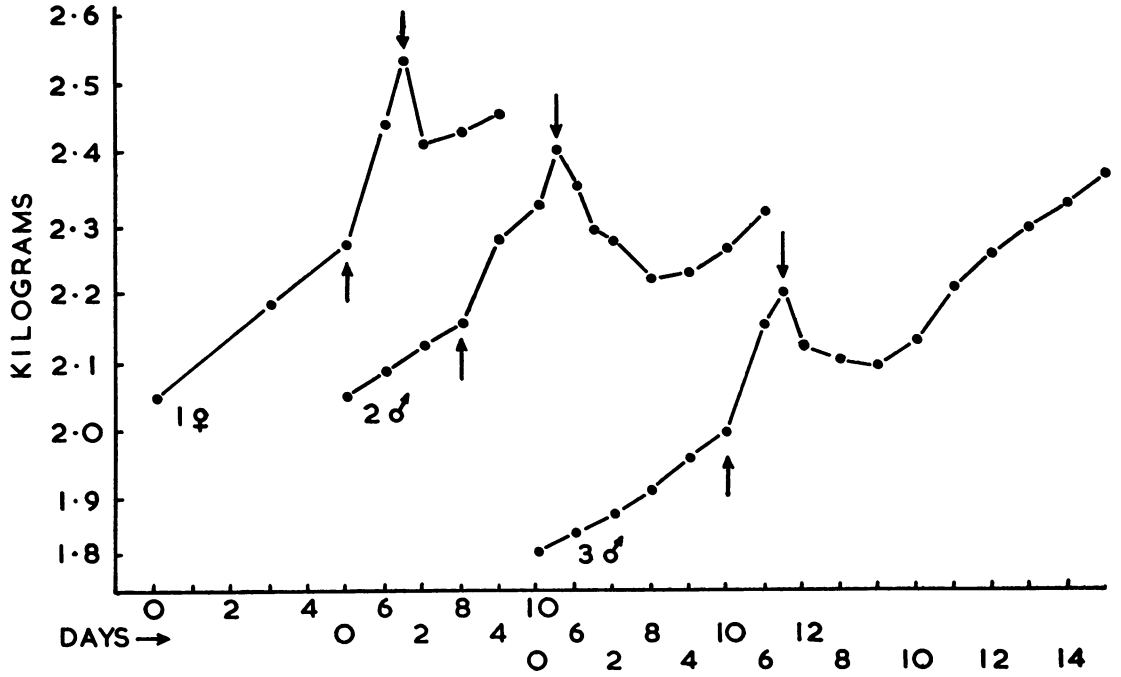

FIG. 3.—The weight charts of three infants before, during and after the period of salt administration.

altered to a more rapid one, which was in fact pathological. In a short time the babies became oedematous and sick, but on putting them back on to their proper intake of water and salt their weights fell and they began to gain weight again at their previous and more satisfactory rate (McCance and Widdowson, 1957).

Table 6 shows exactly the same effect in piglets to which no food was given but only water or salted water. The gain of weight on the solution of salt without food was quite clearly pathological. Table 6, however, shows other features. Firstly, although the amount of water retained in the body was large, it was not large enough to prevent a rise in the concentration of sodium in the serum. This also happened in the babies, and in both species the administration of the salt led to hypertonic expansion of the extracellular fluids. Secondly, the administration of the salt solution led to a fall in the serum urea and this in turn was the result of a smaller breakdown of tissue protein in the starving newborn animal. This result has always been obtained in these experiments. It is difficult at present to say why. It is tempting to suppose that a large volume of extracellular fluid in some way inhibits the breakdown of tissue protein, which can be regarded as one way of promoting growth, and that therefore the rapid growth of the foetus and newborn animal is associated in some way with the large volume of extracellular fluids in its body, but it is perhaps more probable that the effect is due to an alteration in the rate of secretion of one of the suprarenal hormones brought about in response to the pathological increase of these fluids, and part of a stabilizing mechanism. There for the moment the matter must rest.

TABLE 6

EFFECTS OF GIVING NEWBORN PIGLETS WATER OR AN EQUAL VOLUME OF 0·9% SODIUM CHLORIDE SOLUTION

	Water Alone	Water+Salt
Change of weight in 40 hr. (g./kg. birth weight)	−53	+96
Percentage of water in bodies	82·7	87·4
Na balance (mEq./kg./24 hr.)	−0·3	+35·5
Serum Na (mEq./l.)	138	147
Serum urea (mg./100 ml.)	42·2	23·6

(To be continued)

The references for Parts 1 and 2 will be printed together at the end of Part 2 which will appear in the December issue of *Archives*.