THE MAINTENANCE OF STABILITY IN THE NEWLY BORN*

2. THERMAL BALANCE

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Thermal stability, which is one of the hall marks of mammalian efficiency, must always be associated with metabolism and chemical stability, for the production of heat depends largely on biological oxidations and these in turn depend upon the supply of oxygen. Anything which interferes with this constitutes an immediate threat both to chemical stability and thermal stability, but the temperature of the body also plays a vital part in regulating the metabolic rate and hence the demand for oxygen, so that each reacts upon the other.

The Basis of Thermal Control

The maintenance of thermal balance rather than a constant internal temperature may be the real basis of temperature control (Glaser and Newling, 1957), for both the central and superficial temperatures do vary as part of their participation in the overall stability of the adult body, but these are among the finer points at present. Thermal stability is brought about by the production of heat and the loss of heat being kept about the same. Heat production is the result of the metabolic activity of all the cells of the body when it is at rest, together with the additional production due to muscular exertion. The basal production is extensively modified by thyroid activity and affected by the environmental temperature (Osiba, 1957). Heat is lost mainly from the body surface, and if a person were completely insulated against heat loss his temperature would go up at a rate which would bring it to boiling point in about two days if the mechanisms for heat production were not, as of course they would be, inactivated long before this temperature had been reached. The amount of heat lost from the surface of the body would tend to vary only in accordance with air

movement and the surrounding temperature, were it not that the rate of loss can be greatly reduced at low temperatures by constricting the blood supply to the periphery and extremities and allowing them to take up temperatures far below the central parts and not much above those of the surroundings. Animals with fur and birds with feathers can modify their heat losses to some extent by erecting their hair or fluffing out their feathers, and some large animals which live in a cold environment are very well protected against heat loss by long hair and a thick layer of subcutaneous fat. Heat is also lost from the lungs by the evaporation of water and by warming the inspired air, but in man these losses are linked to the metabolic needs and are not varied apart from them. At high environmental temperatures the rate of heat loss in man is adjusted to the requirements of the body by sweating, which deposits a film of water on the skin. The evaporation which follows keeps down the body temperature even when the environmental temperature is higher. In animals without sweat glands this way of losing heat may be replaced by passing air very rapidly in and out over the large wet surfaces provided by their tongues.

Animals vary greatly in their response to a change in their environmental temperature, but there are features common to all. There is a fast response followed by a much slower one if the change persists, and the whole constitutes the process of acclimatization which enables the animal to become master of its new surroundings. A rapid increase in metabolic rate is the immediate response in all warm blooded animals to a fall in environmental temperature, and this is indeed the chief response of mice and other small rodents, for they do little to reduce their loss of heat by varying their insulation or vasomotor control. It is a biological impossibility that they should do so to any extent, for the weight of the insulating material required for such small animals

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at low temperatures would immobilize them. Some strains of mice increase their oxygen consumption by as much as four times when they are transferred from a temperature of 21°C. to -3°C. By doing so and making for themselves good nests (Barnett and Manly, 1958) they are able to maintain a normal body temperature, but they require just that much more food, which in nature they have to find (Barnett, 1956, 1959; Barnett and Manly, 1956; Barnett, Coleman and Manly, 1959). Increased tone and shivering constitute the first line of defence against a sudden fall in the environmental temperature, and this is the role of the skeletal muscles. It is initiated by reflexes from the skin, and if the shivering thus initiated is not enough to maintain the 'core' temperature, the fall in the latter greatly intensifies the muscular response (Giaja and Gelineo, 1931; Pickering, 1958). After the process of acclimatization is complete the metabolic rate remains high, although the animals are no longer shivering. This is usually attributed to increased 'tone' in the skeletal muscles, but what this means in terms of mechanical work and tissue metabolism nobody knows (Baker and Sellers, 1953; Burton and Edholm, 1955; Scholander, 1958). The basal metabolic rate also rises after a time, and this rise persists and can be demonstrated after the animal has been restored to a higher environmental temperature once more (Engelmann, 1930; Sellers and You, 1950). The liver participates in this (Burton and Edholm, 1955) as well as the muscles and heart, but not, it seems, the thymus, testis or brain (Hart, 1958).

A fundamental point in thermal control at all ages, but particularly in the newly born, is the environmental temperature at which the metabolic rate of the animal is at its lowest. This is variously termed the critical temperature or the point of thermal neutrality. It is really a band or range of temperature within which variations in heat loss enable the animal to maintain a normal body temperature with the least possible expenditure of energy. Departure from it in either direction raises the metabolic rate. If the environmental temperature has fallen the rise in metabolic rate will serve a useful purpose in maintaining the temperature in the body desirable for that species, but if the reverse has taken place the body temperature will rise and it is this which produces the rise in metabolic rate (see later). The critical temperature varies with the age of the animal (Cairnie and Pullar, 1957) and the plane of nutrition (Graham, Wainman, Blaxter and Armstrong, 1959), and is considerably higher soon after birth than it is in later life. It also varies from one species to another.

The laws of physics and chemistry provide that

the rates at which chemical reactions proceed vary directly with the temperature of the system in which they are taking place. The metabolic rate of an animal without temperature control, therefore, varies closely and directly with the environmental temperature. If the temperature of an animal with any semblance of temperature control is lowered sufficiently there comes a time when its metabolic rate and oxygen consumption fall in spite of the increase in metabolism which was tending to prevent it, and this can be enormously facilitated by abolishing the normal adaptive response. This is the way in which the body temperature is lowered (Hellings, 1958; Pickering, 1958) in order to reduce the metabolism for therapeutic or experimental purposes, but a subnormal temperature in a newborn baby or any other young animal is no proof that it has a lower metabolic rate than it would have at its critical temperature. In fact, the reverse is much more probable if it is making any adaptive response (Giaja and Gelineo, 1931; Krog, Monson and Irving, 1955; Hart, 1958).

The response of an adult to a change in the environmental temperature is a very complicated one (Scholander, 1958), integrated at various levels and depending upon the central nervous system (Pickering, 1958), and a co-ordinating 'centre' in the hypothalamus (Ranson, 1940; Kennedy, 1953). Successful adaptation depends upon the hypophysis (Thibault, 1949), and the suprarenal glands participate at two stages. Part of the immediate increase in metabolic rate is almost certainly due to the release of adrenalin and nor-adrenalin, although precisely how these operate is obscure (Griffith, 1951). Their effects are not abolished by curare (Hsieh and Carlson, 1957), and they are intensified in an animal which has become fully acclimatized to cold. Thyroidectomy reduces them (Swanson, 1956). The cortex of the suprarenal is also essential for successful acclimatization to a lowered environmental temperature (Ingle, 1958), and is thought to be one of the organs responsible for the higher metabolic rate which develops slowly and persists for some time. The thyroid is also involved in this (You, You and Sellers, 1950).

The energy derived from the oxidation of protein, fat and carbohydrate is used for the synthesis of compounds such as adenosine triphosphate and creatine phosphate, which contain high energy phosphate bonds and with which the cell is able to carry out the work required of it. Some of the energy is 'wasted' and dissipated as heat which the homoeotherm also requires *per se*, but it is generally thought that in the healthy and intact cell most of the oxidation is coupled with the synthesis of these high

energy phosphate bonds and limited by the amount of work required for functional efficiency. Bilirubin and a number of other poisons, such as cyanide, interfere with many of the oxidation processes in a less specific way and reduce the coupling as well. Others, such as dinitrophenol and possibly thyroxin, also interfere with the coupling, but in a different way, for they allow the oxygen consumption and heat production to rise to high levels without the performance of any visible or invisible work. Some such uncoupling, if physiological, or some purposeful deviation of the metabolic pathways to bypass the coupling mechanisms, would produce the heat required by the body for acclimatization more economically than any other way, and the possibilities of this happening in the processes of acclimatization are being actively explored (Depocas, MacLeod and Hart, 1957; Hart, 1958; Potter, 1958; Smith, 1958). Adaptive changes in the enzyme systems are well recognized to take place in the kidney, at any rate in some animals (Rector, Seldin, Roberts and Copenhagen, 1954; Rector and Orloff, 1959), and some such deviation from the more usual metabolic pathways is now accepted as a cause of hereditary obesity in mice (Tepperman, 1958; Zomzely and Mayer, 1958) and possibly in human obesity (Pawan, 1959).

Whatever its size, the body temperature of an adult is largely a matter of its own genetics and biophysical efficiency. The white rhinoceros or the hippopotamus, which both live in equatorial Africa where the temperature may be 32°C. in the shade, and which both weigh upwards of 3,000,000 g., have body temperatures of the order of 35°C. (Allbrook, Harthoorn, Luck and Wright, 1958; Luck and Wright, 1959), whereas a mouse living at -3°C. and weighing about 30 g. has a body temperature around 37.5°C. (Barnett, 1956).

The matter of size, however, is an important one in temperature regulation because small bodies have relatively greater surface areas than large ones and therefore cool more quickly in surroundings below the temperature of their bodies. This has been compensated for, however, in nature by the arrangement that birds and animals, large and small, have metabolic rates in proportion to their surface areas rather than to their weights. This is one of the great biological generalizations, but how it is brought about is quite unknown. Why each cell in a mouse has so much higher a metabolic rate than each one in an elephant is unknown, but the solution of this problem should help us to understand the processes of acclimatization.

The Newborn Animal

Whatever it may do towards maintaining its own

chemical stability *in utero*, the unborn animal has no responsibilities for its body temperature, and most animals are born before they have acquired all the integrated mechanisms they will later require for the control of their body temperatures. The newborn rat is almost poikilothermic at birth and takes up the temperature of its surroundings. Puppies and kittens have little more thermal stability, but less is known about them. The lamb and the pig are both examples of animals with a good measure of temperature control at birth, and so within limits is the human infant. Edwards (1824, 1832), the great pioneer in this subject, showed that this was not just a matter of size, but also one of immaturity. By choosing adults and newborn animals from different species he found out that tiny adult birds like wrens had far greater thermal stability than newly hatched birds such as hawks which were much larger, when both were exposed to an external temperature of 17°C. Edwards also realized that many newborn animals would never survive unless a special environment had been created for them by nature. He pointed out that the proximity of the rest of the litter huddled together in a nest protected each member of the litter from the cold they would have to face in isolation. With this shelter of the nest and the warmth of the mother's body, to which the newborn animal always tends to move, even the newborn rat can achieve a body temperature high enough to enable it to feed and grow, and mice can be reared by their mothers in a good nest at -3°C. (Barnett, 1956) and breed in cold meat stores at much lower temperatures, even down to -21°C. (Laurie, 1946). If the mother of an animal without temperature control leaves the nest and fails to return for some time the temperature of the newborn animals must fall and with it their demands for oxygen. This is probably no disadvantage for a time, for it reduces the consumption of energy material within the body without doing the newborn any harm (Fairfield, 1948). The survival time of eviscerated, and therefore poikilothermic, adult rats is reduced if the temperature is raised from 26° to 38°C., but this effect can be countered to a large extent by the administration of glucose (Ingle and Nezamis, 1950).

The metabolic rate of a poikilothermic animal like the newborn rat varies with its environmental and consequently its body temperature. The oxygen consumption of the newborn lamb, however, rises three to four times between the last days *in utero*, when it has an oxygen consumption in keeping with its mother's surface area, and the second day of life when it has one more in line with its own (Dawes and Mott, 1958, 1959). Pigs have not been investigated *in utero* but their oxygen consumption also

risers rapidly in the first days after birth (Mount, 1958a). With the knowledge available to us at the moment we must regard this rise in oxygen consumption as the response of struggling but still imperfect homoeotherms to a fall in their environmental and also, probably, in their somatic temperature, for after birth pigs have been shown to raise their oxygen consumption steadily as the ambient temperature falls below that of their own point of thermal neutrality (Holub, Forman and Jeřková, 1957; Mount, 1958b). Gajda (1925a, b), another pioneer, put forward a way of expressing all this quantitatively and of comparing the response of one young animal with that of another.

Man certainly, and most large animals also, regulate their thermal balance to a large extent by 'physical' methods, i.e. by varying the dissipation and conservation of the heat produced within them by their natural activities, but there is evidence that this is not so to any great extent in the newborn human infant or animal (Hahn, 1956c; McIntyre and Ederstrom, 1958). Piglets (Mount, 1959) and many other newborn animals with similar possibilities open to them (Baccino, 1935) increase their effective size by huddling together and so reducing their cooling surface, but speaking generally the newborn animal achieves what measure of thermal control it may possess (if in isolation) by 'chemical' methods, i.e. by varying its heat production, and this is not possible before the neurones in the hypothalamus are myelinated (Reynolds, 1953). Adult rodents and particularly mice (Barnett, 1959; Barnett *et al.*, 1959) certainly employ chemical rather than physical methods, particularly in isolation, and this is what makes them a valuable study for those interested in the newborn of larger species. Barnett and Manly (1958) have given an account of the ability of young mice of various ages and strains to survive transference from 21°C. to -3°C., and in this work investigations were made of the role of the thyroid and adrenal glands in various ways.

On the analogy of what happens in adults, it may be presumed that the greater part of any increase in the oxygen consumption registered during the hours following birth or subsequently in response to a fall in the ambient temperature takes place in the skeletal muscles. The lamb and pig may shiver violently soon after birth, but a great increase in the metabolic rate can take place without it (Dawes and Mott, 1958, 1959). It is not known why the oxygen consumption does not reach the level at which it stabilizes for some days, but if the skeletal muscles are as poorly equipped with respiratory enzyme systems as the liver of the rat would appear to be (Dawkins, 1959) it is fully understandable. The

liver of all animals develops many of its functions with great rapidity after birth (Driscoll and Hsia, 1958), and this may contribute something to the increased heat production, but it can have little to do with the thermal regulation of the body, for the respiratory enzymes in the liver of the newborn rat mature in a matter of days, whereas thermal stability is not attained for several weeks and the liver is not the centre of it.

Wherever it takes place, the increased metabolic rate which follows birth in animals with some measure of thermal control at that time can only be brought about by the combustion of protein, fat and carbohydrate. These may have been in the body at birth or be supplied as food. In either case they are the price which the newborn animal has to pay for thermal stability outside the uterus. The newborn poikilothermic rat pays no such price; the mother provides the whole service, and nearly all the food can be used for somatic development. It is worth a thought, therefore, that every degree below their critical temperature at which the pig, lamb or human baby may be held, reduces the amount of material available for survival or growth. This is no doubt why the young rat 10 days old lives no longer without food at an environmental temperature of 20°C. than at 30°C. although it has had a lower body temperature all the time it has been exposed to the lower environmental one (Braun and Mosinger, 1958). We have been able to put a quantitative figure on this by keeping newborn pigs in metabolism cages without food or water for the first 24 hours of their lives. At an ambient temperature of 31°C. these animals lived quite comfortably for at least 48 hours and had blood sugars and body temperatures within normal limits at the end. At an ambient temperature of 12°C., however, the animals could only maintain reasonably normal body temperatures for 8-12 hours. Their temperatures fell more and more rapidly after this and by about 24 hours were usually 20-22°C., their blood sugars were very low and the animals were *in extremis* (Fig. 1). Hypoglycaemia has been observed before in newborn piglets who were at the point of death (Morrill, 1952; Goodwin, 1957) and the administration of glucose is said to have been beneficial (Morrill and Sampson, 1952). Table 1 shows the way in which the ambient temperature affected the breakdown of protein, fat and carbohydrate within the body. In these animals glycogen was the main source of energy, for newborn pigs contain practically no fat, and the Table shows to what extent lowering the environmental temperature increased their rate of utilization. This is not the whole story, however. Once the body temperature falls, deviations from the normal metabolic

FIG. 1.—Rectal temperatures of piglets kept at 12°C. and 31°C. for 24 hours.

TABLE 1
EFFECT OF AMBIENT TEMPERATURE ON BREAKDOWN
OF TISSUE SOLIDS IN STARVING NEWBORN PIGLET

	Solids Catabolized			
	(g./kg./24 hr.)		Percent of Total	
	Hot	Cold	Hot	Cold
Total solids	13.4	28.6	—	—
Protein	0.6	1.7	4.9	6.7
Fat	2.9	3.9	21.5	13.6
Carbohydrate 'by difference' ..	9.9	23.0	74	80
Glycogen directly determined	9.0	19.8	67	69

pattern may follow (Wynn, 1954, 1956), and we have ourselves encountered some of them (McCance and Widdowson, 1959b). A suggestive side issue has opened up in the course of this work. The amount of weight lost and volume of urine formed were similar at 31° and 12°C., but the animals kept at 12°C. metabolized so much more of their body solids that they became more watery than the others and actually developed oedema. Premature babies may do the same even when they are given nothing by mouth. This oedema may have a similar origin.

The development of temperature control after birth can be studied most completely and easily in animals which have very little control when they are born. The puppy has recently been investigated (McIntyre and Ederstrom, 1958) and the mouse (Barnett and Manly, 1958), but the rat has had most attention. Adolph (1948, 1957), Fairfield (1948) and others in America have worked at it extensively and so have a group of active investigators in Czechoslovakia (Hahn, 1956a, b, c, d; Hahn, Křeček and Křečková, 1956; Křeček, Křečková and Martinek, 1957; Hahn and Koldovský, 1958a, b, 1959). Many of the conclusions so far are based

upon results obtained after removing the thyroid or adrenal glands which may be a rather crude technique (Astwood, 1957), and some of them may have been confused by the effects of restraint (Bartlett, Bohr and Inman, 1955; Hahn and Koldovský, 1958b). Full temperature control is not acquired till the animals are about 26 days old. Only at 14 days does the thyroid begin to play any part, and although the newborn animals soon begin to grow hair, this does not improve their thermal control till they are 18 days old. The adrenal glands may also be involved (Tyslowitz and Astwood, 1942; Hubble, 1957). Jailer (1953) thought that they only began to respond to the stimulus of cold about the sixteenth day of life although they were capable of reacting to ACTH and adrenalin before this time. More recent work (Hahn and Koldovský, 1958a) suggests that a response can be detected by the fifth day if the stimulus is not too severe. To what extent these glands function in the newborn pig or man is still unsolved, in spite of all the work which has been put into their investigation by paediatricians (Gardner, 1956; Harlem and Myhre, 1957).

With such poor control of their own body temperatures few animals would live through their first days in the world were it not for the fact that they can tolerate and survive a much greater fall in body temperature than adults of the same species (Adolph, 1951). In that investigation Adolph showed that some adult guinea-pigs, rabbits and cats survived body temperatures of 18°C., and rats 14°C., whereas golden hamsters could be cooled with impunity to much lower body temperatures. Newborn guinea-pigs were cooled successfully only to 15°C., but these animals are very mature at birth. Newborn kittens and rabbits were cooled to 6°C. and rats and hamsters survived after their temperatures had been as low as 0°C. Work on hypothermia in adults has gone forward very rapidly since Adolph's publication (Andjus and Smith, 1954; Goldzweig and Smith, 1956; Colloquium, 1957), and it is now known that by taking the right precautions remarkably low body temperatures can be achieved even in man (Drew and Anderson, 1959; Drew, Keen and Benazon, 1959). Rats and monkeys have been cooled to 5°C. with recovery (Niazi and Lewis, 1954, 1957). The concentration of carbon dioxide in the tissues may be important for survival (Miller and Miller, 1958), as it is in oxygen deficiency. A young woman, who was found in the snow with a body temperature of about 16°C., has recovered although extensively injured by frostbite (Laufman, 1951). Other examples of accidental hypothermia in man, not quite so severe, and not complicated by frostbite have been recorded by Rees (1958).

The Human Infant

Physiologically the human infant born at term seems to fall into the natural scheme of things so far as its thermal stability is concerned. In cold surroundings it can maintain a normal body temperature better than the puppy, kitten, rabbit or rat but probably not as well as the guinea-pig, and certainly not as well as the lamb. The full term infant is so much larger than the newborn pig that the control of its body temperature must always be easier, but it seems to have about the same measure of thermal control. It has been known for many years (Preyer, 1885; Raudnitz, 1888; Burnard and Cross, 1958; Smith, 1959) that the body temperature tends to fall soon after birth and then to rise again within the next 12 hours to a more normal adult level. This is exactly what one would expect from work on the rise in oxygen consumption which follows birth in the pig or lamb, and the way in which newborn infants respond to a change in their environmental temperature (Mordhorst, 1932). In all respects the premature infant has much less stability (Blackfan and Yaglou, 1933). In all infants much depends on the ambient temperature, but the chances of hypothermia must always be high so long as the basal metabolic rates remain below those of adults per unit of surface area. This has always been found to be the case (Marsh and Murlin, 1925; Du Bois, 1936; Day, Curtis and Kelly, 1943; Boekelman, 1957), and these rates would certainly have been lower had they been measured in the zone of thermal neutrality.

Like all other newborn animals the human infant is very tolerant of low body temperatures, and moderate hypothermia has been advocated for premature infants with the idea that it would reduce their metabolic rate and oxygen requirements. This must remain *sub judice* at present and each case will always require separate assessment, but the work of Silverman, Fertig and Berger (1958) indicates that hypothermia is not good paediatrics. Uncontrolled exposure to cold is certainly an insidious and dangerous enemy (Mann and Elliott, 1957). Babies born in very cold weather in homes that are inadequately heated are sometimes admitted to hospital suffering from the effects of this. By the time these babies reach the eye and the touch of an expert they may have passed from a physiological to a pathological state, and present with some superadded infection. They always feel cold, but in spite of this they may appear surprisingly well, with red face and hands. Sometimes the external cold has made the extremities oedematous and the skin hard and white. The protracted exposure lowers their body temperature internally and makes them apathetic and unwilling

to take food, and perhaps because of this they sometimes have blood sugars low enough to cause convulsions. They may die before or during treatment from what appears to be respiratory failure, and pulmonary haemorrhage has often been found after death.

From what is known about animals one must suppose that the thyroid and suprarenal glands are integral parts of the stabilizing mechanisms, but our knowledge of their role in thermal regulation or anything else at birth is woefully small (Gardner, 1956; Harlem and Myhre, 1957; Khalil, 1958), and there is scope for some imaginative work on this subject in animals and then in mankind.

Once a baby has become pathologically chilled, glucose should probably be given cautiously before the temperature is raised, for hypoglycaemia may be expected, and warming without giving glucose may precipitate convulsions in piglets.

Up to this point one may say that newborn animals have very variable but always poor temperature control, and in their usual surroundings tend to get cold. Life in nature must always be a compromise, in this instance between the well-being of the mother and the newborn. Young animals tolerate a subnormal body temperature extremely well, but there is no evidence that it is ever in itself beneficial or should be allowed, and there is good evidence that newborn animals might benefit if they could spend the first critical days of their lives within their range of thermal neutrality. Such ambient temperatures, however, would sometimes be harmful to the maternal organism.

The Lesser of Two Evils

The lethal effects of a complete or partial failure of the respiratory exchanges have already been described. The tolerance of the newborn for a lack of oxygen has also been discussed, the reasons for it and its results in terms of chemical stability. A change-over from aerobic to anaerobic metabolism has, however, got other important consequences, for anaerobic metabolism produces much less heat. The complete oxidation of a molecule of glucose to CO₂ and water, for example, provides at least 10 times more heat than its conversion to lactic acid, which is as far as the process can go in nitrogen (Hendricks, 1957). This fall in heat production makes no difference to the body temperature of a poikilotherm such as the newborn mouse, but it tends to lower the body temperature of others (unless they are in very warm surroundings), particularly of those with imperfect control of their body temperature. As already described, if adaptation is not taking place, any fall in body temperature slows down all

the chemical processes of the body, including the utilization of the glycogen stores and the accumulation of acid metabolites, either of which may be fatal. Notwithstanding any bad effects which hypothermia itself may have, many experiments have demonstrated the survival value of a fall of body temperature when the animal is facing immediate extinction from anoxaemia. Thus Fazekas, Alexander and Himwich (1941) and Himwich (1953) found that the survival time of day-old and therefore still poikilothermic rats in nitrogen was raised from 20 minutes to 50 minutes by lowering their body temperature from 34°C. to 24°C. (see also Adolph, 1948, 1957). Selle and Witten (1941) made some experiments with a bearing upon this. They showed that the isolated heads of newborn rats gave more gasps per minute when the temperature was raised, but not more gasps *in toto*. Consequently, raising the temperature reduced the time for which the heads went on gasping. Cooling the heads had the opposite effect. More recent and more extensive experiments on newborn guinea-pigs have shown that cooling the animals in ice water up to the neck prolongs their life when they are made to breathe a mixture of 95% nitrogen and 5% carbon dioxide (Miller and Miller, 1953, 1954; Miller, 1954).

A reduction in the partial pressure of oxygen in respired air has been a common enough human experience since men began to mountaineer, and the effects have been well investigated; respiratory failure and distress are dangers at all times of life. Cardiac failure and abnormalities may produce very similar end results. It is generally recognized in adults that there is rarely, if ever, any reduction in oxygen consumption when the pressure of oxygen in the ambient air falls, even to the low levels met with at very high altitudes (Barcroft, Elliott, Fraser, Herkel, Matthews and Talaat, 1934; Houston and Riley, 1947; Rothschild, 1947; Frank and Wezler, 1948; Pugh, 1957). The oxygen tension falls in the arterial blood, but a sustained increase in respiration and alveolar ventilation helps to maintain the supply of oxygen to the tissues. This is true also of the adult dog (Cordier and Mayer, 1935; Gorlin and Lewis, 1954) and to a somewhat lesser extent of the rabbit (Hamon, Kolodny and Mayer, 1935), and no doubt of most other adult mammals over a certain size (Cross, Dawes and Mott, 1959). A reduction in the percentage saturation of the arterial blood, therefore, does not materially affect the heat production of adult men, sheep or dogs. The smaller mammals, however, do not react in this way (Béhague, Garsaux and Richet, 1927; Gellhorn and Janus, 1936), except when they are held within their range of thermal neutrality (Lintzel, 1931), and

at usual environmental temperatures the oxygen consumption and with it the body temperature of mice begin to fall when the percentage of oxygen in the surrounding air is reduced to about 16% (Chevallard and Mayer, 1935), with a corresponding fall in the percentage saturation of the arterial blood. The fall in body temperature so diminishes the demands of the tissues for metabolic exchange that it prolongs the survival time of these animals (Strughold, 1954), and this has repeatedly been demonstrated experimentally in a number of ways (Campbell, 1936, 1938). It is possible that the thyroid is involved in this fall of temperature (Smith, Emmens and Parkes, 1946-1948).

Newborn animals, including the human infant, behave like the small adult rodents. This was first observed by Cross, Tizard and Trythall (1955, 1958), who showed that when the oxygen in the ambient air of a newborn baby was reduced from the normal 21% to 15% there was only a trifling increase in ventilation rate, and the consumption of oxygen fell by some 17%. The respiratory effects in infants have also been observed by Behrle and Smull (1957), and it has been claimed that reducing the oxygen in the ambient air has a place in the management of infants (Sjöstedt and Rooth, 1957). The fall in oxygen consumption was confirmed by Moore (1956a, b), who used puppies and kittens as his experimental animals. Similar effects have been noted in the lamb (Acheson, Dawes and Mott, 1957; Cross, Dawes and Mott, 1958b). Hill (1958) has reconfirmed all these results in kittens, and added the important point that the oxygen consumption only falls to any extent if the animals are being held below their critical temperature. This suggests that the decrease in oxygen consumption takes place mainly in those organs in which it is thought to increase when the environmental temperature falls below the critical one. The organs mainly involved are probably the skeletal muscles, and work on the lamb supports this suggestion (Cross *et al.*, 1958b, 1959). It is known that animals do not shiver when they are anoxic. If the reflex circuit required for shivering and tone in the skeletal muscles at this age could operate only when the tension of oxygen in the tissues was sufficiently high, a great deal of these facts could be very simply explained, for then the thermoregulatory metabolism of the skeletal muscles would virtually cease when the tension of oxygen fell. Alternatively, one of the oxidizing enzymes in the muscles may become inoperative when the tension of oxygen in the tissues falls. It is impossible to decide between these suggestions at present, even if either is right, for it has not yet been shown, and this is a vital theoretical point, whether the reduction

in aerobic metabolism is replaced by an equivalent amount of anaerobic metabolism. The second theory suggests that it would be. At all events, as might have been predicted on either theory, all the investigators are agreed that a fall in body temperature follows the reduction in oxygen consumption (Moore, 1956b; Brodie, Cross and Lomer, 1957). Burnard and Cross (1958) showed this in experiments which had been arranged for them by nature in a group of full-term infants who had suffered from some degree of asphyxia at birth. Other things being equal, one must suppose that a fall in oxygen consumption *per se* will mitigate the effects of partial asphyxia or hypoxaemia if they are prolonged, and at most environmental temperatures any reduction in oxygen consumption, whatever its cause, must be followed by a fall in the production of heat, particularly in those organs which are responsible for maintaining the temperature of the body above that of its surroundings. Everything which is known suggests that the fall in body temperature, which will invariably follow, will further mitigate the effects of the deficiency of oxygen and prolong the period of survival. Within the zone of thermal neutrality hypoxaemia did not lead to the same reduction of oxygen consumption (Hill, 1958) and consequently there should have been less fall in body temperature. One would expect both these statements to be true of the foetus *in utero* yet, strangely enough, progressive hypoxaemia in the foetus does lead to a progressive reduction in its consumption of oxygen and the same seems to be true of the newborn animal immediately after birth (Dawes, 1959; Cross *et al.*, 1959; Dawes and Mott, 1959). In these experiments on the foetus the lamb was being maintained at a constant temperature in a saline bath, but its body temperature must be equally well maintained *in utero*, so there can be no fall in it there.

The pathological sequence is now clear enough to indicate that if anoxaemia has been a cause of a fall in the body temperature of the human infant, treatment should begin with the administration of glucose. This will enable the anaerobic metabolism to go on as long as possible, and the acidosis which will inevitably be created by it should be countered by simultaneous administration of bicarbonate. There is no concrete evidence at present whether the hypothermia should be put right before, during or after the relief of the anoxaemia, but there are many indications that one should begin by correcting the hypoxaemia.

When I was privileged to give the Goulstonian lectures at the College of Physicians in 1936 I waxed very enthusiastic about the future of biochemistry. I recalled Prout's discoveries in it over 100 years

before and I suggested that its influence on medicine was still only beginning to be felt and that there was no reason why neurology might not become just as chemical a subject as nutrition, or that certain problems of psychology and even of human behaviour might not be solved in the future by the biochemists (McCance, 1936). As I sat down the President rose to his feet and castigated me properly for my presumption, and in particular for supposing that anything which came out of a test tube could ever influence the psyche of man. I felt utterly crushed and went home that night feeling that I had been a very silly young man. Times have changed very rapidly, and biochemistry has been acclaimed by all to be one of the great conquering forces in the world of medicine of today. More and more biochemists are trying to isolate functions, cells, even parts of cells and enzyme systems, and to study them apart from their natural surroundings. This is most valuable work and no one could admire it more than I do, although I am not able to keep up with the pace, but many of the adaptations to extra-uterine life will not be solved by organic chemistry. Most of them involve the integration of several functions, and sometimes the co-ordinated responses of mother and young. I do not wish to go back now on one word which I said in 1936 and I am not yet as old as the President was at that time, nor will I ever have his wisdom, but I can see the dangers now and I am inclined to think that no army of biochemists, equipped with all the photometers and chromatography in the world, will ever solve these problems by themselves. The study of isolated systems can be very misleading and it tends to breed isolated minds. There will always be a place in physiology and in medicine for men like Sir Leonard Parsons who are interested in the study of the whole animal and have the breadth of vision necessary for it. The study is a specialization in itself, and perhaps the most difficult one of all. Those who attempt it will never any more be able to understand all the biochemistry behind the isolated functions they are trying to co-ordinate. They must always be prepared to talk humbly to the experts (other experts!) for the best information available about it, and use the knowledge to further the welfare of the animal to which they are devoting their lives.

I have received help over these lectures from people who work all over the world and I have visited some of them in places as far apart as Prague and Vancouver. It would be difficult to acknowledge them all. I must, however, single out our secretaries, the nurses, the hospital staff, the animal attendants, and all those past and present members of the department who have made the lectures possible at all. They are my joint authors, in fact, if not in name.

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