Adaptation to extraterine life involves the newborn infant in a series of biological adjustments to a totally new set of environmental conditions. Prime among these is the accommodation to a thermal environment that, in all but the most tropical countries, represents a distinctly "cold" challenge. The failure to accommodate to this cold stress has historically been recognized as perhaps the earliest distinguishable characteristic (other than size) of the premature as opposed to the term neonate. In this difference, i.e., that the premature infant is unable to maintain his body temperature in the face of a cooler environmental one, lies the rationale for the history and origins of incubators in the care of the premature baby.

Credit for initiation of the modern incubator goes to France in the person of Pierre-Constant Budin, a pupil of Professor Tarnier's in Paris, just prior to the turn of the century. Both Tarnier and Budin had speculated on the role of temperature in the survival of small infants and, in 1900, Budin reported a striking difference in mortality of infants weighing less than 2000 gm at birth based on rectal temperatures.[1] Thus, if the rectal temperature was less than 32°C, the mortality rate was 98%; between 32°C and 35°C it was 90%; but if it remained normal it was only 23% -- still a respectable figure some 70 years later. Budin had also designed an incubator that provided for heating of the air, a one-way air flow, additional humidity and temperature monitoring of the environment.
At that time there appeared in Budin's laboratory Martin Couney who had been born in Alsace and had studied medicine in Berlin and Leipzig. Unable to practice in France, he became Budin's assistant in the development of the incubator; but in the world of science nothing really counted in those clays until it had received German approval. Professor Budin saw in the Berlin Exposition of 1896 a chance to publicize the conservation of premaures. He chose his Alsatian disciple, Couney, to demonstrate his discoveries. It was during one of several periods of international rapprochement and the German physicians were eager to collaborate in the demonstration. Couney established a pavilion with six incubators, and Virchow, the head of the Berlin Charite Hospital, willingly loaned him six premature infants from the maternity ward. This was considered a small risk since they were expected to die in any case. Before the Exposition opened, Couney had to think of a German title for the exhibit. He chose *Kinderbrutanstalt* meaning, literally, "child hatchery." [2]

The hatchery was celebrated in comic songs and musical gags in Berlin, even before the Exposition opened, so that from the first day of the Exposition the pavilion was thronged with people each of whom paid one German mark to look at the babies. What had begun as a sober, scientific demonstration became a crowd-pleasing show that outdrew the Congo Village, the Tyrolian Yodellers and the skyrides. From a medical point of view the demonstration proved a success since all of the babies survived, largely due to the fact that Couney had selected for care infants that had already shown the capacity to survive at least the first five days of life. He brought each infant to a weight of 5 pounds and did not lose a single one during the entire Exposition.

Invited to continue his exhibit at the Victorian Exposition in Earl's Court, London, in 1897 (an enormous undertaking which celebrated the Diamond Jubilee of Queen Victoria's reign), Couney accepted. When the time came, however, the conservative London hospitals declined to lend Couney any British babies. However, they did not object to the use of French (or possibly other imported) infants for this purpose and Couney then obtained from his patron, Budin, in Paris, a number of premature infants whom he transported in three wash-baskets across the channel on a boat to England, utilizing a heating system of pillows placed over hot water bottles. Once again the show was a success financially with the admission charge of one mark now altered to one shilling sterling.

Following his successes in both Berlin and London, Couney, by now having acquired a taste for show business, departed for America. In 1898 he opened his first show utilizing premaures in incubators at the Omaha Trans-Mississippi Exposition. He returned briefly to Europe for the Paris Exposition of 1900 and came again to America for the Buffalo Fair of 1901 after which he settled in the United States and became an American citizen. For the next half century, "Couney babies" were exhibited in a variety of county fairs and traveling shows across large parts of America, particularly in the mid-west. In 1922 he made the acquaintance of Julius H. Hess, during an exhibition at White City Stadium in Chicago, a meeting which is partly related to the subsequent opening of the first premature station at Michael Reese Hospital in Chicago in that year. Couney established a permanent exhibition in Coney Island and in 1939 organized and presented a major pavilion at the New York World's Fair in a building designed by Skidmore & Owings, thus adding architectural prestige to his growing reputation as both a showman and "incubator doctor." By the time of his death in 1952 it is estimated that approximately 80,000 premature
infants had been raised across the country in the course of Couney's shows and exhibitions.

Medical response to Dr. Couney and his exhibitions was not always favorable. An excellent account both of the particular exhibition in St. Louis in 1904, as well as the controversy that had raged in the pages of the Lancet in London during and immediately before and after the Earl's Court exhibition in 1897, may be found in a paper by Zahorsky in the St. Louis Courier of Medicine for December, 1904 entitled: "The Baby Incubators on the 'Pike': A Study of the Care of Premature Infants in Incubator Hospitals Erected for Show Purposes".[3] The Lancet, in its editorial columns of May 29th, 1897, discussed the care of infants in incubators and its possible relationship to neonatal mortality rates and noted that Messrs. Samuel Schenkein and Martin Couney had opened an exhibition of baby incubators during the Victorian Era Exposition at Earl's Court. Further mention of the exhibition is made in the issue of July 17th of that year. After announcing that the members of the press were invited to inspect the incubators at Earl's Court, it is stated that the incubators were in charge of a trained nurse from Paris who was assisted by wet nurses who furnished the food for the infants.

The financial success of the incubator show at Earl's Court motivated other showmen to open a similar exhibition, as a result of which, Messrs. Couney and Schenkein in a letter to the Lancet dated September 18th deemed it their "duty to warn members of the medical profession, also nurses, parents, and public institutions not to entrust their children to any applicant whatsoever without first taking the precaution to assure themselves that they will not be made the victims of showmen, as well as inexperienced or irresponsible persons who seek to trade upon the established reputation of the invention that has been recognized by both the medical and lay press."

That there were many imitators seems apparent from an editorial in the Lancet of the following year (February 8, 1898) in which the editor expressed regret that the success at Earl's Court has attracted the attention and efforts of others. The methods used at the London World's Fair were especially attacked because the air was not obtained from the outside. The incubators at Barnum and Bailey's Circus seemed to have been under better management but the Lancet indignantly exclaimed, "What connection is there between the serious matter of saving human life and the bearded woman, the dog-faced man, the elephants, the performing horses and pigs, and the clowns and acrobats that constitute the chief attraction of Olympia?"[3] Despite the showmanship, Couney had demonstrated, perhaps better than anyone else could have and certainly on a much larger scale, that the provision of adequate thermal support and an appropriate thermal environment was clearly capable of markedly influencing the outcome and enhancing the survival of premature infants.

THEORETICAL CONSIDERATIONS

The reasoning behind Budin's observations is rooted in the physiologic properties of man as a homoiothermic animal—a condition he shares with all mammals. Unlike the poikilotherms (i.e., reptiles), whose body temperature will drift toward that of the environment (hence the use of the term "cold-blooded"), the homoiothermic organism, when exposed to a cold environment must increase heat production in order to maintain its body temperature. Physiologically cold is thus any temperature lower
than the internal body temperature.

There are two methods of accomplishing this increase in heat production in the cold: a physical method of muscular contraction and shivering and a chemical method capable of increasing heat production in the absence of muscular activity. The latter often is referred to as nonshivering or chemical (as opposed to muscular, shivering or physical) thermogenesis. Studies in adult experimental animals and man suggest that, quantitatively, shivering is the more important mechanism. In the newborn, however, the reverse situation applies. Thus, the newborns of most mammalian species-man included-do not shiver readily in the cold, yet they show an increase in both oxygen consumption and heat production when exposed to a cool environment suggesting that chemical thermogenesis would appear to be not only functioning but of paramount importance in maintaining the thermal stability of the newborn.

This difference in the major mechanism of heat production in the newborn versus the adult has resulted in a good deal of investigative effort into the activating mediator and intermediary mechanism of the neonatal nonshivering system. Although the system appears to be catecholamine-dependent, the nature of the mediator itself differs in the adult as opposed to the newborn. While epinephrine (adrenaline) appears to be the major responsible agent in human adults, newborn infants exposed to cold (with resultant increases in oxygen consumption and metabolic activity) show large increases in norepinephrine (noradrenaline) excretion with little change in epinephrine levels. Thus, the newborn infant utilizes a different system that is itself mediated differently from that of his adult counterpart.

The exogenous infusion of both norepinephrine and epinephrine results in an increase in plasma nonesterified fatty acids (NEFA). The infusion of norepinephrine in the newborn infant results in an increase in oxygen consumption. Studies in our laboratory have demonstrated a rise in both NEFA levels and body temperature following norepinephrine infusion and an in vivo rise in both NEFA and norepinephrine, with subsequent adequate defense of the body temperature, when newborn infants are exposed to cold. Combining these observations leads to the view that in the human newborn infant the defense against cold is mediated via an increase in norepinephrine and its effects on intermediary lipid metabolism.

The catecholamines (both epinephrine and norepinephrine) regulate NEFA by activation of an adipose tissue lipase. Brown fat (it is brown because of its rich vascular supply) appears to be implicated in this reaction as the site of heat production. Brown adipose tissue can be found in most newborn animals. Its existence has been verified anatomically in the newborn infant, where its presence has been demonstrated both internally and at the body surface. Dawkins and Hull showed that brown adipose tissue from newborn rabbits has a rate of \textit{in vitro} oxygen consumption twenty times that of adult rabbits in which the fat is predominantly white. The overall \textit{in vitro} rate of lipolysis in brown adipose tissue was also found to be three times greater than in white adipose tissue. Dawkins and Hull suggested that the thermogenesis is largely a local phenomenon occurring within the brown fat itself, and that, under the influence of the catecholamines, triglycerides are split into glycerol and NEFA. The NEFA is either oxidized, re-esterified to triglycerides or released into the circulation. In their view, 30% of the NEFA is oxidized directly, 60% is re-esterified and 10% is released into the circulation. The oxidized...
fraction represents an obvious thermogenic reaction. In addition, Ball and Junges\cite{23} have pointed out that the apparent purposeless hydrolysis and resynthesis of triglycerides is potentially a highly exothermic process. It thus appears that the increase in plasma NEFA mirrors, rather than causes, chemical thermogenesis in the cold and reflects the much greater lipolytic activity occurring with the adipose tissue itself.

An intriguing observation regarding the ontogeny and function of brown adipose tissue in the human neonate has been made by Heim, Kellermayer and Dani.\cite{24} Infants who die in the first months of life and who have suffered from inanition but have not been exposed to cold show depletion of the white fat stores but relative intactness of the brown fat stores. By contrast, infants who die well nourished but exposed to cold show a depletion of the brown fat stores, with the white fat relatively intact. It is also interesting to note that the gradual disappearance of the brown fat stores within the first year of life correlates well with the time of conversion from nonshivering to shivering thermogenesis and the clinical ability of the infant to shiver when exposed to cold.

MATURATION OF THERMOGENIC RESPONSES

With this information as a base, one can approach the major thermal problem confronting the premature infant, i.e., his inability to maintain internal homoiothermy without the support of incubators or other heating devices. As is well known, the small premature infant, if removed from the temperature of an incubator (32-34°C), even to a relatively warm room (27°C), is unable to accommodate even to this small ambient (environmental) temperature difference and the body temperature falls. Although norepinephrine excretion appears adequate in the premature under non-stress thermal conditions, the evidence suggests that, unlike his full-term counterpart, he is unable to increase this quantitatively in the "cold."\cite{13} This hypothesis has been tested prospectively in a group of 9 premature infants who ranged from 1200 to 1850 gm in birth weight, with a gestational age less than 34 weeks. On initial study, 6 of the 9 infants increased norepinephrine excretion, whereas 3 failed to do so. Mean fall in rectal temperature for the entire group in the cool zone was 2.4°C. The 3 non-responding infants showed the largest fall (3-5°C) as opposed to a maximal fall of 2.2°C in the 6 responding infants. When restudied 2 weeks later, all 9 infants showed an increase in norepinephrine excretion in the "cold." The increases themselves were quantitatively greater than in the first study, and mean rectal temperature fall for the group was now only 0.9°C, not exceeding 2.2°C in any of the subjects (Table 1).

Table 1

<table>
<thead>
<tr>
<th>Maturation of Thermoregulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fall in body temperature and rise in norepinephrine excretion in 9 premature infants after lowering ambient temperature (mean values). For further details, see text.</td>
</tr>
</tbody>
</table>
The sequence of events in another single such immature but appropriate weight for gestational aged infant is shown in Table 2.

Table 2
Maturation of Norepinephrine Secretion and of Thermal Stability in an Immature Infant

<table>
<thead>
<tr>
<th>Age (days)</th>
<th>Weight (g)</th>
<th>Warm (ng/kg/min)</th>
<th>Cold (ng/kg/min)</th>
<th>Change in Temperature (rectal)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>1285</td>
<td>0.898</td>
<td>0.867</td>
<td>-4.5°C</td>
</tr>
<tr>
<td>47</td>
<td>2400</td>
<td>1.197</td>
<td>3.314</td>
<td>-1.5°C</td>
</tr>
</tbody>
</table>

When initially studied at 12 days of age, there was no norepinephrine increase in the cold, and the rectal temperature fell by 4.5°C. In the second study, at 47 days of age, there was a striking increase in urinary norepinephrine excretion and the resultant fall in rectal temperature was limited to 1.5°C. These findings suggest that the norepinephrine response is a major mechanism in the newborn infant's defense against cold and that its maturation in time parallels the development of thermal stability in the premature infant. They also permit at least a partial answer to the longstanding vexing question "Why is it really necessary to supply external heat to a small premature baby?" To this it is now possible to reply in the following manner:

It is necessary to do so because the small premature infant does not possess the ability to increase heat production in a cool environment; that this ability is related to the increase in norepinephrine in the cold;
and that the appearance of this increase in the premature is the physiologic correlate of the ability to limit the degree to which body temperature falls when the challenge of a cold environment is placed before him.

THE THERMAL ENVIRONMENT

It is generally assumed that the temperature of the fetus is identical with that of the mother and is determined by that of the amniotic fluid. Theoretical considerations would, however, allow for a gradient in which the temperature of the fetus exceeds that of the mother in order to permit heat transferred during metabolic processes to the maternal compartment.\[25\] The principal site of heat dissipation in the fetus (unlike the newborn, in whom it is the body surface) is the placenta, which has a high thermal diffusion capacity. The combination of this physical attribute of the placenta and the high proportion of the total cardiac output going to it does not effectively permit the fetus to control its temperature independent of that of the mother, so that, despite the existence of the gradient, the maternal temperature appears paramount in determining the thermal situation of the fetus.

With the transfer to extrauterine life, however, the infant is now subject to external factors that will provoke and, in turn, regulate the adaptive maneuvers he must make to maintain thermal stability. Consideration of these involve an understanding of the concept of the so-called neutral temperature zone.\[11,9\] This zone, sometimes referred to as the "zone of maximal thermal comfort," may be defined as the environmental temperature at which metabolism as reflected by oxygen consumption is minimal, yet sufficient to maintain the body temperature. Lowering the temperature below this zone will cause an obligatory rise in metabolic rate, as will raising the temperature above it. In human adults, the "neutral" range is about 25-30°C. For newborn infants, the reported range is narrower and at a higher level (32-34°C). A consideration of this concept would indicate that attempts at reducing environmental temperature below this range to reduce the infant's metabolic activity as a therapeutic measure are not only incorrect but will, in fact, result in quite the opposite effect, i.e., that of raising it. The advantages of deep hypothermia, as used in surgical situations, are dependent on the so-called Q 10 Effect. This is a reduction in metabolism that occurs as a consequence of a fall in deep body temperature. In an anesthetized (nonshivering) adult, this value is 2.5, which means that if body temperature falls 10°C, metabolism will decrease by a factor of 2 1/2 times. This latter effect can be obtained only through the use of strictly regulated and adequately controlled situations and should not be confused with the ill-advised and contra-indicated efforts to just "cool the baby a little."

True thermoneutrality, however, involves factors other than just the temperature of the environment. Heat loss can occur in four separate and distinct ways and the true neutral zone must take account of minimizing all four routes of such loss.

The methods by which heat loss from the body can occur are:

1. Convection -- a function of both the surrounding temperature and air flow.
2. Radiation -- a function of the temperature of solid objects surrounding the subject.
3. Evaporation -- both from the lungs and from the body surface. The former is dependent on alveolar ventilation, whereas the latter is a function of the relative humidity of the surrounding environment.

4. Conduction -- a function of the temperature in which the subject is resting.

It is thus evident that optimal neutral conditions require the consideration of these factors. In clinical practice, the most important of these are the provision of adequate humidity to guard against evaporative losses and the prevention of heat loss due to radiation. Adamsons et al.,[26] have noted that minimal oxygen consumption within the neutral zone occurs when the gradient between skin and environmental temperature is less than 1.5°C, suggesting a further refinement of the conditions of true thermoneutrality. In their study, oxygen consumption began to rise at a rate of approximately 0.6 ml/kg/min., once this value for the skin-environmental gradient was exceeded.

At neutral thermal conditions, losses by conduction are negligible unless the subject is lying on a cold surface. This source of heat loss should be kept in mind when an infant is allowed to remain in the delivery room after birth. Placing the infant on a cold, wet delivery table will magnify this source of heat loss, and provision must therefore be made for a warm surface container into which the baby should be transferred immediately after birth. A preheated crib or incubator is adequate for this purpose. As the newborn infant does not sweat readily, evaporative losses from the skin are relatively small. These can be further reduced by properly humidifying the surrounding atmosphere. It must be remembered, however, that whereas one can readily increase the humidity within the incubator, considerations of the comfort and working capacity of the attending personnel limit the level to which this can be carried out in the nursery environment itself. The infant with respiratory difficulty and an increased respiratory rate will also increase evaporative heat losses from the lung, a factor noted clinically in the easy tendency to hypothermia seen in infants with respiratory distress syndrome, or other conditions with tachypnea, and hyperventilation.

In adults, the remaining heat losses are about equally divided between convection and radiation. Standard nursery conditions with higher air temperatures, even more so inside incubators, and minimal air currents effectively reduce convection losses to the point at which radiant losses account for about two-thirds of the total. The importance of this factor in the neonate in a nursery is critical. The temperature measured inside the incubator is that of the ambient air. Since radiant heat loss is a function not of air temperature (it is independent of it) but of the temperature of the surrounding objects (incubator wall, inside and outside walls of the room, etc.), knowledge and regulation of the incubator temperature alone do not take account of these losses.

Some clinical examples may best serve to illustrate this point. Thus, if an incubator wall is chilled by close proximity to an air conditioner or a cold window, the baby will lose a considerable amount of heat despite a constant, warm incubator temperature. The most serious extension of this occurs in the transport of sick infants in small, single-walled airplanes, where the effect is more readily magnified as a result of the extremely low temperatures on the outside wall of the plane. The converse of this situation seen in terms of heat gain occurs in the easy and often alarming hyperthermia which occurs if the infant is placed in the sunlight near the window.
CONSEQUENCES OF THERMAL IMBALANCE

In addition to the dangers of scalding and physical injury resulting from a too-hot environment, the metabolic demands on the infant increase as the temperature is raised above that of the "neutral" zone. Adams et al.\[27\] have demonstrated an increase in oxygen consumption in newborn premature infants at 36-38°C ambient temperature. Oxygen consumption values exceeding 10 ml/kg/min. (minimal rates usually range from 4.6 to 4.8 ml/kg/ min.) have been observed in heat-stressed newborns with only slightly elevated body temperatures.\[26\]

In addition to the difficulties encountered with such sustained or relatively prolonged periods of hyperthermia, both rewarming and thermo-regulatory procedures may carry dangers of their own. In both newborn infants and newborn animals, rapid rewarming by high-wattage radiant heaters or exposure to a very warm environment has resulted in apnea. The mechanism of such "heat-induced apnea" is not known, but it should be realized that once the infant is put into a positive thermal environment his metabolism falls to the neutral level, thus eliminating the urgency implied in the attempts to increase his body temperature too rapidly.\[28\] Further confirmation of this phenomenon has directly been observed in two other studies relating to infants in servo-controlled incubators. Daily et al.\[29\] reported that infants have apneic spells more commonly when maintained in environments heated in response to skin temperatures below 36.5°C as compared to 36.0. Skin temperature is generally agreed to be about 1°C below rectal temperature. Perlstein et al.\[30\] have reported a higher proportion of apneic spells occurring during periods of a rise in the air temperature in such an incubator. Both studies indicated a need for tighter control and more finite study of the optimal modes of operation of such units (see below).

HYPOTHERMIA

The maintenance of an adequate thermal environment and protection against excessive heat loss has been shown to enhance the prospects for survival of premature infants. Several elegant studies can be documented to support this contention.\[31,32,33\] Accidental lowering of the environmental temperature for prolonged periods may result in actual physical cold injury. Even in the absence of obvious tissue destruction however, the progressive reduction in heat content of the infant may ultimately no longer be compatible with life. Mann and Elliott\[34\] reported their experience in treating 16 hypothermic infants in whom deep body temperature had fallen to between 27°C and 32°C. Less than half of these infants survived.

A number of physiologic derangements may result from the challenge of hypothermia to the newborn. To the extent that these are attempts to compensate for the stress of "cold," they represent a beneficial response of the organism to the challenge. Nonetheless, they may of themselves result in serious challenges to the integrity of functioning systems and thereby further place the infant at risk, with a subsequent reduction in his chances for survival.
Constriction of skin blood vessels occurs in response to cold, both in full-term and pre-term infants.[11] The effect of this peripheral vasoconstriction is to increase the internal (core-skin) temperature gradient, thereby increasing tissue insulation to its maximal value. The effectiveness of this response is better in the full-term baby because of his greater soft-tissue mass. Even when maximally constricted, however, the tissue insulation of a low birth weight infant is low by comparison with the full-term infant and similarly for both pre-term and full-term vis-a-vis older infants and adults. This defect is essentially a function of small body size and is not modified to any important extent by gestational differences.[35]

The obligatory increase in metabolic rate resulting from a cold environment may impose serious consequences on the infant. Thus, a baby already in respiratory difficulty is faced with a need to increase his oxygen consumption, something that can be accomplished only at the expense of increasing his minute ventilation. The infant with respiratory distress syndrome already breathing at 80-100 per minute may be unable to meet this challenge, and the demand itself may be the final precipitating event in the onset of irreversible respiratory failure. To some extent, there is a partially protective effect of hypoxia in such a situation. Experimental evidence in both newborn infants and experimental animals has shown that moderate acute hypoxia has no effect on minimal oxygen consumption but that it does reduce the metabolic response to cold.[36,37,9] The elevation of arterial $P_0_2$ by administration of oxygen appears capable of restoring the ability of the depressed human newborn to increase the metabolic rate in the cold.[38] The phenomenon may be a two-edged sword, since, while it can reduce the obligatory increase in metabolic demand for the hypoxic infant, it may also make it more difficult for him to maintain himself in thermal equilibrium when cold-stressed. In contrast to acute hypoxia, chronically low $P_0_2$ does not interfere with metabolic responses to cold even in the presence of an elevated $P_0_2$.[39] The reasons for this difference are not known but may involve a process of adaptation and adjustment by the infant to a chronically unfavorable situation.

Hypothermia effects changes in acid-base homeostasis that favor the development of metabolic acidosis.[40] Several factors combine to promote this trend. The increase in metabolic rate imposed by the cold stress will, if prolonged, result in such changes. To this is added the effect of any persistent vasoconstriction, with subsequent reduction in tissue perfusion and metabolism, leading to the accumulation of ketone bodies. Moreover, the altered relationship of glucose to free fatty acids (see below) under cold stress, with its resultant hypoglycemia and accompanying inability to utilize glucose as a primary metabolic source, further potentiates this tendency. The over-all effect is thus toward acidemia and a fall in pH.

Acidosis not only imposes its own demand for counterregulatory homeostatic mechanisms, but may, in addition, play a major role in perpetuating the cycle of pulmonary deterioration in infants already suffering from respiratory disorders. Through its action as a potent pulmonary vasoconstrictor, the acidosis, by reducing pulmonary perfusion, can materially influence the ability of the organism to oxygenate itself. The resultant hypoxemia further increases the acidosis, with the establishment of a vicious circle of progressive downhill deterioration and increasing impairment. Such a view of the pathophysiology of the respiratory distress syndrome places a crucial focal point of both development of
the disease and its management on factors maintaining the adequacy of the pulmonary circulation.\[41]\n
Moreover, since the synthesis of surfactant that appears to be involved in the development of the disease to begin with, and whose reestablishment appears crucial if recovery is to ensue, seems to be dependent on pulmonary blood flow,\[42,43,44]\ncontrol of the pulmonary vasculature emerges as a major problem in the disease, and such challenges that tend to impair it become serious pathophysiologic factors. Stephenson et al.\[45]\nhave demonstrated a fall in arterial P0 2 in hypothermic full-term newborn infants in the absence of any change in pH. The mechanism of this drop is not known, but has been postulated to involve the action of norepinephrine released as a result of the hypothermic exposure.\[13]\n
Norepinephrine increases pulmonary vascular resistance.\[46,47]\nThis, in turn, would result in an increased right-to-left shunt via both the still-patent ductus arteriosus and functionally open foramen ovale.\[48]\nIn addition, the increased resistance may also change pulmonary ventilation-perfusion relationships. Both of these effects would operate in the direction of lowering the arterial oxygen tension.

In addition to the possibility of hypothermia-induced acidemia and hypoxemia, the cycling effect in terms of temperature loss ensuing from the disease itself can also be appreciated from the increased evaporative water loss occurring from the lungs in the affected infant with his increased respiratory rate and ventilatory efforts. Thus, not only may hypothermia worsen the disease, the disease itself may, in turn, increase the hypothermia. It is a circle that needs to be broken by strenuous efforts to maintain total homeostasis of multiple parameters throughout its entire course if it is to be managed successfully.

HYPOGLYCEMIA

Hypothermia results in a fall in blood glucose, as a consequence of which the hypothermic infant often is hypoglycemic as well.\[34]\n
The hypoglycemia is the result of the elevation of nonesterified fatty acids occurring in the cold\[17\] which, in turn, leads to a fall in blood glucose, an effect consistent with the observed inverse relationship between blood glucose and NEFA levels.\[49\] In clinical practice, two precautions should therefore be observed in respect of this relationship. The infant exposed to cold may be profoundly hypoglycemic, and steps should be taken both to determine blood glucose levels and to energetically provide adequate supplemental amounts of parenterally administered glucose. Conversely, a true index of glucose homeostasis cannot be obtained in a hypothermic infant, and therefore any studies of neonatal glucose metabolism should be done only in a neutral thermal environment or after a previously "cold" infant has been "warmed."

HYPOTHERMIA AND THE INDUCTION OF KERNICTERUS

Kernicterus at relatively low levels of serum bilirubin has been reported, especially in premature infants, both under clinical conditions associated with acidemia\[50\] and following the administration of sulfisoxazole (Gantrisin).\[51\] The induction of kernicterus is dependent on such factors as will either dissociate bilirubin from its albumin-binding sites or, by providing substances that will compete for a binding site with bilirubin, predispose to the presence of more free (unbound) bilirubin. If the bilirubin is unconjugated (indirect-acting with the van den Bergh reagent), its solubility in lipid media and relative
insolubility in water will facilitate its egress from the serum and into rich lipid-containing areas such as skin and brain.

Acidosis is known to dissociate bilirubin from its albumin-binding sites.[52] Moreover, there is a greater affinity of brain mitochondria for bilirubin as the pH is lowered.[53] The sulfisoxazole effect is the result of competition for the bilirubin albumin-binding site with an increase in the free, unbound, bilirubin fraction as the result of displacement of bilirubin by the competing anion.[54,55,56] Hypothermia may predispose to the recurrence of kernicterus via both pathways. The acidosis occurring in the "cold" will promote bilirubin albumin dissociation while the rise in NEFA will provide a potentially potent competitor for the albumin-binding sites.[57]

That "cold" may be a clinically important inducing agent for such kernicterus is apparent from our experience with the occurrence of kernicterus in 23 premature infants at low levels of serum bilirubin. All had maximal indirect-acting serum bilirubin levels less than 23 mg/100 ml. Seventeen had maximal levels less than 20 mg/100 ml and in 5 of these infants the level was less than 15 mg/100 ml.[58] These cases occurred over a 4-year period in two referral nurseries in a major metropolitan area that receive patients from an area encompassing some 60,000 live births annually. All the infants designated as developing kernicterus died, and the presence of kernicterus was confirmed at autopsy in all of them. Eighteen of these 23 infants had documented evidence of significant antecedent hypothermia, with rectal temperatures less than 35.5°C. It is important to note that all but one of these infants was born outside of the two hospitals in question, with the hypothermic episode occurring during transport of the infant to the referral center.

CLINICAL SIGNIFICANCE OF HYPOTHERMIA

In clinical practice, a fall in temperature may be a sign of severe and important underlying systemic disease. Hypothermia may be the first and often only sign of sepsis in the newborn. Often the disorder is manifested by a loss of thermoregulatory ability reflected as a fluctuating, uneven temperature curve whose overall tendency is toward a progressive decline in body temperature. Central nervous lesions such as birth asphyxia, meningitis and, in particular, intracranial hemorrhage, may also show a similar picture as a result of destruction or irritation of central thalamic thermoregulatory pathways.

In the nursery, such a situation may first reveal itself as a progressive need to increase the environmental heat in an effort to maintain body temperature and will be reflected by continued upturning of the thermostatic control of the incubator in which the infant is being kept. In this connection, it is of the utmost importance to recognize that the normal full-term baby should not require the use of an incubator or other supplementary heating device to maintain his body temperature in an adequately heated nursery (25-27°C). If he does, then a thorough and diligent search for either other environmental factors causing excessive heat loss or systemic illness in the infant must be instituted. The situation should never be ignored, or its clinical significance underestimated.

The administration of cold, unhumidified oxygen directly from a wall source or a tank may be an
important and often unrecognized source of cold stress to the infant. This is a not infrequent occurrence when an oxygen line is placed directly into an incubator to further oxygen-enrich the environmental air over and above that which may be obtained via the heated, nebulized inflow arrangement through the incubator itself. If such an extra line is needed, efforts must be made to see that the oxygen so delivered is both adequately heated and humidified by first passing it through a suitable heating nebulizer. A similar situation pertains in many delivery rooms and cardiac catheterization laboratories, where oxygen may be administered dry and cold directly from a tank or wall source. Even if the thermal environment is otherwise adequate, the application of a cold stimulus to small localized areas of the body surface, in particular the forehead, and trigeminal area of the face\cite{59,60} will trigger the obligatory increase in oxygen consumption and metabolic rate that follows exposure to environmental cold.

Many of the routine practices and environmental conditions in delivery rooms tend to promote an already easy tendency to heat loss in the immediate postnatal period. Under normal delivery room conditions, deep body temperature of the human newborn falls 2-3°C.\cite{61} The fall is most rapid in the initial minutes after birth, at which time the rates of fall of deep body and skin temperatures are about 0.1°C per minute and 0.3°C per minute, respectively. This corresponds to a heat loss of approximately 200 cal/kg/min. Since maximal heat production in adult man on exposure to cold is only about 90 cal/kg/min., it is evident that the body temperature of the newborn baby would fall even if heat production per unit of body mass were two times that of the adult.\cite{25}

Several factors contribute to this high rate of heat loss, the principal one being evaporation of amniotic fluid from the skin. Moreover, at the time of delivery, deep body temperature of the newborn is about 0.5°C and skin temperature about 2.5°C higher than that which later pertains in extrauterine life.\cite{25} Thus, for a given environmental temperature, the gradient between skin and environment will be greater and the resultant heat flow from one to the other more easily facilitated.

To this heat-losing situation must be added a number of environmental factors in the delivery room itself. Placing the baby on a cold delivery table will increase conductive heat losses. The table often is wet, resulting in a further evaporative heat loss from the infant. Moreover, air currents and a lower temperature resulting from air-conditioning units in the room will further augment such losses. Should the infant require resuscitation, the situation is, on many occasions, allowed to deteriorate even further. All too often the infant is intubated, bagged, and resuscitated but is allowed to become progressively cold, thereby establishing a self-defeating circle of metabolic events. Even under these emergency circumstances, a properly warmed micro-environment should be designated in which such measures can be carried out effectively. The use of overhead sources of radiant heat that permit adequate working space may provide such a facility. The infant should be removed from the delivery room and transported in a warm carrier to the nursery as soon as his condition permits. The practice of keeping the infant for prolonged periods in the delivery room lacks any physiologic basis and may indeed be harmful.

Transfer of high-risk full-term and premature infants to referral centers is becoming increasingly popular together with renewed interest in facilities for neonatal intensive care and the regionalization of such centers.\cite{62} Such transport with currently available facilities imposes a serious hazard of cold exposure
with all of the resultant physiologic impositions upon the infant in an attempt to compensate for cold stress. It is evident that an urgent need exists for improvement both in methods of transport and in the design and construction of portable incubators that will allow for working access to the infant while maintaining adequate thermal conditions during the move. The suspicion that hypothermia in transit may contribute to the induction of kernicterus at low levels of bilirubin provides further evidence for the need for such optimal conditions.

DESIGN OF INCUBATORS

Pierre-Constant Budin's original incubator provided for heating of the air, one-way airflow, additional humidity and temperature monitoring of the environment. Among the patents for incubators filed by Julius Hess was one in 1932 which also proposed a mechanism for the addition of supplemental oxygen. Accepting that such an addition may be desirable, the major function of incubators remains the suitable provision of adequate amounts of external heat. A number of recent innovations have led to the use of infrared and low-energy radiant sources in both closed and open-ended units that can be servo-controlled via a skin-sensing mechanism so as to provide a thermal environment constantly dictated by the infant's own body temperature.[31,32,63,64] The advantages of such a system of control would seem obvious. However, the use of a servo-mechanism deprives the clinician of a valuable sign in diagnosing serious disease. Under a servocontrolled system, fluctuations in temperature will not be apparent, other than by a monitoring device that could record the increasing frequency of an on-off cycle as the servo-mechanism compensates for a fall in body temperature and the subsequent increased thermal demand on it. The observations regarding apnea and heating cycles further warrant careful examination of and the focusing of attention on this problem.

The problem exists, however, not only in the nursery but also in the operating and delivery rooms. All too often insufficient attention is given to maintaining an appropriate thermal environment. Although the importance of maintaining the infant's core temperature at surgery has become increasingly recognized and methods for so doing are currently in use in many neonatal surgical centers,[65] it must be recognized that even if the core temperature is adequately maintained, the metabolic adjustments necessary to achieve it may impose an enormous physiological stress on the infant, even though this would not be reflected in a fall in core temperature. When the core temperature does fall, it means that the compensatory responses have been attempted and still found to be insufficient so that the actual fall in core temperature should only be viewed as the extreme end result of the failure to provide an adequate thermal environment.

Finally, there are other problems relating to ease of sterilization and the problem of "water bugs" in incubators as a source of infection. Noise levels within the incubator from their motors may be of considerable importance for future hearing development, particularly if the incubator is combined with a negative-pressure vacuum-pump type of respirator.[66] Electrical hazards both to the baby and operating personnel need to be considered, as do air currents resulting from variable flow rates and patterns within the units themselves. In this latter problem, the use of an internal thermometer within the incubator enclosure to measure air temperature may be misleading, as the direction of the air flow patterns may be
uneven and there can exist significant differences between the air temperature at the site of the thermometer and that at the site of the baby. Clearly, there is room for improvements and refinements, all of which begin with primary basic understanding, not only of the need for thermal neutrality in the newborn infant but also of the mechanisms and adjustments which operate to bring it about.

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