A model for predicting insensible water loss in premature neonates

by

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NOMENCLATURE

C = constant (cm)

C_0 = concentration of water within the papillary dermis (g/cm^3)

C_1 = concentration of water at the interface between the viable epidermis and stratum corneum (g/cm^3)

C_2 = concentration of water at the surface of the stratum corneum (g/cm^3)

C_p = heat capacity ($kcal/g \cdot {}^oC$)

D_0 = reference diffusivity, determined by extrapolating experimental data to 0K (cm^2/s)

D_1 = diffusivity of water through the hydrated skin layer (cm^2/s)

D_2 = diffusivity of water through the stratum corneum (cm^2/s)

D_{AB} = molecular diffusivity of water vapor and air (cm^2/s)

D_p = cylinder diameter (cm)

$D(T)$ = diffusivity as a function of temperature (cm^2/s)

E = activation energy of diffusion (kcal/mole)

G = mass velocity ($g/cm^2 \cdot s$)

GA = gestational age (wk)

h_c = convective heat transfer coefficient ($kcal/cm^2 \cdot {}^oC \cdot hr$)

h_r = radiative heat transfer coefficient ($kcal/cm^2 \cdot {}^oC \cdot hr$)

$\mathcal{H}$ = partition coefficient (g H_2O per cm^3 air/g H_2O per cm^3 stratum corneum)

H_{vap} = heat of vaporization (kcal/g)

j_1 = flux of water through the hydrated skin layer ($g/cm^2 \cdot s$)

j_2 = flux of water through the stratum corneum ($g/cm^2 \cdot s$)

j = flux of water through the skin ($g/cm^2 \cdot s$)

j_M = mass transfer j factor (dimensionless)

k = thermal conductivity ($kcal/cm \cdot {}^oC \cdot hr$)

k_C = mass transfer coefficient (cm/s)

Mo = metabolic rate ($kcal/cm^2 \cdot hr$)

N = population (number of individuals)

Nmax = maximum population which can be supported (number of individuals)

N_{Re} = Reynold's number (dimensionless)

P_a = partial pressure of water in the ambient air (atm)

P_S = partial pressure of water in the air at the skin's surface (atm)

PCA = postconceptual age (wk)

PNA = postnatal age (day)

Q_{conv} = heat transfered through convection ($kcal/cm^2 \cdot hr$)

Q_{evap} = heat transfered through the evaporation of water ($kcal/cm^2 \cdot hr$)

Q_{rad} = heat transfered through radiation ($kcal/cm^2 \cdot hr$)

r = rate of increase (day^{-1})

R = gas constant ($kcal/mole \cdot K$)

t = time (day)

T = temperature (K)

Ta = ambient air temperature (^oC)

T_C = average temperature of the core layer (^oC)

T_m = average temperature of the muscle layer (^oC)

T_S = average temperature of the skin layer (^oC)

Tsu = skin surface temperature (^{o}C)

v = incubator air velocity (cm/s)

X_c = thickness of the core layer (cm)

X_m = thickness of the muscle layer (cm)

X_{mc} = average distance between the core and muscle layers (cm)

X_{sm} = average distance between the muscle and skin layers (cm)

Greek

α = constant (cm)

β = constant (cm)

δ_{PD} = thickness of the papillary dermis (cm)

δ_{SC} = thickness of the stratum corneum (cm)

$\delta_{SC,max}$ = maximum thickness of the stratum corneum (cm)

$\delta_{SC,O}$ = thickness of the stratum corneum at birth (cm)

δ_{VE} = thickness of the viable epidermis (cm)

δ_{VE}(PNA=0) = thickness of the viable epidermis at birth (cm)

γ = constant (day^{-1})

μ = viscosity (g/cm·s)

ρ = density (g/cm^3)

GLOSSARY

Diffusivity - an empirical value which relates the flux of a material to its concentration gradient when the material is moving by the mechanism of passive diffusion

Fick's first law - law which describes passive diffusion where the diffusion of molecules occurs due to a concentration gradient

Gestational age - the estimated period from fertilization to birth

Insensible perspiration - water loss which occurs by evaporation from cells

Mitosis - cell division

Necrotizing enterocolitis - an inflammation of the gastrointestinal tract which can progress to gangrene of the intestines and the second leading cause of death for premature infants

Neonatal period - first 27 days of life

Neonate - the infant during the first four weeks of life

Partition coefficient - an empirical value which relates the equilibrium concentration of a component in one phase to the equilibrium concentration of that component in another phase

Patent ductus arteriosus - the reopening of a passageway within the heart that normally exists during fetal life, this causes blood to flow from the aorta to the pulmonary artery and results in the recirculation of arterial blood through the lungs

Periderm - a temporary protective skin layer which covers a fetus during the first two trimesters

Premature infant - born before 37 weeks of gestation

Post conceptual age - age from the time of fertilization

Postnatal age - age from the time of birth

Sensible perspiration - water loss which occurs through sweating

Term infant - born after approximately 40 weeks of gestation

INTRODUCTION

The skin forms the entire outer covering separating the body's interior from the environment. It is the largest organ, accounting for approximately 16% of the total body weight for humans. Although skin is water resistant, it is not waterproof, and interstitial body water slowly diffuses to the skin's surface where it evaporates into the air. This type of water loss is called insensible perspiration and we are normally unaware of its occurrence. Water may also cross the skin as sensible perspiration. Sensible perspiration is produced by the sweat glands and acts as one of many regulatory mechanisms for maintaining normal body temperature.

The uppermost layer of skin, the stratum corneum, contains the protein keratin and is responsible for the skin's water resistant properties. It is understood that water moves through the skin layers by the mechanism of passive diffusion and that the presence of keratin greatly reduces the diffusivity of water through the cornified layer. If the stratum corneum is damaged or absent, as for burn victims or premature infants, the resulting increase in skin permeability can be life-threatening, since the heat and water balance are drastically altered.

It is well known that keeping premature infants warm after birth greatly reduces their mortality rate. Two types of warming devices are currently used in neonatal critical care units. The convective incubator, which is the older method, circulates warm humid air in an enclosed environment. The more recently developed warming device, the radiant

warmer, supplies heat through a radiant energy source located above the infant. These devices maintain an infant's body temperature by controlling one or more modes of thermal transfer.

Thermal energy transfer between an infant and the environment can occur through conduction, convection, radiation, and the evaporation of water. Since the thermal conductivity of a nursery mattress pad is usually low and since only about 10% of an infant's body surface area is in contact with the mattress, heat loss through conduction is relatively small and is usually inconsequential. Heat transfer by convection and radiation have been well studied for the case of the premature infant and heat transfer coefficients for these routes of thermal exchange are known. Heat transfer through the evaporation of water has also been extensively studied, but factors which control this mode of thermal transfer are poorly understood and correlations available to predict this loss are usually based on curve fitting. A consequent uncertainty encountered in neonatal critical care involves the amount of calories and water to be administered to each infant. For instance, too little water can lead to dehydration whereas too much water can increase the risk of patent ductus arteriosus.

Since most term infants and all premature infants do not yet have the ability to produce sensible perspiration or sweat, insensible perspiration accounts for almost all of the water lost through the skin. Evaporation of insensible perspiration is a major route of heat loss in premature infants. In fact, evaporative losses can easily exceed an infant's total metabolic heat output, particularly if the infant is very

premature. This large heat and water loss occurs due to the underdeveloped nature of the stratum corneum. For the term infant and the adult, the stratum cornuem serves as a major barrier to the diffusion of water. For example, the insensible water loss for an adult human is approximately 11 $g/m^2 \cdot hr$, whereas the insensible water loss for a very premature infant can be as high as 110 $g/m^2 \cdot hr$.

The purpose of this work is to develop a phenomenologically based, quantitative description for insensible water loss in premature infants. It focuses on how skin development affects the energy and water balance of the premature infant. Principles of heat and mass transfer are applied along with transient material and energy balances to develop a quantitative description of the effect of skin underdevelopment on the rate at which water penetrates the skin. The ability to quantitatively predict an infant's rate of water loss will make the determination of water and nutrient requirements more accurate. Moreover, an understanding of the physiological processes which determine the insensible water loss may aid in designing incubators which are the most conducive to the premature infant during his/her untimely adjustment to life outside the womb.

DISCUSSION OF BACKGROUND MATERIAL

Structure of Human Skin

The skin is composed of two main layers: a surface layer which consists of stratified epithelial cells, the epidermis, and a deeper, connective tissue layer, the dermis or corium. Collagen fibers from the dermis extend into the subcutaneous layer, which is rich in adipose tissue, thereby connecting the skin to the rest of the body. The skin and its accessory structures which include hair, nails, and glands, constitute the integumentary system and is diagrammed in Figure 1.

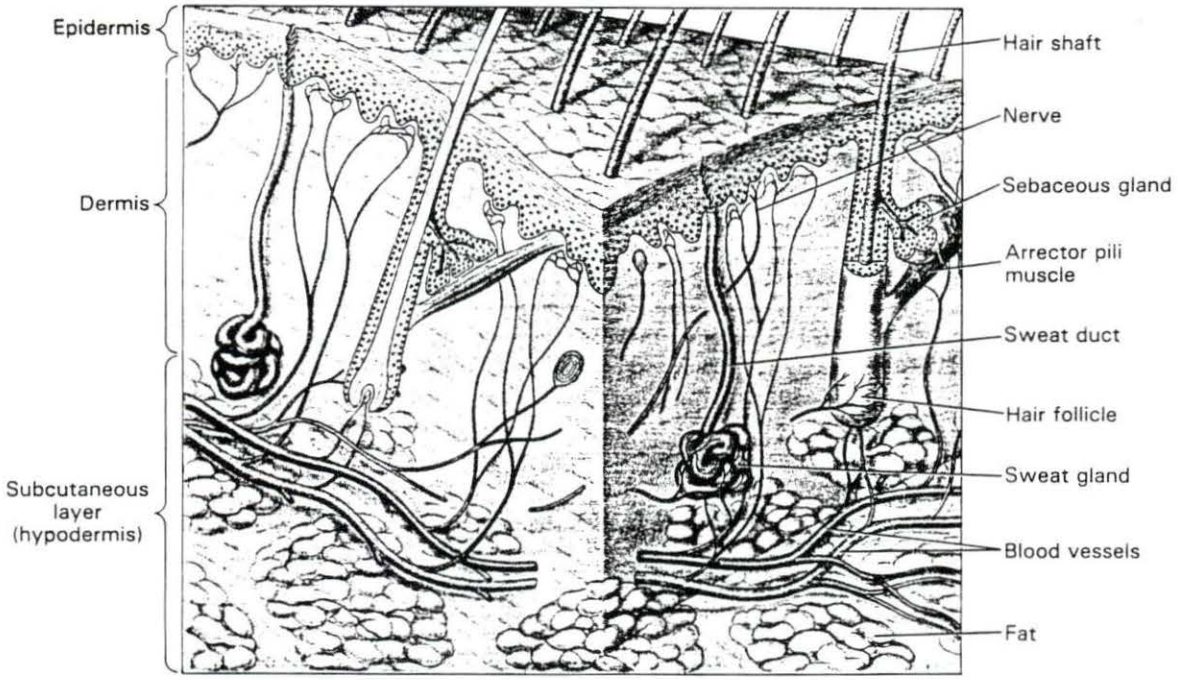

Figure 1: The general organization of the integument (taken from Martini, 1989)

Histologists have divided the epidermis into four layers or strata. The deepest epidermal layer is known as the stratum basale. Mitosis occurs within this layer of columnar cells and differentiation takes place as the daughter cells migrate towards the surface of the skin. Approximately four weeks are required for a daughter cell to reach the surface of the skin (Martini, 1989). The stratum spinosum lies adjacent to the stratum basale. It consists of irregularly shaped cells, some of which may also undergo mitosis. For this reason the stratum basale and the stratum spinosum are sometimes referred to as the stratum germinativum (Spence, 1986). Standard procedures for studying the stratum spinosum under the light microscope shrinks the cytoplasm and the cells resemble tiny pincushions (Martini, 1989). The name for this layer was derived from this spine-like appearance. The next superficial layer is the stratum granulosum. These cells manufacture and store granular packets of the protein keratohyalin, a precursor of filaggrin, which forms the matrix material found in mature keratin (Steinert & Cantieri, 1983). As more protein is produced, the cells flatten out and their nuclei begin to disintegrate. Consequently, cells in the outermost portion of the stratum granulosum begin to die. The uppermost layer is the stratum corneum. This dead cellular layer contains the protein keratin which gives skin its waterproof properties. Thick skin covers areas of the body which are subjected to constant pressure and abrasion, such as the palms of the hand and soles of the feet. Thick skin contains an additional layer between the stratum granulosum and the stratum corneum. This clear cell layer is known as the stratum lucidum. The

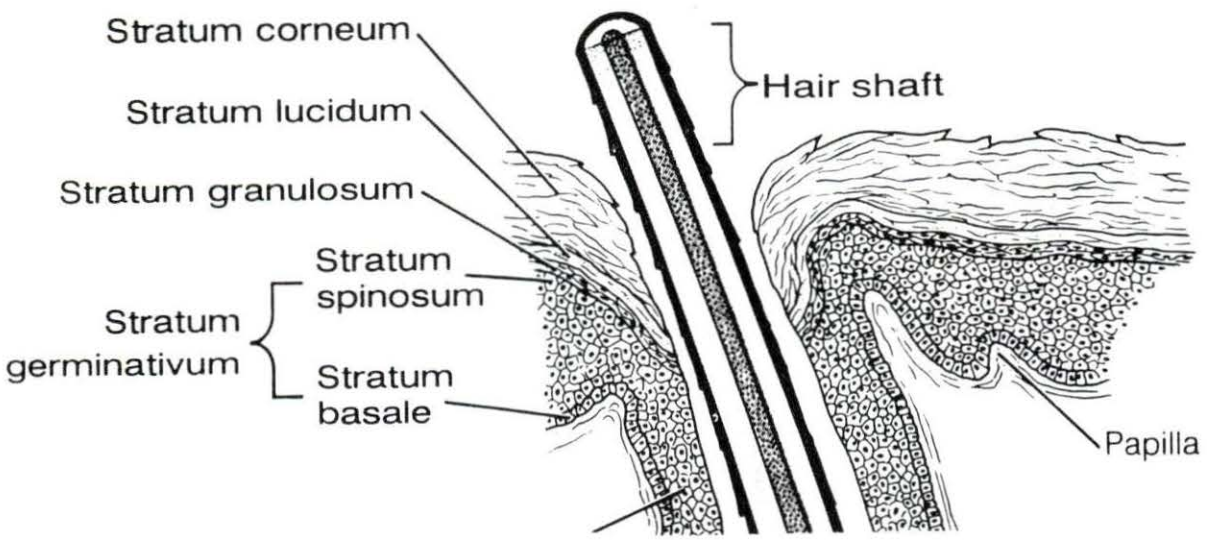

Figure 2: The epidermis (taken from Spence, 1986)

epidermal layers are illustrated in Figure 2.

The dermis is composed of two regions, the papillary dermis and the reticular dermis. The papillary layer lies beneath the epidermis. This layer of loose connective tissue has finger like papillae which project upward towards the epidermis. The papillae contain a dense network of capillaries which supply nutrients to the epidermis since blood vessels do not penetrate epithelium. The lower region of the dermis is the reticular

dermis. It consists of dense connective tissue with elastic and collagenous fibers. The collagen fibers strengthen the dermis whereas the elastic fibers allow the skin to stretch and contract.

Keratinization of the Epidermis

The term keratinization refers to the process which epidermal daughter cells, or keratinocytes, undergo to form hardened cells filled with protein (Fraser et al., 1972). Epidermal keratin consists of two components. The first of these is the keratin filament which constitutes up to two-thirds of the terminally differentiated stratum corneum. The second component is filaggrin, a histidine-rich protein which becomes enmeshed with the filaments (Steinert & Cantieri, 1983). Available data have established that keratin proteins are synthesized by the classical protein synthesis process (Steinert & Cantieri, 1983). In this process, messenger RNA (mRNA) is produced by transcription of DNA in the nucleus of the cell. Within the sequence of nitrogen bases, DNA contains the information to synthesize over 100,000 different proteins (Martini, 1989). The mRNA diffuses from the cell's nucleus to cytoplasm to interact with one or more ribosomes. The ribosome aids in reading the genetic information contained within the mRNA and a protein is synthesized by interactions with transfer RNA (tRNA) molecules, each of which carries a single amino acid (Martini, 1989).

From electron microscope studies, it can be determined that fibrous proteins are present in the basal layer of epidermal cells. Many cell types contain similar protein fibrils, but epidermal cells have the

special ability to convert these fibrils into keratin filaments (Jarrett, 1973a). As an epidermal cell transverses through the skin layers, keratin filaments are produced, and it has been found that the proteins contained within the filaments are extremely heterogeneous (Steinert & Cantieri, 1983). During keratinization, which occurs in the upper portion of the stratum granulosum, disulfide crosslinks are formed between the keratin filaments (Jarrett, 1973a).

As an epidermal cell migrates through the stratum granulosum, large accumulations of the protein keratohyalin, the precursor of filaggrin, are formed. Magnification of cells within the stratum granulosum show that the keratin filaments pass through the protein granules. As cells move through the stratum granulosum, there is an abrupt transition to the stratum corneum cell-type involving the complete filling of the cell with protein and destruction of the nucleus and virtually all of the organelles including the protein granules (Fraser et al., 1972). Most stratum corneum cells are completely filled with filaments about 70 angstroms in diameter embedded in a protein matrix material which is principally filaggrin (Fraser et al., 1972).

The rate limiting step for the production of the keratin proteins was found in several instances to reside in the transcription of messenger RNA (Freedberg, 1983). A polypeptide with a molecular weight of approximately 5500 has been found to enhance basal cell proliferation and keratinization of epidermal tissue. This polypeptide is known as epidermal growth factor (EGF) and has been detected in human urine, milk, plasma, saliva, and amniotic fluid (King & Carpenter, 1983). It has

been found that EGF, administered subcutaneously or orally, acts directly on the epidermis by stimulating RNA synthesis, protein synthesis, cell division, and eventually keratinization (King & Carpenter, 1983). This information suggests that EGF may aid in controlling the rate of epidermal growth and keratinization.

Prenatal Development of Skin

From the beginning of life, the epidermis and dermis are distinctly different layers. The epidermis develops from the embryonic ectoderm whereas the dermis originates from the mesoderm.

The epidermis In the human embryo at three weeks, the epidermis consists of a single layer of cuboidal cells. Around the seventh week, a second layer of flattened cells forms over the initial cuboidal basal layer (Corliss, 1976). This protective layer is known as the epitrichial layer or more commonly, the periderm. Towards the ninth week the basal layer becomes thicker and an intermediate layer, the stratum intermedium, is formed (Corliss, 1976). From the tenth to the sixteenth week the number of layers in the stratum intermedium increases. Around the eighteenth week the skin has a definitive structure and at twenty-one weeks keratinization is present in the uppermost layers (Hoyes, 1968). By the twenty-sixth week a stratum corneum is present and most of the periderm has been pushed off by growing hair. Also at this time, the sebaceous glands become active and secrete an oily material called sebum. The sebaceous secretions added to sloughed off periderm cells forms a whitish cheesy

substance, the vernix caseosa. This substance persists for several days after birth and may function in protecting the fetus from maceration by the amniotic fluid (Hamilton et al.,1966). From the twenty-sixth week to the fortieth week, the skin layers continue to grow and the epidermis of a term infant is almost identical to that of an adult (Holbrook, 1982). The precise timetable of these events may vary slightly for different regions of the body (Pinkus, 1910). Figure 3 illustrates the stages in the development of the epidermis.

The dermis The fetal dermis changes dramatically during prenatal life. The dermis of an eight-week embryo consists of 95% water, very little collagen, and an abundant amount of sugars (Serri and Cerimele, 1971). At this time, collagenous fibers have formed a network at the dermal-epidermal junction (Holbrook & Smith, 1981). From the eighth week until term, collagen fibers continue to form and thicken in diameter. Elastic fibers are secreted in the reticular dermis at approximately 22 weeks and in the papillary dermis at roughly 28 weeks (Holbrook, 1982). When comparing the dermis of a premature infant or term infant to an adult, the structure is similar but the fiber bundles are smaller in diameter. The fiber bundle diameter is smallest for the premature infant and largest for the adult, however, fewer differences exist within the papillary dermis than for the reticular dermis (Holbrook, 1982).

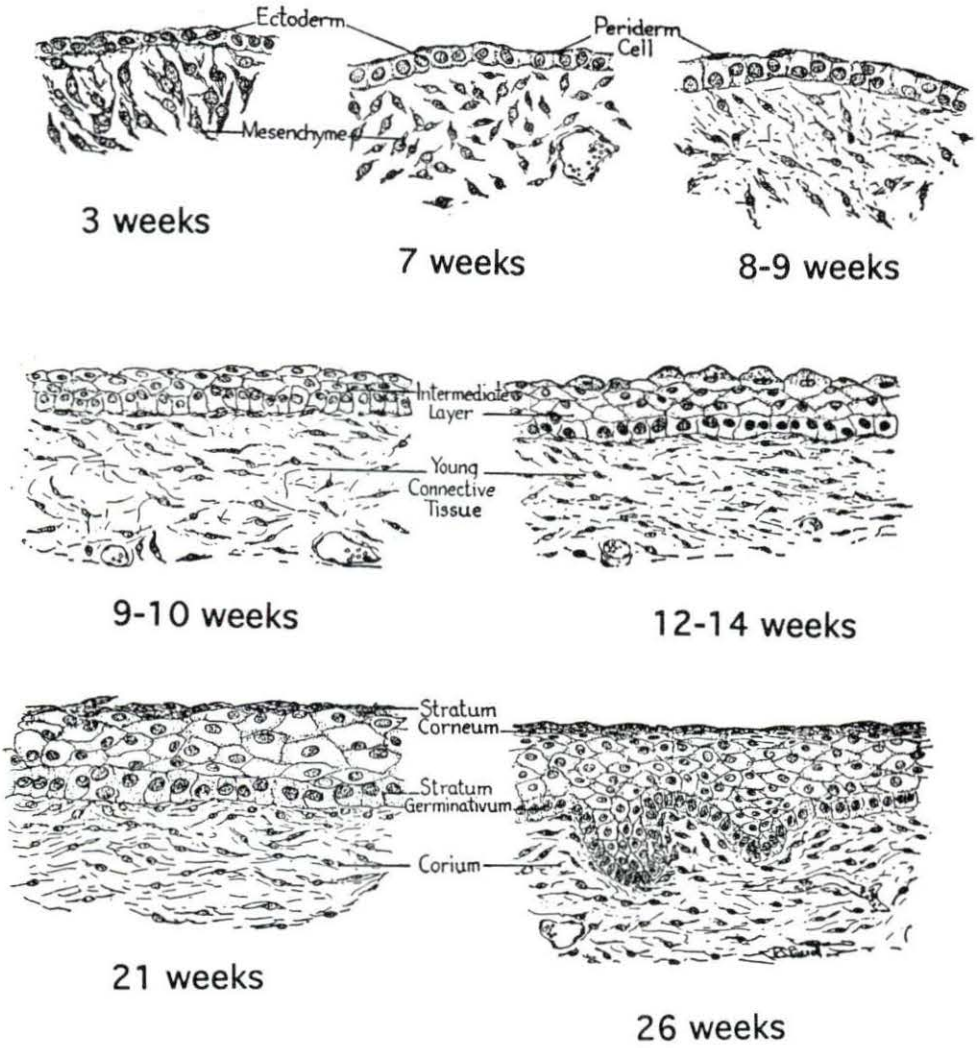

Figure 3: The stages of epidermal development (Adapted from Corliss, 1976)

Consequences of Underdeveloped Skin in Premature Neonates

The thickness of the epidermal layers, particularly the stratum corneum, varies substantially with an infant's gestational age (Evans and Rutter, 1986). The cornified skin layer is the primary barrier to the diffusion of interstitial water from the body to the environment. Consequences of a thin stratum corneum include a high insensible water loss and subsequent difficulties in maintaining a proper fluid balance and body temperature.

Since oral feeding is often not possible, many premature infants need to be supplied with calories, water, and electrolytes (Vaughnan and McKay, 1975). The amount of fluid administered is often decided arbitrarily and can vary greatly depending on the philosophy behind the calculations (Hammarlund, 1991). Over hydration can increase the risk of patent ductus arteriosus, congestive heart failure, and necrotizing enterocolitis (Bell and Oh, 1983). Conversely, dehydration results from administering too little fluid. Therefore, maintaining adequate hydration is a critical and unfortunately difficult task for personnel involved in neonatal intensive care.

The premature infant has a large surface area-to-mass ratio when compared to the term infant, although the resting metabolic rate is similar for both when expressed per kilogram of body weight (Hull, 1988). An infant can lose heat to the environment through convection, conduction, radiation, and the evaporation of water. Since these modes of thermal exchange are functions of body surface area, the premature infant is at a disadvantage in terms of thermoregulation due to size

alone. A high rate of insensible water loss worsens the situation for the preterm infant, since every gram of water requires about 570 calories to evaporate. For premature infants under 32 weeks of gestation, the evaporation of insensible perspiration is the major route of heat loss (Hull, 1988). Two warming devices, the convective incubator and the radiant warmer, have made it possible to maintain a premature infant's core temperature at 37°C.

MODEL DEVELOPMENT

Description of the Model

The skin behaves as if it consists of two layers, each of which have different diffusion properties. Previously, the percutaneous absorption of liquids and gases has been mathematically described by modeling the skin as a composite membrane (Scheuplein, 1978 and Cussler, 1984).

The upper portion of skin which resists the diffusion of materials can be divided into three layers: the papillary dermis, the viable epidermis, and the stratum corneum. These three layers act in series to constitute a composite membrane. For an adult, the portion of the upper papillary dermis which resists the diffusion of water is approximately 150 μm thick (Scheuplein , 1978). The thickness of the viable epidermis and the stratum corneum is 40.7 μm and 9.3 μm, respectively (Holbrook, 1982). Since the diffusivity of water in the stratum corneum is 3 to 4 orders of magnitude less than that for the viable epidermis and papillary dermis, these latter hydrated layers can be treated as one phase and described with a single diffusivity (Scheuplein, 1978). This model is illustrated in Figure 4.

From Figure 4, it can be seen that several parameters must be known before applying this model to the development of skin. These parameters include the variation of water concentrations (C_O, C_1, and C_2) and layer thicknesses (δ_{PD}, δ_{VE}, and δ_{SC}) over time, the diffusivity of water in each layer, and the ambient conditions.

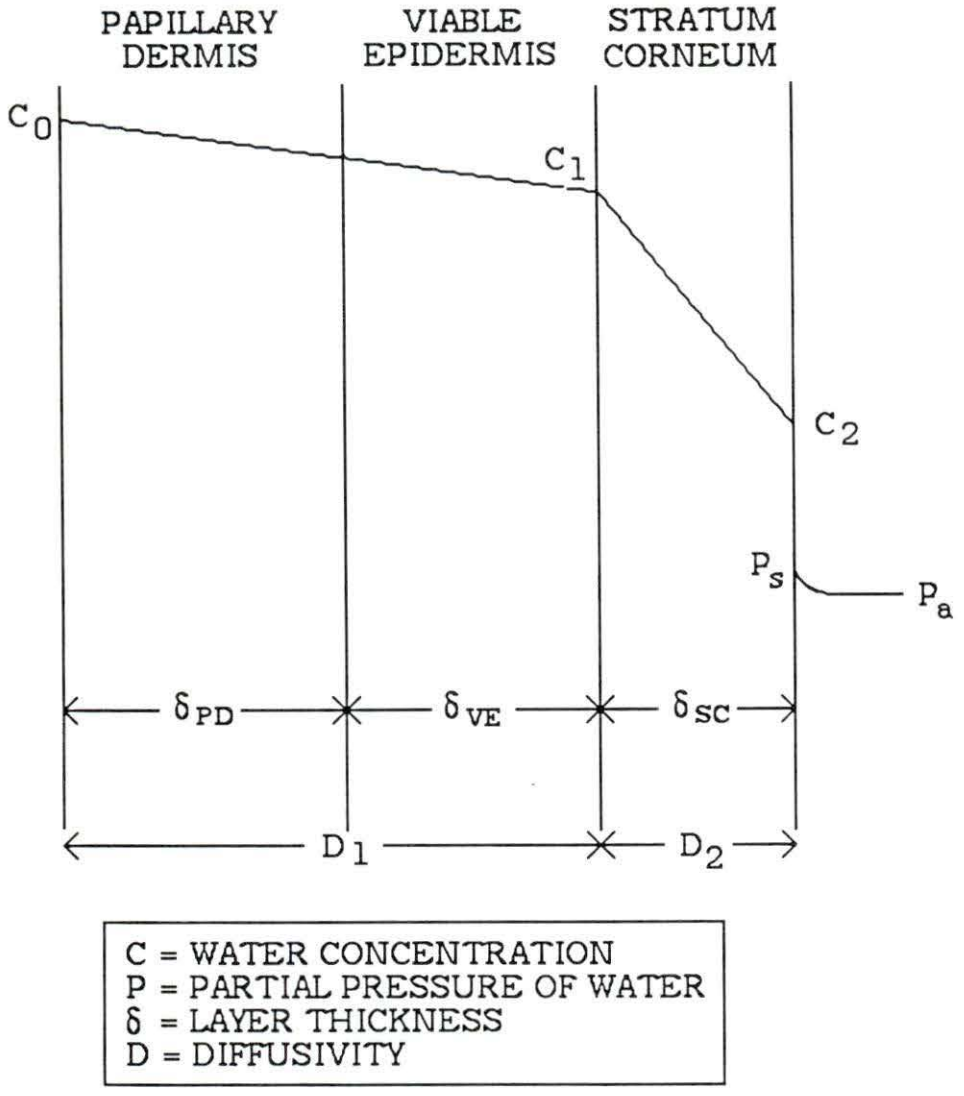

Figure 4: Skin as a composite membrane (Adapted from Scheuplein, 1978)

Assumptions Made Relating the Model to Prenatal Skin Development

The skin layers obey Fick's first law of diffusion It has been shown that the transfer of isotopic water is linear with the gradient over a fivefold range in concentration difference (Parmley and Seeds, 1970). Since the time required to measure the insensible water loss through the skin of premature neonates is small compared to the time required for further development, a steady state situation may be assumed. Fick's first law of diffusion can then be applied to each layer and equated yielding:

$$j_1 = D_1(C_O-C_1)/(\delta_{PD} + \delta_{VE}) \quad (1)$$

$$j_2 = D_2(C_1-C_2)/\delta_{SC} \quad (2)$$

eliminating C_1 by recognizing that $j_1=j_2$:

$$j = (C_O-C_2)/[(\delta_{PD}+\delta_{VE})/D_1 + \delta_{SC}/D_2] \quad (3)$$

The diffusivity of water through the skin layers is known The diffusivity of water in the hydrated skin layer and the cornified layer has been determined from absorption experiments as a function of temperature (Scheuplein, 1978). It has been shown that the diffusivity of water through the skin is independent of the direction of flow (Parmley & Seeds, 1970 and Rothman, 1954). In other words, the diffusivity is the same regardless of whether the water is flowing from the skin's surface

into the dermis or from the dermis to the skin's surface. The diffusivity can be expressed as a function of temperature using an Arrhenius equation (Scheuplein, 1978) of the form:

$$D(T) = D_O \exp(-E/RT) \quad (4)$$

For the diffusion of water through hydrated stratum corneum, the activation energy is 15.7 kcal/mole and the reference diffusivity is 69.5 cm^2/s. Likewise, the activation energy is about 4.70 kcal/mole and the reference diffusivity is 0.063 cm^2/s for the hydrated skin layer (Scheuplein, 1978).

The thickness of the papillary dermis remains constant with age Only the outer portion of the papillary dermis resists the diffusion of water (Scheuplein, 1978). A histological comparison showed that the structure of the dermis was similar when comparing the skin of a premature infant, a term infant, and an adult, and that fewer differences existed between the papillary dermis than for the reticular dermis (Holbrook, 1982). Since the outer 150μm of the papillary dermis resists the diffusion of water for an adult, this value should be similar for preterm and term infants and remain constant with age.

The thickness of the viable epidermis and stratum corneum increases linearly with gestational age By measuring the thickness of the viable epidermis as a function of gestational age, it was found that there is a steady increase in thickness from 24 weeks to term (Evans and Rutter, 1986). Figure 5 shows this relationship which can be

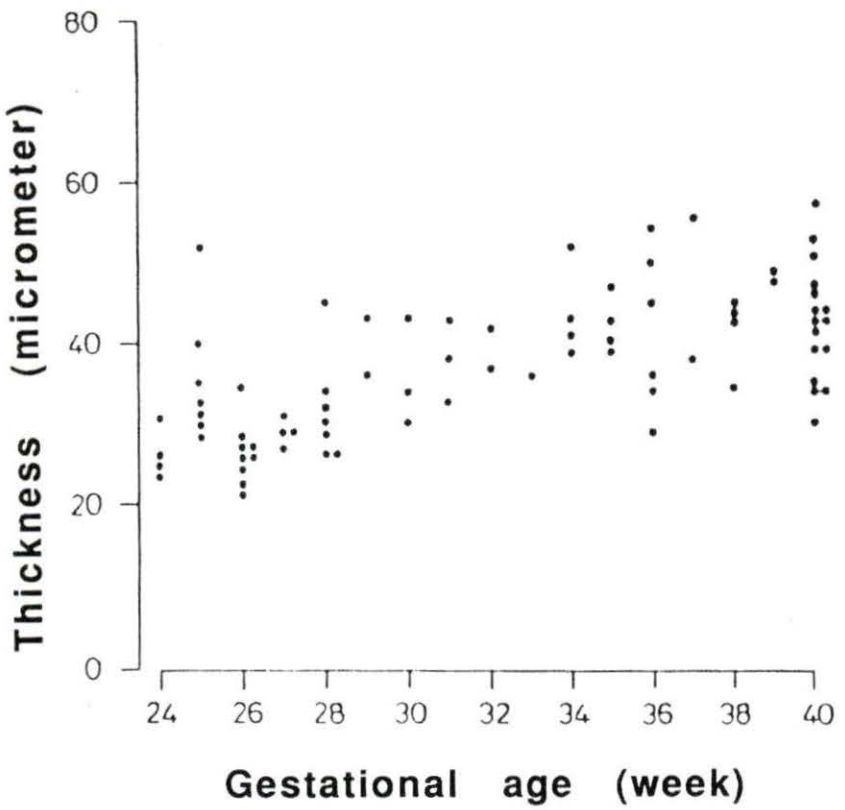

Figure 5: The effect of gestational age on the thickness of the viable epidermis (taken from Evans and Rutter, 1986)

approximated by:

$$\delta_{VE} = 7.5\text{x}10^{-5}(GA) + 1.1\text{x}10^{-3} \qquad (5)$$

The thickness of the stratum corneum was found to be 4.1μm and 9.3μm for a 30 week and 40 week infant, respectively (Holbrook, 1982). Since keratinization of the upper skin layer begins during the 21st week

of fetal life (Hoyes, 1968), the thickness of the stratum corneum is close to zero at this time. These three data points are shown in Figure 6 and the thickness of the stratum corneum can be estimated by:

$$\delta_{SC} = 4.9x10^{-5}(GA) - 0.00104 \quad (6)$$

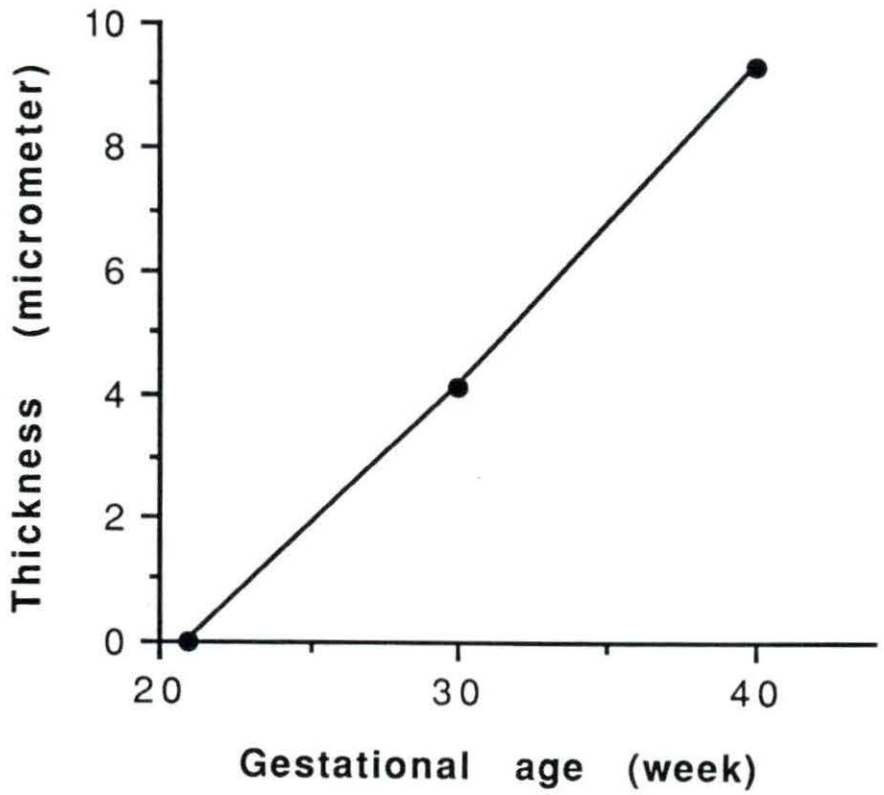

Figure 6: The effect of gestational age on the thickness of the stratum corneum

C_O is a function of gestational age For an adult, C_O is about 0.879 g/cm^3 (Scheuplein & Blank, 1971). Since the papillary dermis of a term infant is similar to that of an adult (Holbrook, 1982), then C_O will also be approximately 0.879 g/cm^3 for a term infant. The water content of whole fetal skin varies with gestational age and this linear relationship is shown in Figure 7. Assuming that the concentration of water within the papillary dermis varies proportionally to the concentration of water in whole skin, with respect to gestational age, the following relationship is obtained:

$$C_O = -3.45\text{x}10^{-3}(GA) + 1.017 \qquad (7)$$

This assumption seems reasonable when recalling that the dermis makes up the majority of the skin.

The concentration of water at the surface of the stratum corneum (C_2) is close to equilibrium with water in the ambient air C_2 can be estimated from water vapor isotherms for excised stratum corneum (Scheuplein & Blank, 1971). In other words, the partial pressure of water at the air-skin interface is approximately equal to the partial pressure of water in the ambient air. These partial pressures can be related to C_2 with a partition coefficient where:

$$P_a \approx P_S = \mathcal{H}C_2 \qquad (8)$$

The partition coefficient or Henry's Law constant can be determined by

calculating the slope of the water vapor isotherm. From a water vapor isotherm constructed in a temperate environment (Blank, 1952), it can be found that $\mathfrak{H}$ is 8.04×10^{-5} g H_2O per cm^3 air/g H_2O per cm^3 stratum corneum for a relative humidity between 40% and 70%.

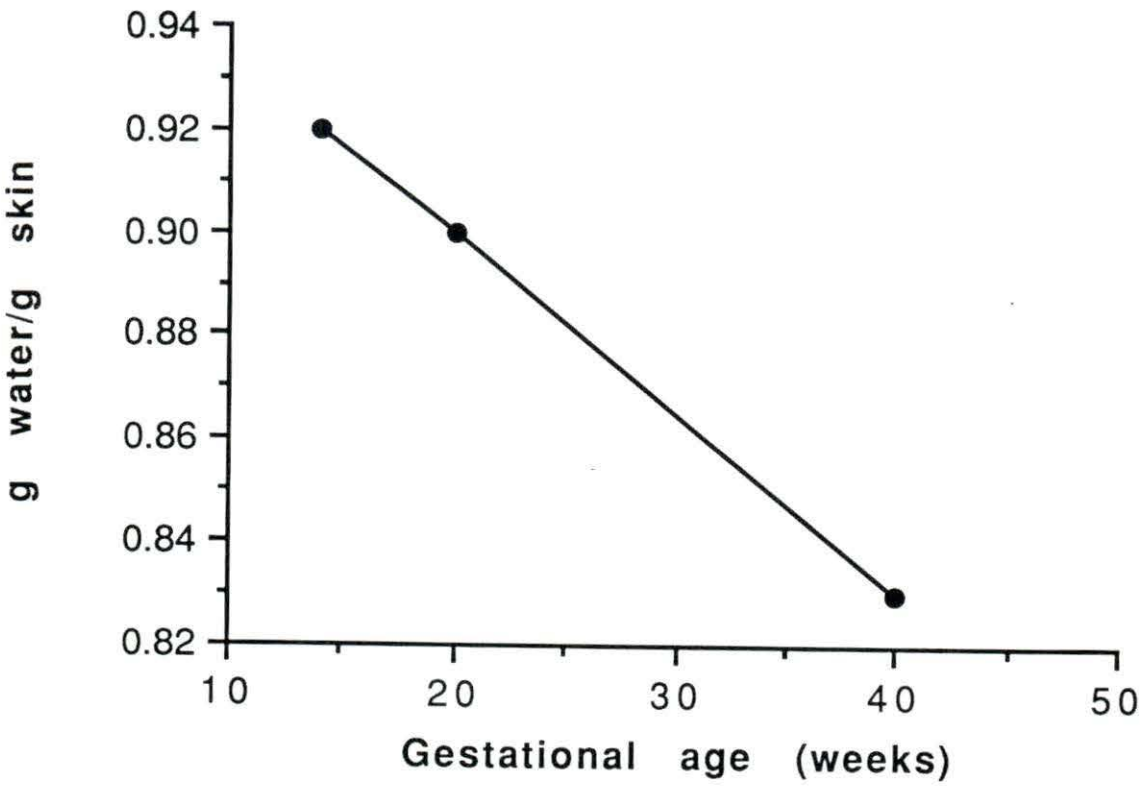

Figure 7: Effect of development on water in fetal skin (taken from Widdowson & Dickerson, 1960)

The diffusional resistance due to the boundary layer of air at the surface of the infant's skin can be estimated from a mass transfer correlation The resistance to the diffusion of water can be calculated for the hydrated skin layer and the stratum corneum if the diffusivities and layer thicknesses are known. These resistances are shown in the denominator of equation 3. An additional resistance to the diffusion of water exists in the boundary layer of air surrounding the infant and can be expressed as a reciprocal of the mass transfer coefficient. Reasonable heat and mass transfer results can be obtained for an infant by assuming a cylindrical shape while keeping the volume and surface area constant (Coffey & Seagrave, 1972). The mass transfer coefficient can then be determined from a correlation such as that shown in Figure 8 since the air velocity within an incubator is approximately 0.15 m/s (Wheldon, 1982). The mass transfer j factor is related to the mass transfer coefficient by the following expression:

$$j_M = k_C/v(\mu/\rho D_{AB})^{2/3} \qquad (9)$$

The flux of water can then be expressed in terms of the mass transfer coefficient:

$$j = k_C(P_S - P_a) \qquad (10)$$

By combining equations 3, 8, and 10, C_2 and P_S can be eliminated and the following relationship is obtained:

$$j = (\mathcal{H}C_O - P_a)/[\mathcal{H}(\delta_{PD} + \delta_{VE})/D_1 + \mathcal{H}\delta_{SC}/D_2 + 1/k_C] \qquad (11)$$

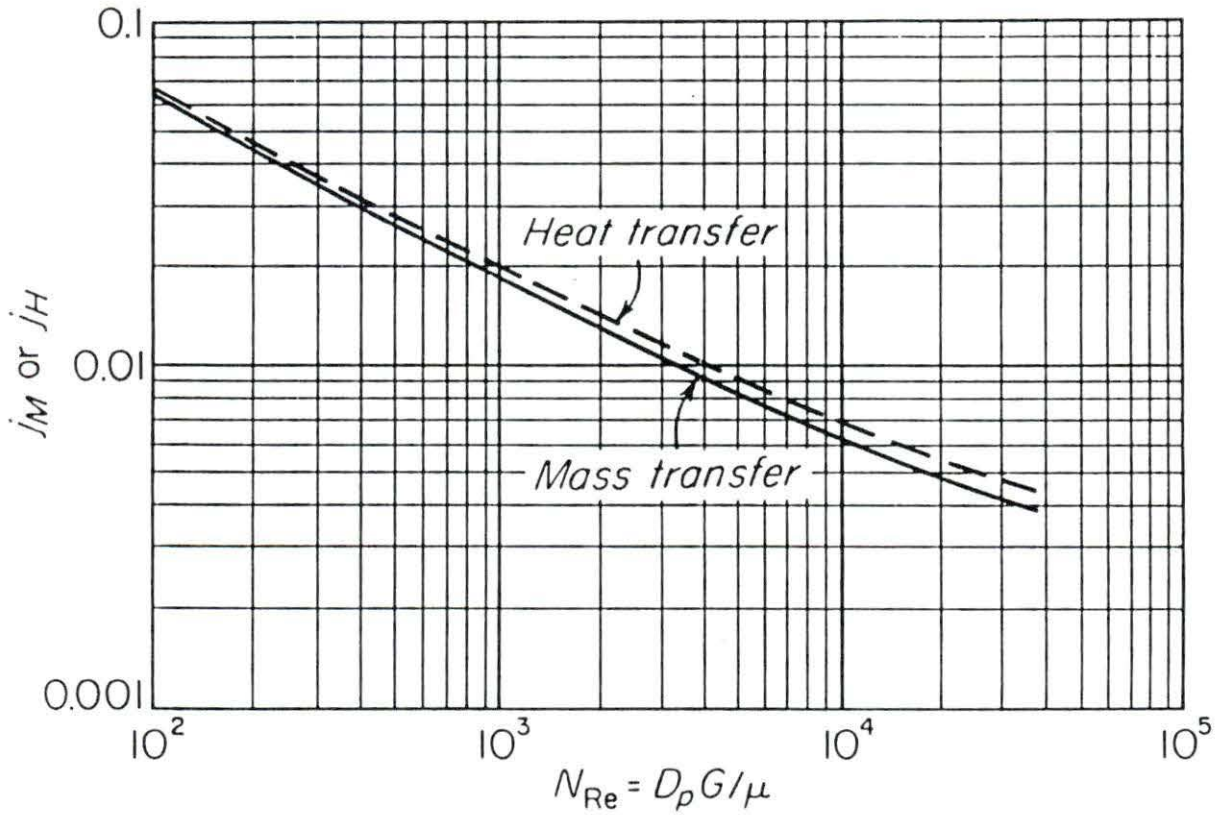

Figure 8: Heat and mass transfer j factors for flow past single cylinders (taken from McCabe, Smith, & Harriott, 1985)

Results I - Water Loss as a Function of Gestational Age

By applying equations 4, 5, 6, 7, and 11 to the model diagrammed in Figure 4, the insensible water loss can be predicted as a function of prenatal age. The results are plotted with actual data (Hammarlund, 1983) in Figure 9.

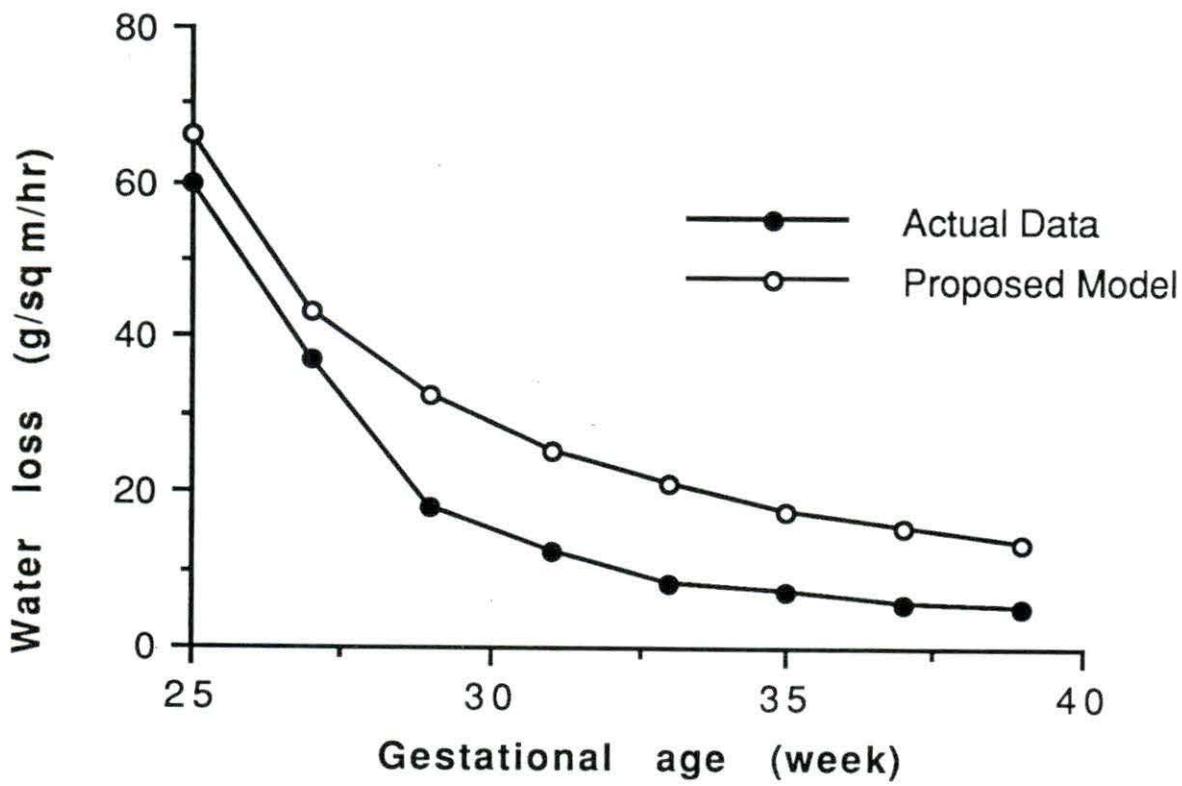

Figure 9: Insensible water loss as a function of gestational age
Temperature = 35.5°C, Humidity = 50%, Postnatal age = 0
(actual data taken from Hammarlund, 1983)

Assumptions Made Relating the Model to Postnatal Skin Development

The dermis of a preterm infant develops at the same rate during prenatal life as for postnatal life As the dermis develops, the water concentration decreases due to the formation of protein fibers (Widdowson, 1969) until the structure of the dermis resembles that of an adult. The growing protein fibers displace the water and it was shown in Figure 7 that the water concentration decreased linearly with gestational age. Assuming that protein fibers are produced at the same rate during postnatal life as for prenatal life, the concentration of water in the dermis, C_O, can be estimated during postnatal life from equation 7 where:

$$C_O = -3.45\text{x}10^{-3}(\text{PCA}) + 1.017 \qquad (12)$$

The viable epidermis of a preterm infant grows faster during postnatal life than during prenatal life The thickness of the viable epidermis has been measured as a function of gestational age and postnatal age (Evans & Rutter, 1986). These data show that the rate of epidermal growth is roughly twice as fast during postnatal life as it is during prenatal life, and this growth continues until the thickness of the viable epidermis reaches the value seen for adults and term infants. Therefore, the postnatal development of the viable epidermis can be estimated from equation 5:

$$\delta_{VE} = \delta_{VE}(\text{PNA}=0) + 2.14\text{x}10^{-5}(\text{PNA}) \qquad (13)$$

The thickness of the stratum corneum increases rapidly after birth The postnatal development of the stratum corneum has been previously studied (Evans & Rutter, 1986) and this relationship is shown in Figure 10. The thickness of the stratum corneum was assessed using an arbitrary scoring system where 0=barely visible, 1=thin layer, 2=medium layer, and 3=thick layer.

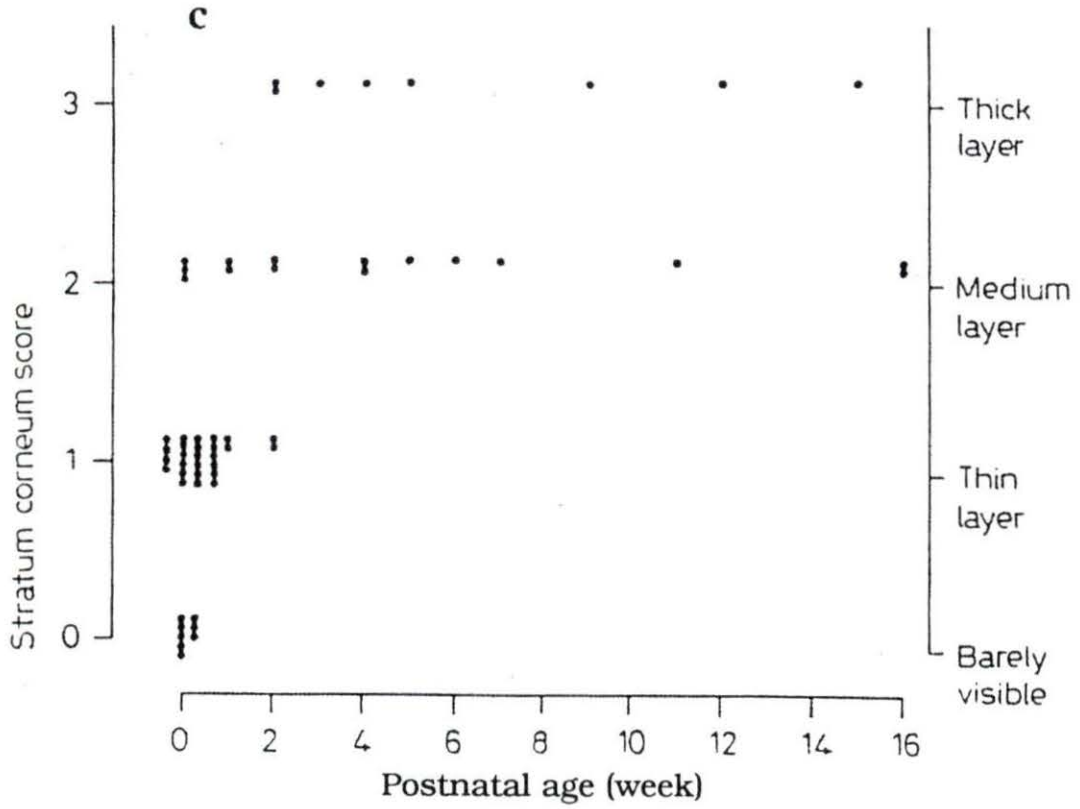

Figure 10: Development of the stratum corneum in 59 infants born between 24 and 30 weeks of gestation, showing the effect of postnatal age (taken from Evans & Rutter, 1989)

The stimulus for repopulation of skin cells is likely to be a depopulation of cells in the basal layer (Fowler & Denekamp, 1976). After removing layers of stratum corneum from human skin by cellotape stripping, it was found that there was a rapid transit of cells from the basal epidermal layer to more superficial layers (Fowler & Denekamp, 1975). By varying the number of stratum corneum layers removed, a graded response was found. Therefore, an absence of cornified cells promotes the proliferation of basal cells and epidermal differentiation by stimulating the migration of basal cells. This process may be mediated through the action of epidermal growth factor (EGF), a polypeptide which has been found in bodily fluids and shown to stimulate epidermal growth and development (King & Carpenter, 1983). The rapid growth of the stratum corneum observed in the skin of premature neonates may also be controlled by this same mechanism because their skin has a very thin cornified layer. Since the mechanism for repopulation of epidermal cells involves the depopulation of cells in the stratum corneum, and a greater depopulation results in an increased response, the mechanism may be described using a logistic model which is commonly seen in biological systems. In this model, the rate at which a population grows is proportional not only to the number of elements but also to the difference between the maximum population which can be supported (N_{max}) and the actual population (N). This model is given by the following equation:

$$dN/dt = rN[(N_{max}-N)/N_{max}] \qquad (14)$$

Since the thickness of the stratum corneum is proportional to the number of cornified cells, equation 14 can be rewritten as:

$$d(\delta_{SC})/dt = r\,\delta_{SC}[(\delta_{SC,max}-\delta_{SC})/\delta_{SC,max}] \quad (15)$$

By separating the variables and integrating equation 14, the thickness of the stratum corneum can be related to time.

$$\int_{\delta_{SC,O}}^{\delta_{SC}} [1/\delta_{SC}(1-\delta_{SC}/\delta_{SC,max})]\, d(\delta_{SC}) = \int_{0}^{PNA} r\, dt \quad (16)$$

$$\ln[\delta_{SC}/(1-\delta_{SC}/\delta_{SC,max})] - \ln[\delta_{SC,O}/(1-\delta_{SC,O}/\delta_{SC,max})] = rPNA \quad (17)$$

Equation 17 can be rearranged to give the following expression:

$$\delta_{SC} = C/[\exp(-rPNA) + C/\delta_{SC,max}] \quad (18)$$

where

$$C = \delta_{SC,O}/(1-\delta_{SC,O}/\delta_{SC,max}) \quad (19)$$

$\delta_{SC,max}$ is the maximum thickness of the stratum cornuem and is approximately 9.3μm. $\delta_{SC,O}$ is the thickness of the stratum corneum at birth, and can be determined from equation 6 which give the thickness of the cornified layer as a function of gestational age. r is related to the postnatal growth of the stratum corneum. The thickness of the stratum

corneum increases rapidly after birth and after 2-3 weeks of postnatal life, the epidermis of the most premature infant is histologically similar to that of a term infant (Evans & Rutter, 1986). From this information and the data given in Figure 10, it can be found that r is approximately 0.25 day^{-1}. Substituting C and r into equation 18, the thickness of the stratum corneum can be predicted as a function of postnatal age and gestational age. This relationship is shown in Figure 11.

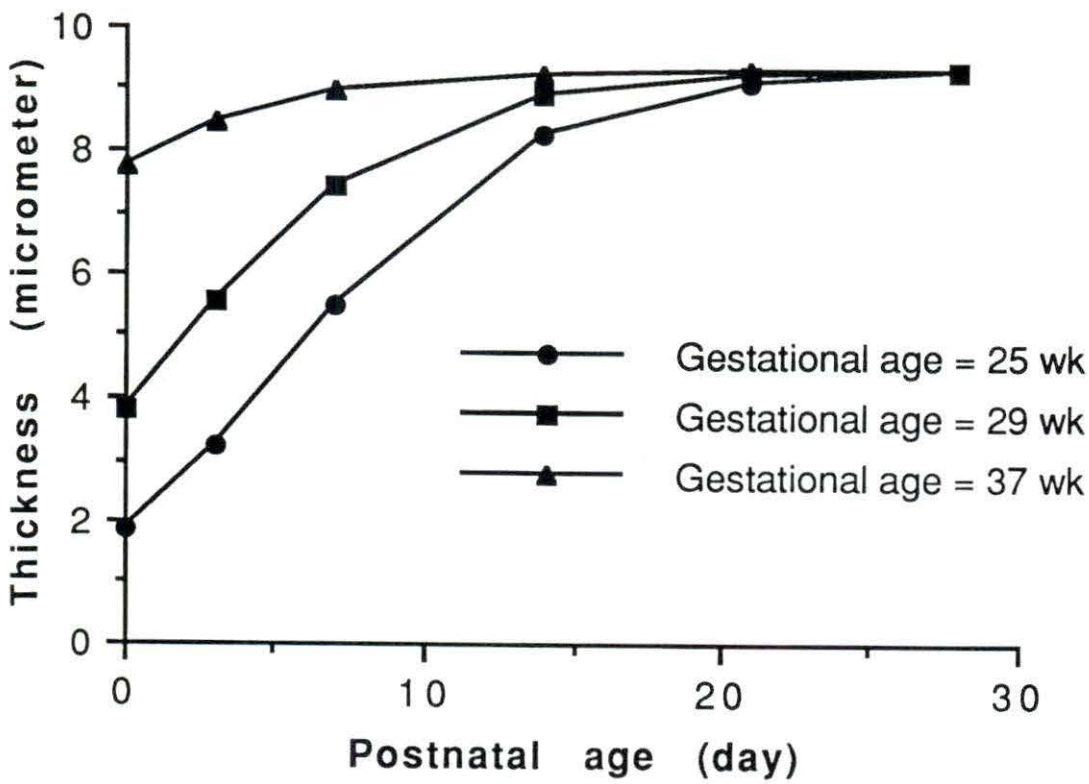

Figure 11: Estimating the postnatal growth of the stratum corneum for various gestational ages

Results II - Water Loss as a Function of Gestational Age & Postnatal Age

By applying equations 4, 11, 12, 13, and 18 to the model diagrammed in Figure 4, the insensible water loss can be predicted as a function of gestational age and postnatal age. The results are shown with actual data in Figures 12a through 12c.

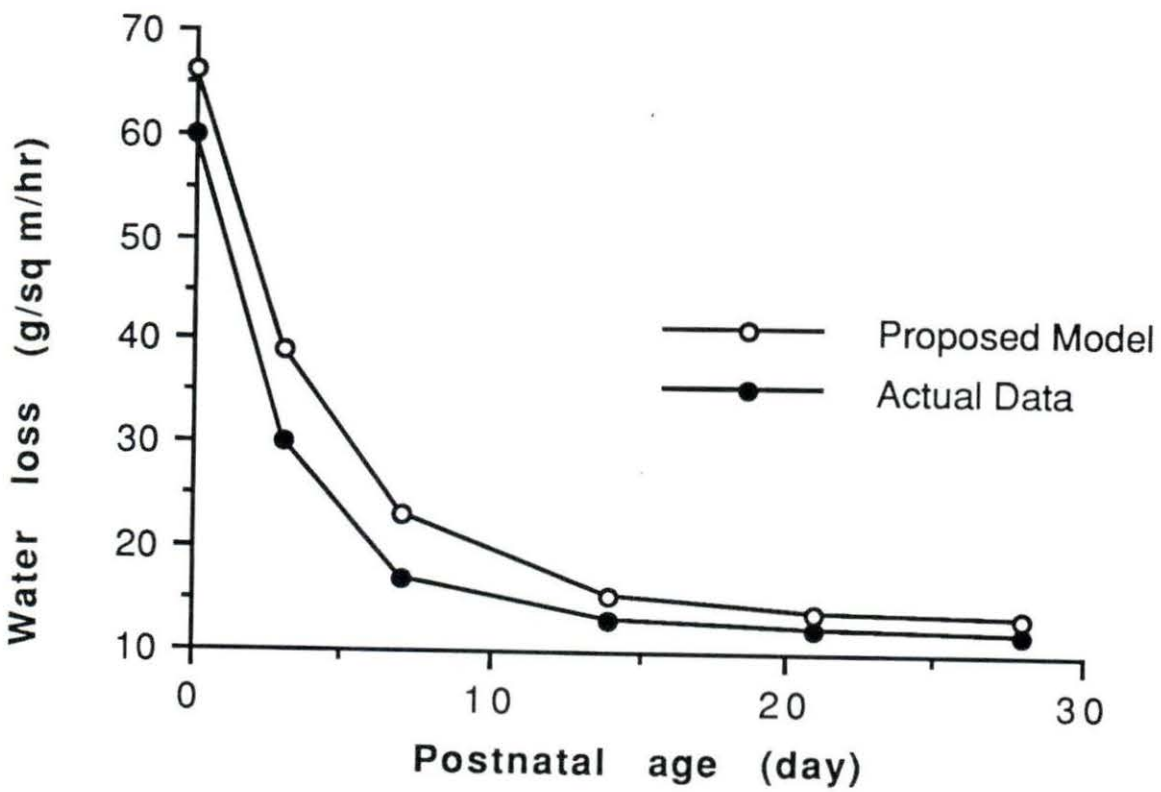

Figure 12a: Insensible water loss as a function of postnatal age
Temperature = 35.5°C, Humidity = 50%
Gestational age = 25 weeks
(actual data taken from Hammarlund, 1983)

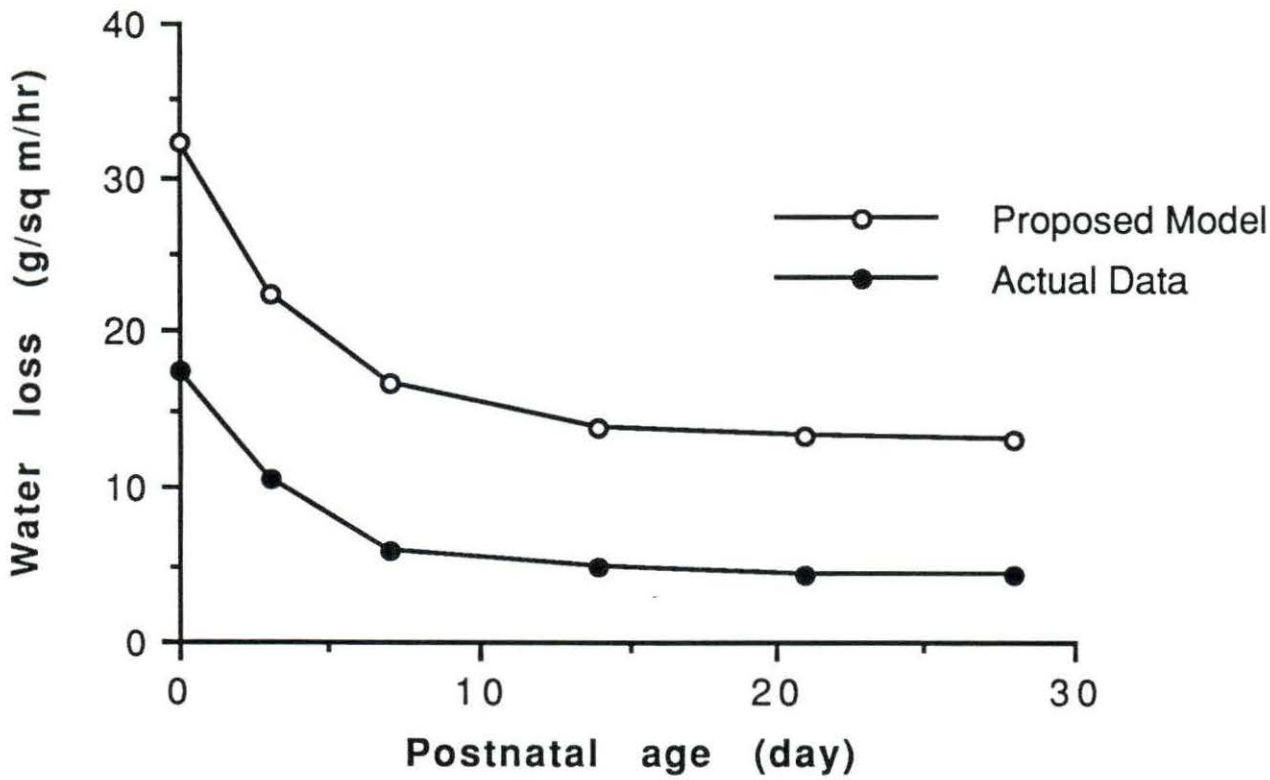

Figure 12b: Insensible water loss as a function of postnatal age
Temperature = 35.5°C, Humidity = 50%
Gestational age = 29 weeks
(actual data taken from Hammarlund, 1983)

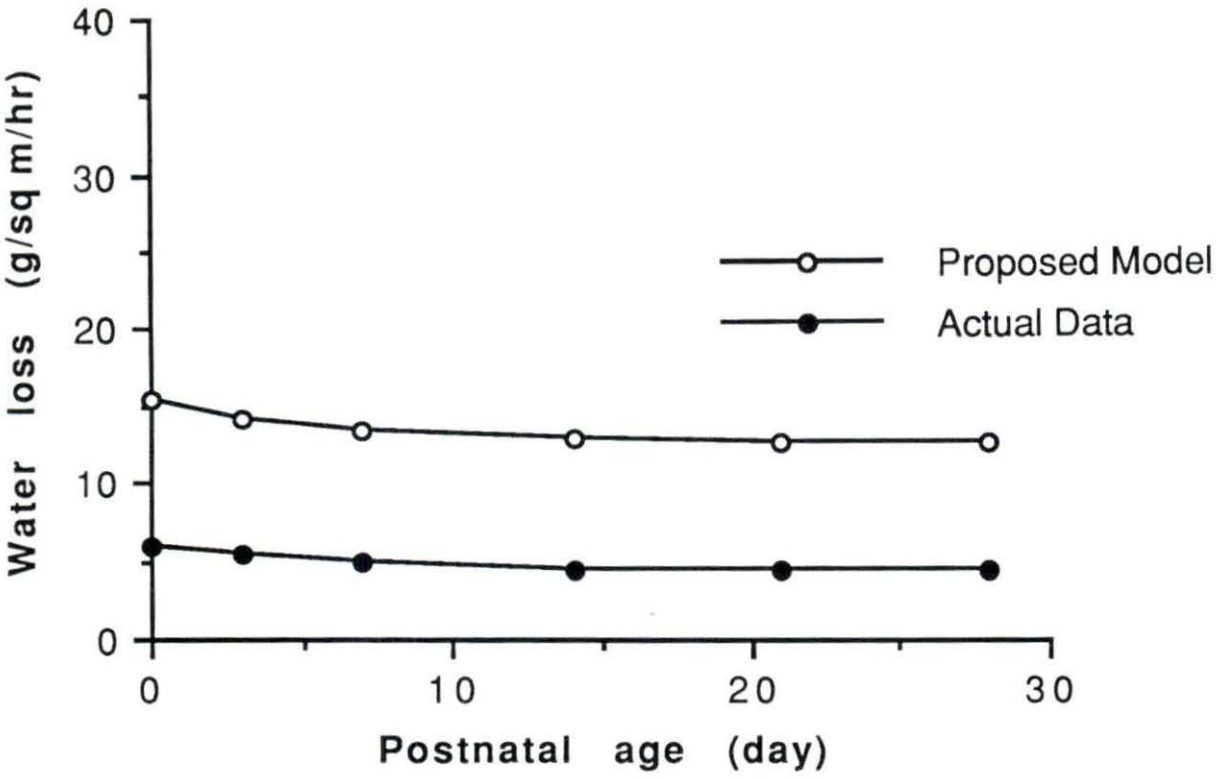

Figure 12c: Insensible water loss as a function of postnatal age
Temperature = 35.5°C, Humidity = 50%
Gestational age = 37 weeks
(actual data taken from Hammarlund, 1983)

Energy and Mass Balance

The model described in the previous sections predicted the insensible water loss through a steady state mass balance where the amount of water entering a particular skin layer was equal to the amount of water leaving that layer. To simplify the model, a constant temperature of 35.5°C was assumed for the hydrated layer, stratum corneum, and ambient air. By constructing an energy balance around an infant, a temperature gradient can be imposed throughout the skin layers and the body temperature can be predicted over time.

To simplify an infant's complex geometry, a layered cylinder model may be used with reasonable accuracy (Coffey and Seagrave, 1972). The cylinder is divided into three layers which represent the body core, muscle, and skin. The skin layer can be further divided to include the layers that resist the diffusion of water, namely the hydrated layer which includes the upper portion of the papillary dermis plus the viable epidermis and the stratum corneum. This model is diagrammed in Figure 13.

An energy balance can be written for each layer yielding:

$$\rho C_p \Delta X_c [dT_c/dt] = M_o - k(T_c - T_m)/\Delta X_{mc} \qquad (20)$$

$$\rho C_p \Delta X_m [dT_m/dt] = k(T_c - T_m)/\Delta X_{mc} - k(T_m - T_s)/\Delta X_{sm} \qquad (21)$$

$$\rho C_p \Delta X_s [dT_s/dt] = k(T_m - T_s)/\Delta X_{sm} - Q_{conv} - Q_{rad} - Q_{evap} \qquad (22)$$

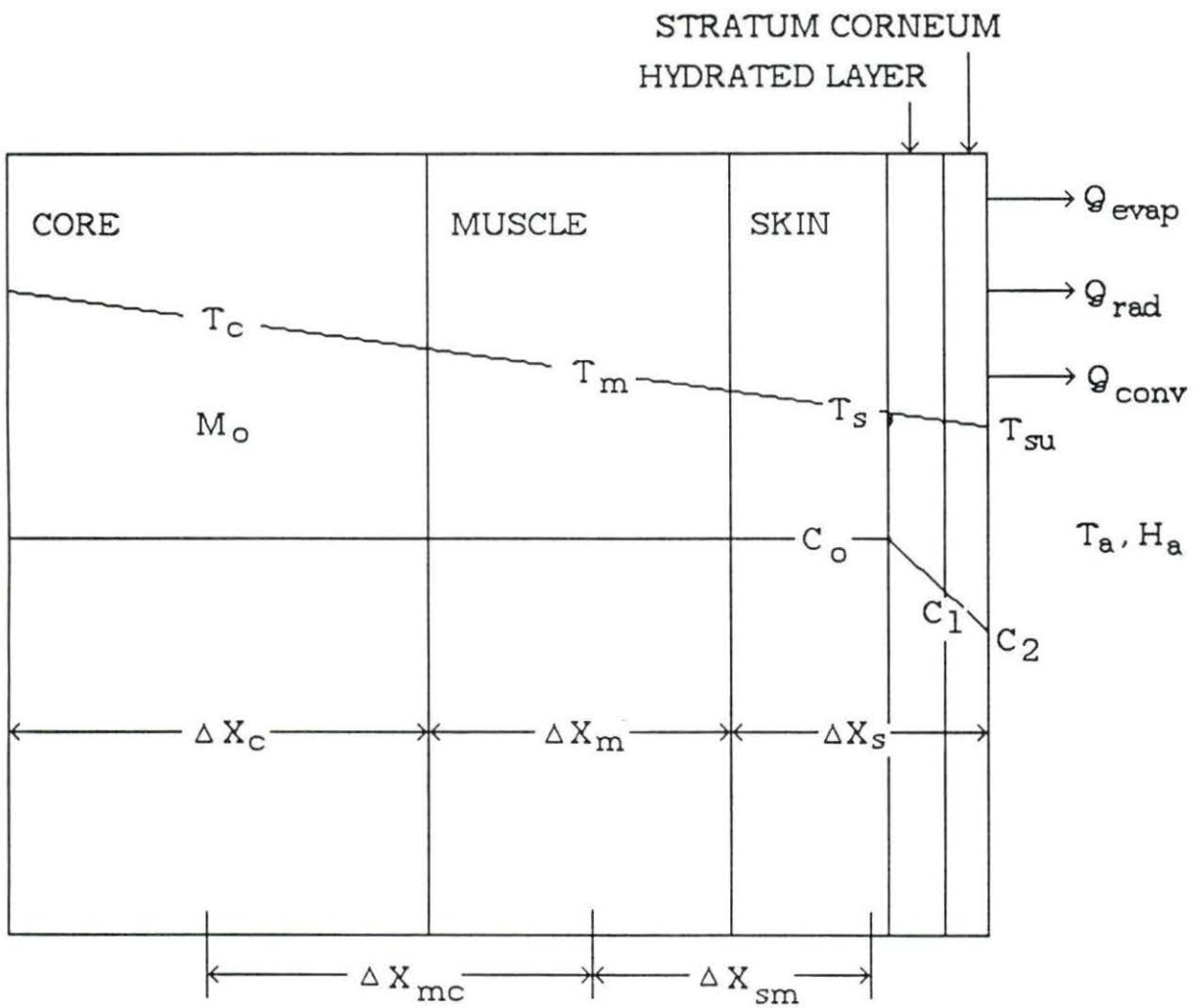

Figure 13: Layered cylinder model (Adapted from Coffey & Seagrave, 1972)

where:

$$Q_{conv} = h_C(T_{su} - T_a) \quad (23)$$

$$Q_{rad} = h_r(T_{su} - T_{rad}) \quad (24)$$

$$Q_{evap} = j\Delta H_{vap} \quad (25)$$

The water mass balance constructed around the hydrated layer and stratum corneum is given by:

$$\Delta X_{HL+SC}[dC_{ave}/dt] = (C_0-C_2)/[(\delta_{PD}+\delta_{VE})/D_1 + \delta_{SC}/D_2] - k_C(P_S-Pa) \quad (26)$$

Since the concentration of water within the core, muscle, and skin remains fairly constant for a hydrated infant, the accumulation term in the water mass balance will be negligible.

$$\Delta X_{HL+SC}[dC_{ave}/dt] = 0 \quad (27)$$

and

$$(C_0-C_2)/[(\delta_{PD}+\delta_{VE})/D_1 + \delta_{SC}/D_2] = k_C(P_S-Pa) = j \quad (28)$$

By including the partition coefficient, equation 11 is obtained from equation 28.

Since the thermal conductivity, k, is approximately the same for each layer (Coffey & Seagrave, 1972), the temperature profile will be linear for the model diagrammed in Figure 13. Therefore, once T_m and T_s are known, the average temperature of the hydrated layer and the stratum corneum can be calculated algebraically to determine the diffusivities for these layers. Calculations were made for a model in which the thermal conductivity of the epidermis was set to the appropriate value, 0.18 kcal/m·^{o}C·hr (Rothman, 1954) as opposed to 0.60 kcal/m·^{o}C·hr which is a suitable value for the more hydrated body layers (Coffey & Seagrave, 1972). This did not affect the outcome of any of the calculations made for this model due to the relative thinness of the epidermis. Therefore, a constant thermal conductivity was used to simplify all of the calculations which follow.

The thicknesses of the core, muscle, and skin layers have been determined for a term infant (Coffey and Seagrave, 1972) and body weight has been measured as a function of gestational age and postnatal age (Lubchenco et al., 1963 and Babson, 1970). Assuming that the body layers proportionally increase in thickness as an infant grows, the thickness of each body layer can be determined as a function of gestational age and postnatal age. Since the thickness of the hydrated skin layer and the stratum corneum are known (see equations 5, 6, 13, and 18), the heat loss due to the evaporation of insensible perspiration can be determined from equation 25. The heat loss through convection and radiation has been previously studied, and heat transfer coefficients for these modes of thermal transfer are known (Wheldon, 1980).

By setting equations 20, 21, and 22 equal to zero, the steady state energy balances can be solved by setting one of the unknown temperatures. A practical application of the steady state balances is to set the core temperature at 37°C and determine the ambient or incubator temperature necessary to maintain the infant's core temperature. Imposing a temperature gradient throughout the skin lowered the water loss values given in Figures 9 and 12 by about 4%. In table 1, the ambient temperature (T_a) and skin surface temperature (T_{su}) calculated from the model are compared with actual data (Hammarlund & Sedin, 1979) for various gestational ages.

The unsteady state energy balances can be solved if the ambient temperature and initial core, muscle, and skin temperatures are known. This situation could arise if the infant, initially at steady state, was placed in another environment where the ambient conditions were known. An example of this situation would include the time immediately after birth. The infant would be in a thermal steady state within the womb but would rapidly lose heat once exposed to the delivery room air. A similar situation would occur when an underdeveloped infant was removed from his/her incubator, perhaps to undergo medical procedures which cannot be performed within the confined incubator space. The unsteady state energy balances would indicate the amount of time available before the infant's core temperature dropped to critical levels.

Figures 14a, 14b, and 14c show the effect of exposing infants of various gestational ages to an environment with a temperature of 25°C and relative humidity of 50%. The initial core, muscle, and skin

Table 1: Comparison of ambient and skin surface temperatures predicted by the model to actual data
Postnatal age = 0 day (Actual data taken from Hammarlund & Sedin, 1979)

Gestational age (week)	Predicted ambient temp (°C)	Actual ambient temp (°C)	Predicted skin surface temp (°C)	Actual skin surface temp (°C)
25	38.8	38.8	36.4	36.3
33	35.5	34.2	36.1	35.8
39	34.2	33.5	35.9	35.3

temperatures are determined from the steady state energy balances. The consequence of varying the humidity is shown for a 25 week infant in Figures 15a, 15b, and 15c.

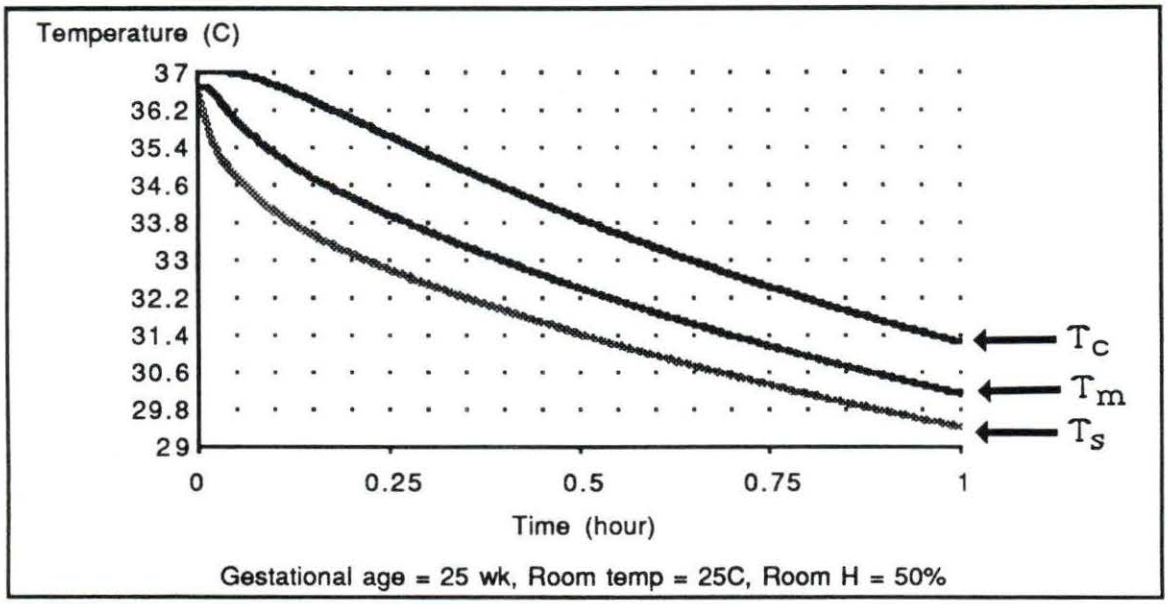

Figure 14a: Core, muscle, and skin temperature over time as predicted by unsteady state energy balances
Ambient temperature = 25°C and humidity = 50%
Gestational age = 25 weeks

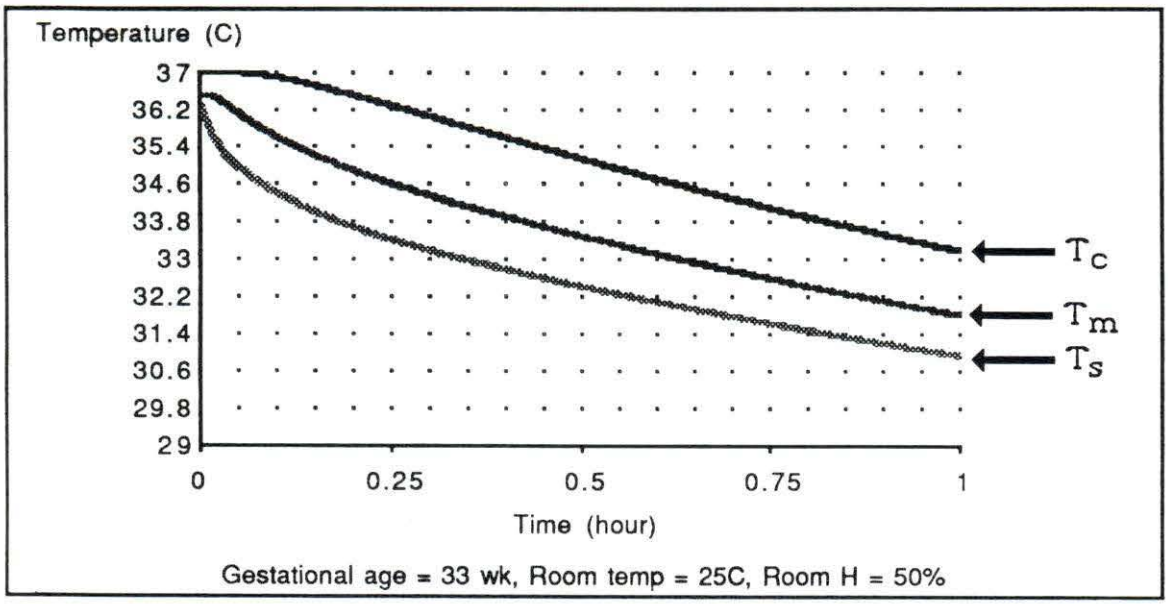

Figure 14b: Core, muscle, and skin temperature over time as predicted by unsteady state energy balances
Ambient temperature = 25°C and humidity = 50%
Gestational age = 33 weeks

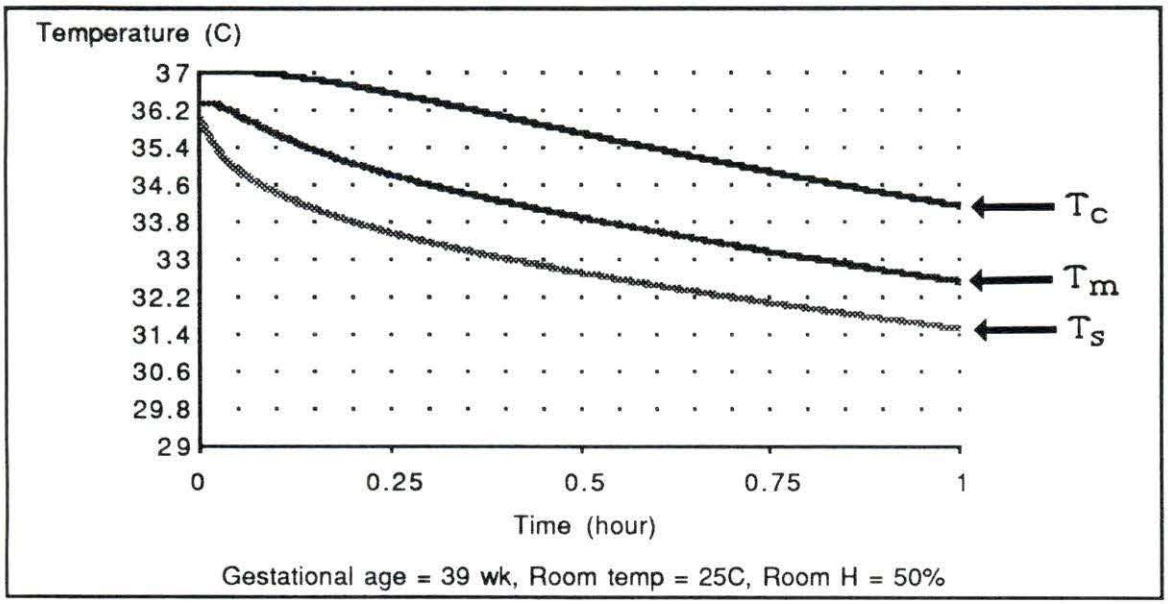

Figure 14c: Core, muscle, and skin temperature over time as predicted by unsteady state energy balances
Ambient temperature = 25°C and humidity = 50%
Gestational age = 39 weeks

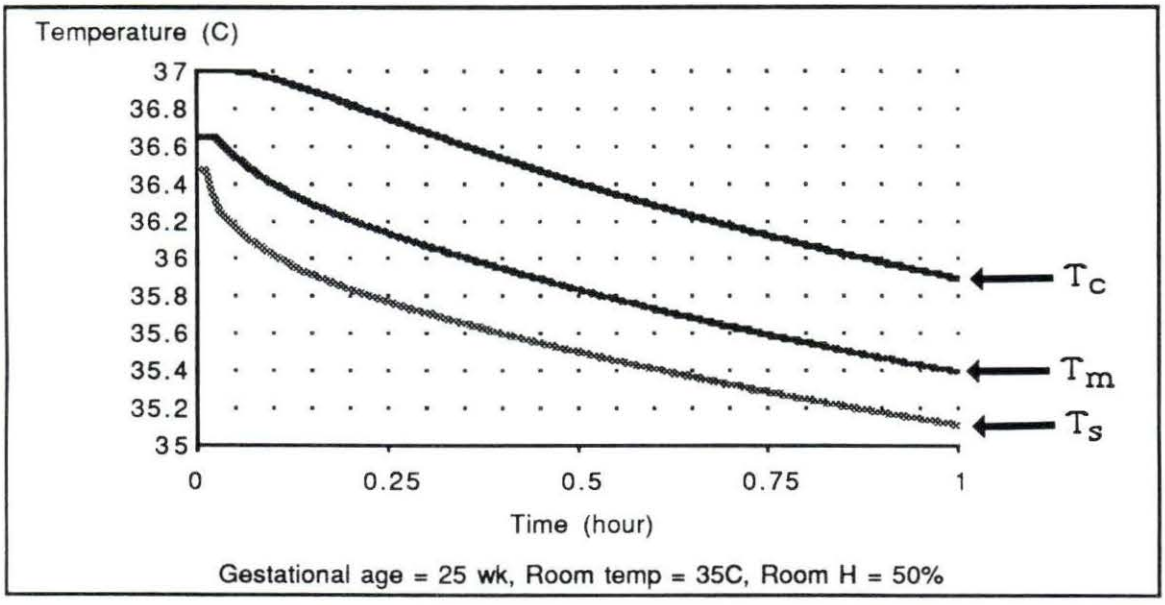

Figure 15a: Core, muscle, and skin temperature over time as predicted by unsteady state energy balances
Ambient temperature = 35°C and humidity = 50%
Gestational age = 25 weeks

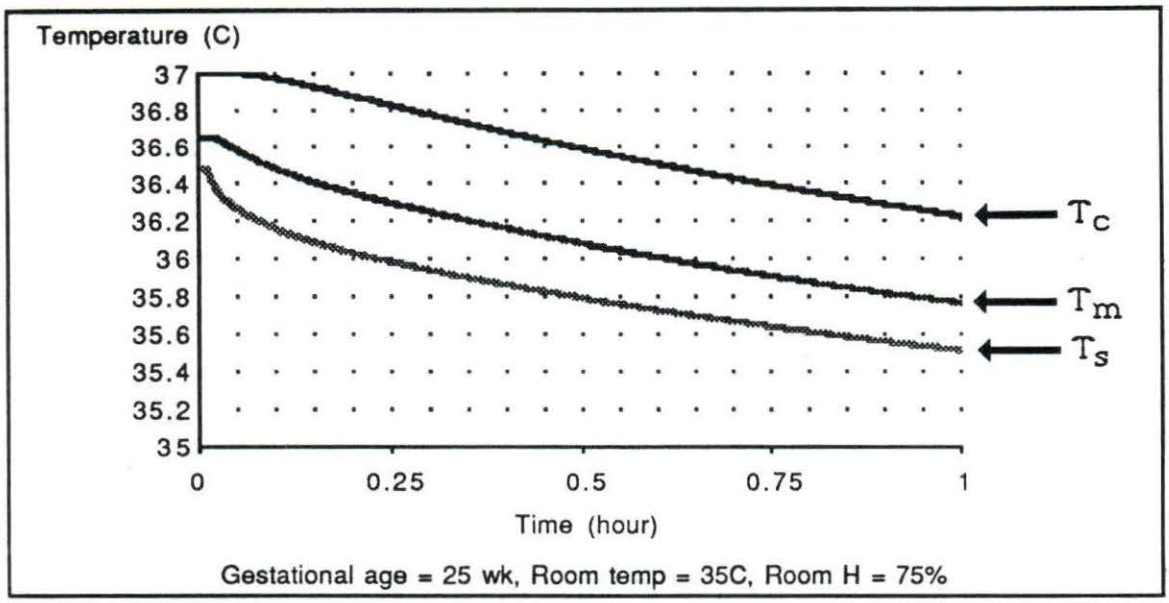

Figure 15b: Core, muscle, and skin temperature over time as predicted by unsteady state energy balances
Ambient temperature = 35°C and humidity = 75%
Gestational age = 25 weeks

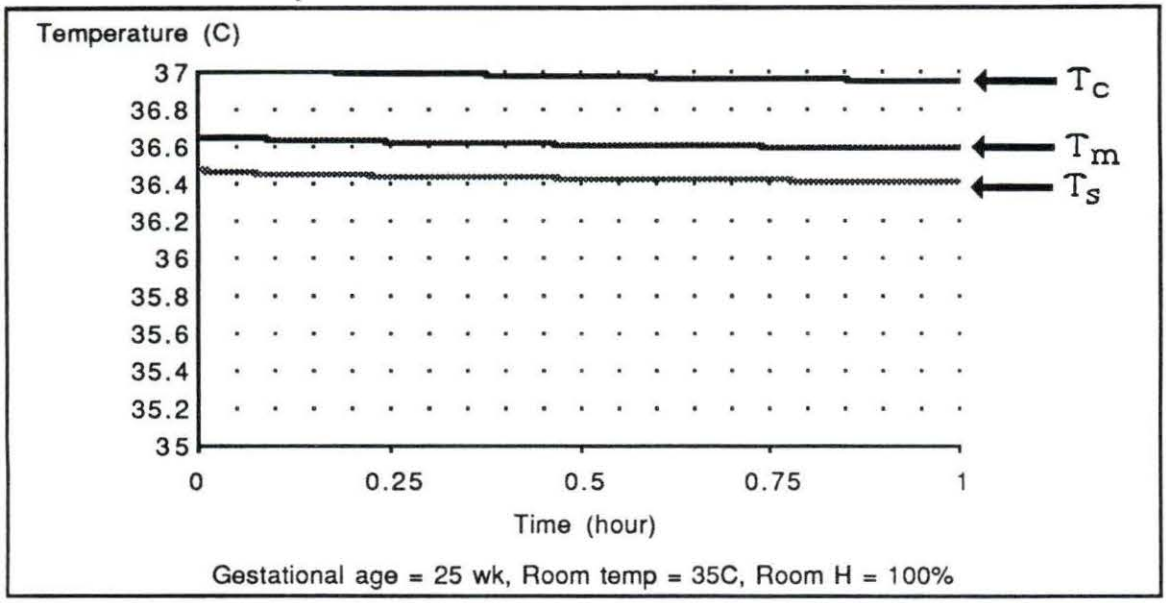

Figure 15C: Core, muscle, and skin temperature over time as predicted by unsteady state energy balances
Ambient temperature = 35°C and humidity = 100%
Gestational age = 25 weeks

DISCUSSION

In Figure 9, the measured and predicted insensible water loss is plotted as a function of gestational age. As can be seen in this diagram, the proposed model overestimates the actual water loss particularly for gestational ages over 28 weeks. Adult skin has approximately the same measured insensible water loss as predicted by the model at 40 weeks of gestation. Previous studies have found that the stratum corneum is a more effective barrier to the diffusion of water for term infants than for adults (Wilson & Maibach, 1980 and Rutter & Hull, 1979). A study which measured the insensible water loss for term infants during the first four weeks of life found that water loss actually increased during the third and fourth week (Hammarlund, 1982). This result suggests that the skin of term neonates changes after birth and becomes more adult-like, with regard to water transport, as the postnatal age increases. The discrepancy between the model results and actual data seen in Figure 9 is most likely caused by the presence of vernix lipids or by structural differences between neonatal and adult skin which were not addressed in the model.

The stratum corneum of an adult appears dry and scaly when compared to the greasy, vernix-coated skin of a newborn term or moderately premature infant (Holbrook, 1982). During the third trimester, the sebaceous glands become active and sebaceous secretions accumulate on the surface of the fetus (Holbrook, 1983). The vernix caseosa, a white cheesy layer found on the surface of older fetuses, is

formed from the sebaceous secretions and sloughed off periderm cells which have become partially keratinized (Serri & Cerimili, 1971). Vernix lipids are similar to adult sebum but also include sterols and sterol-esters (Holbrook, 1983). A function of the vernix caseosa may include protecting the fetus from maceration by the amniotic fluid (Hamilton, Mossman, and Boyd, 1972). During the early stages of pregnancy, the amniotic fluid is isotonic when compared to fetal and maternal plasma but it becomes hypotonic and slightly more acidic as term is approached (Schindler, 1982 and Fairweather & Eskes, 1973). Consequently, the vernix caseosa may give the skin additional water resistant properties by forming a layer of lipids and partially keratinized cells at the surface of the skin. The presence of this extra layer would cause the proposed model to over estimate insensible water loss because the additional resistance to the diffusion of water would not be accounted for in the model (see equation 11). The effects of applying an additional water resistant layer have been previously studied. Artificial, polyurethane skin has been adhered to the skin of premature neonates and shown to drastically reduce the insensible water loss (Vernon et al., 1990). The inconsistency between the model and actual data exists mainly for gestational ages over 28 weeks, which is roughly the time that corresponds to the formation of the vernix caseosa. Therefore, the presence of an additional water resistant layer provides a reasonable explanation for the discrepancy seen in Figure 9.

Keratin is formed from very complex and heterogeneous molecules (Steinert & Cantieri, 1983). The sequence of amino acids or primary

structure of the molecules greatly influences the final configuration of the keratin. Details of the ultra structure of keratin have yet to be determined although models consistent with available experimental data have been presented (Steinert & Cantieri, 1983). Keratin is a very versatile substance. It not only forms the water resistant barrier in mammalian skin but also composes hair, nails or claws, feathers, reptilian scales, and porcupine quills, and other structures. Therefore, it is possible that the molecular structure of epidermal keratin is slightly different for neonates than for adults. Furthermore, this difference may arise because the aqueous environment in which the infants develop is so unlike the environment to which adults are exposed. The cells found in neonatal stratum corneum are smaller and more uniformly sized than the cells found in adult stratum corneum (Holbrook, 1983). If the structure of the keratin molecules, the structure of the keratin containing cells, or the composition of the keratin containing cells in neonatal skin is altered from that seen in adult skin, then properties the stratum corneum could vary between these two skin types. Since the diffusivity and water concentration at the skin's surface used in this model was determined from adult skin (Scheuplein, 1978), the actual values for neonates may be different and could cause the discrepancy seen in Figure 9. However, this explanation would not elucidate why the model predicts insensible water loss more accurately for shorter gestational ages than for longer gestational ages unless the changes have occurred due to the presence of the vernix caseosa.

Figures 12a, 12b, and 12c show the variation of insensible water

loss with postnatal age for various gestational ages. The model and actual data show the same trend of decreasing water loss with increasing postnatal age, but as previously seen in Figure 9, the model overestimates the water loss for longer gestational ages and the overestimation continues as the postnatal age increases. This discrepancy between the model and actual data could be caused by the presence of sebaceous secretions or by structural difference between neonatal and adult skin.

The sebaceous glands remain active throughout the neonatal period (Holbrook, 1983). As previously discussed, the presence of sebaceous secretions could cause the model to overestimate insensible water loss by forming an additional water resistant layer at the surface of the skin. This would explain the discrepancies seen between the model and actual data in Figures 12b and 12c. Sebaceous gland development and function are believed to be controlled by transplacentally acquired maternal androgens and sebaceous gland activity continues throughout the neonatal period due to the lingering influence of these androgens (Holbrook, 1982). Enzymes present in fetal skin convert the maternal androgens to functionally active compounds such as 5α-dihydrosterone (Holbrook, 1983). The combined effect of the enzymes may enable fetal sebaceous glands to utilize dehydroepiandrosterone, a circulating maternal androgen present in high concentrations during intra-uterine life (Sharp, Hay, and Hodgins, 1976). For the enzymes studied which were involved with the conversion of maternal androgens, enzymatic activity increases with gestational age with some tapering off as term is

approached (Sharp, Hay, & Hodgins, 1976). Consequently, very premature infants may be born before sufficient enzymatic activity is present to convert the maternal androgens and stimulate sebaceous gland secretion. As the very premature infant developed outside the womb, enzymatic activity may increase although the infant would no longer be exposed to the maternal androgens. Therefore, the sebaceous glands of very premature infants may not actively secrete sebum during the neonatal period because their glands were never exposed to an active form of the maternal androgens. Very premature infants are born without a vernix caseosa and may never develop the greasy lipid-coated skin which is seen for moderately premature and term infants. Since an addition layer of lipids may form on the skin of moderately premature and term infants but may not form on the skin of very premature infants, the model should predict insensible water loss more accurately for shorter gestational ages as seen in Figure 12a.

The postnatal growth of the epidermis occurs rapidly for infants born prematurely (Evans & Rutter, 1986). It has been found that rapid epidermal growth can alter the structure seen in normal proliferating epidermal cells (Wright, 1983). As previously discussed, structural differences between neonatal and adult skin could account for discrepancies seen between the model and actual data. This explanation could account for inconsistencies seen in Figures 12b and 12c but would not explain why the model is more accurate at shorter gestational ages unless the presence of sebaceous secretions caused a structural difference which altered the diffusivity or water content of the stratum

corneum.

Most homeostatic systems in the human body use negative feedback as a control mechanism. One example is the regulation of normal body temperature (Martini, 1989). Maintaining an adequate stratum corneum may also be another example of negative feedback control. It has been shown that the depletion of cornified cells causes a depletion of basal cells and that it is a loss of basal cells that stimulates rapid epidermal growth (Fowler & Denekamp, 1975). By varying the number of stratum corneum layers removed, a graded response, in terms of cell proliferation, was found (Fowler & Denekamp, 1975). This response may be mediated through the action of a systemic growth factor such as epidermal growth factor (EGF) (Evans & Rutter, 1986). EGF has been found to enhance keratiniztion by stimulating the production of messenger RNA (mRNA) (King & Carpenter, 1983). The transcription of mRNA from DNA has been shown in several instances to be the rate limiting step for the production of keratin proteins (Freedberg, 1983). Figure 16 illustrates a negative feedback mechanism which may regulate stratum corneum thickness after a depletion in the cornified cell population has occurred. The control loop is repeated until the population of cornified cells has reached the appropriate value. This control mechanism is proposed for cases where the basal layer has not been damaged as a result of depleting the stratum corneum. Examples of this situation include the skin of prematurely born infants where an adequate stratum corneum has not yet developed and the skin of first degree burn victims where only the top epidermal layers have been

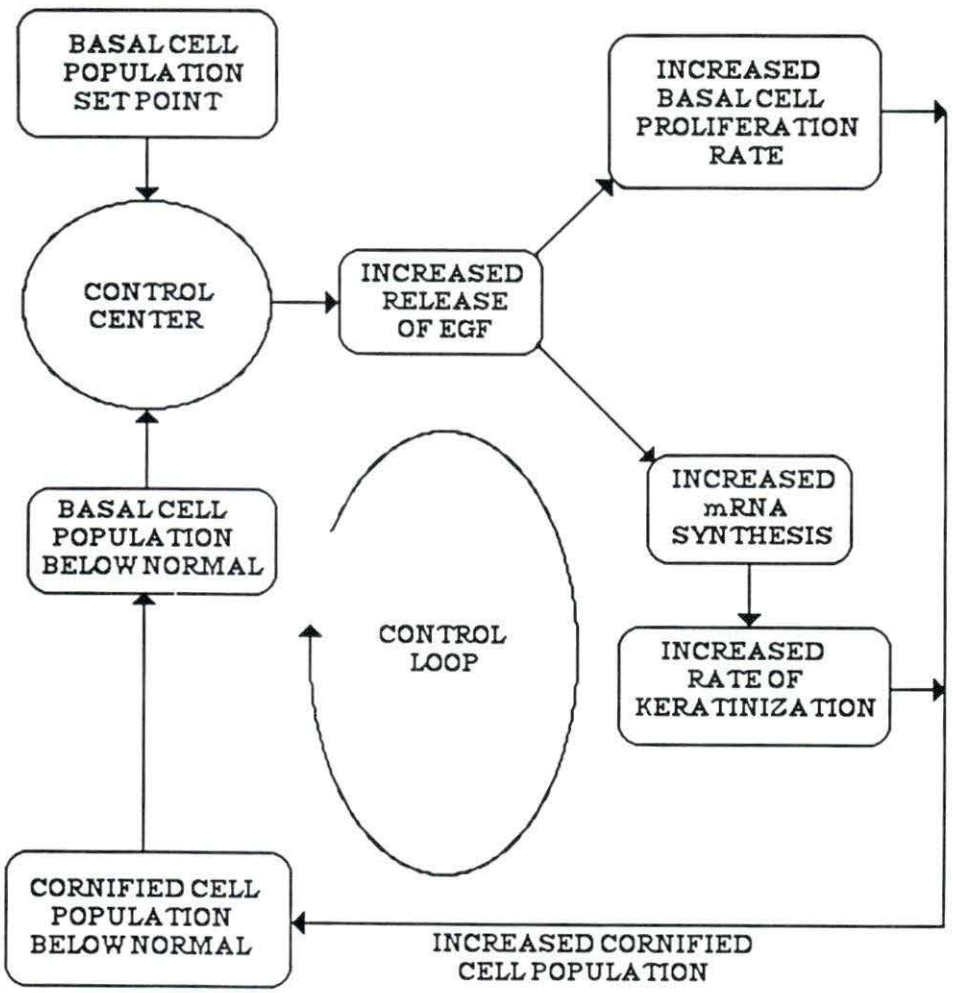

Figure 16: Possible negative feedback control mechanism which may regulate stratum corneum thickness for a depleted cornified cell population

damaged. The proposed control mechanism would not be accurate for victims of second and third degree burns because in this situation the basal epidermal layer has been damaged thereby causing a delay in the healing process (Fowler & Denekamp, 1976).

The model suggests that a temperate and humid environment is best for keeping a newborn premature infant warm and well hydrated. This environment would maintain the infant's core temperature while keeping the insensible water loss to a minimum. Since the air within a radiant warmer is the same as the room air, this type of warming device should be avoided for very premature infants because the humidity may be low. Many studies have observed higher evaporative water losses for infants within radiant warmers as opposed to infants within convective incubators (Wheldon & Rutter, 1982). The convective incubator provides an enclosed, warm and humid environment. Therefore, the heat balances, mass balance, and rate expressions indicate that the convective warmer should be more advantageous for the premature infant than the radiant warmer. Figures 15a, 15b, and 15c show how the body temperature of a 25 week infant changes when he/she is exposed to a cool environment for various humidities.

To improve the model, additional properties of neonatal skin should be studied. Some histological differences have been seen between the skin of premature neonates, term neonates and adults (Holbrook, 1982). Since the diffusivity of water through the various skin layers and the concentration of water within the skin were determined from adult skin, determining these parameters for neonatal skin should increase the

accuracy of the model. Any error due to the difference between the structure of keratin or keratin containing cells may be eliminated by determining these properties for neonatal skin. The presence of an additional layer derived from sebaceous secretions should be examined for the skin of premature and term infants. If such a layer does exist, the diffusivity of water through this layer, the variation of layer thickness with gestational age, and the variation of layer thickness with postnatal age should be determined experimentally. Better agreement between the model results and actual data would likely result if a third lipid-like layer is added to model diagrammed in Figure 4. To include this lipid layer in the model, the variation of layer thickness with gestational age, the variation of layer thickness with postnatal age, and the diffusivity of water through this layer need to be determined experimentally.

CONCLUSIONS AND RECOMMENDATIONS

The insensible water loss from premature neonates can be estimated by modeling the skin as a composite membrane and applying Fick's first law to each layer. Studies involving human skin development have made it possible to apply the proposed model to an infant's prenatal and postnatal growth, however, the proposed model overestimates the insensible water loss for gestational ages greater than 28 weeks. The most plausible cause of this overestimation is the presence of a water resistant, lipid-like layer at the surface of the infant's skin. Another possible explanation is that structural differences may exist between adult and neonatal skin. Since the properties of skin, such as water concentration and diffusivity of water through each layer, were determined from adult skin, the actual value for neonatal skin could be different and this may have caused discrepancies seen between the model results and actual data.

The sebaceous glands become active during prenatal life due to the influence of maternal androgens and then continue to remain active throughout the neonatal period under the lingering effect of these androgens. During the third trimester, a layer of sebaceous secretions and sloughed off periderm cells, known as the vernix caseosa, forms over the infant. Consequently, the vernix coated skin of moderately preterm and term neonates appears greasy when compared to the skin of an adult. The presence of a water resistant, lipid-like layer at the skin's surface would cause the proposed model to overestimate insensible water

loss because the resistance to the flow of water due to this layer could not be accounted for in the model. To include the effects of an additional water resistant layer, properties of the layer, such as thickness over time and diffusivities, must be determined experimentally. The model may be more accurate for gestational ages under 28 weeks since fetal skin, prior to this time, may not contain the enzymes necessary to convert the maternal androgens to an active form for the subsequent activation of the sebaceous glands. Therefore, since very premature infants may never be exposed to an active form of the maternal androgens, a lipid-like layer produced from sebaceous secretions may never form.

Studies involving the histology of skin have found that the structure of cornified cells is different when comparing neonatal and adult skin. Furthermore, rapid epidermal growth, such as that which occurs for infants born prematurely, may cause additional structural differences. Since the properties of skin necessary to calculate insensible water loss from the proposed model have only been determined for adult skin, the actual value for neonatal skin may be different due to structural dissimilarities. Using inaccurate values with the model may have caused the discrepancies seen between the calculated water loss values and actual values.

To improve the model, further studies related to fetal and neonatal skin need to be conducted. Water concentration as a function of temperature and humidity as well as the diffusivity of water through each skin layer needs to be determined for neonatal skin. A histological investigation should be able to conclude if a water resistant layer

derived from sebaceous secretions forms over moderately premature and term infants. If such a layer does exist, its properties and thickness over time needs to be determined. By improving upon the proposed model, insensible water loss from premature newborns could be predicted with excellent accuracy. Since the amount of fluids administered to premature newborns is presently decided arbitrarily and since serious complications can arise from over hydration or dehydration, this model or an improved model should help to alleviate some of the problems faced in neonatal critical care.

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