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THE PHYSICAL ENVIRONMENT AND THE PREMATURE INFANT

E. Mead Johnson Award Address

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I AM MOST grateful to the Academy for naming me as the recipient of an E. Mead Johnson Award for 1958 and pleased beyond measure by this great honor. I cannot allow this moment to pass without acknowledging with pleasure my debt of gratitude to Dr. Richard Day, who first awakened in me a curiosity about the meaning of proof for a clinician and to Dr. John W. Fertig for his patience as teacher, critic and collaborator.

This decision of the Awards Committee has given me cause for reflection. I interpret it to signal approval of and benevolent interest in the use of the planned trial as a device to help answer questions at the clinical level. I am encouraged to think that the rules of evidence that have applied in the laboratory are now increasingly consulted on ward rounds. Mr. John W. Gardner, president of the Carnegie Corporation, recently commented[1] upon the difficulties that result from the acceptance of a double standard of excellence at different levels of human activity; he stated that, ". . . The society which scorns excellence in plumbing because plumbing is a humble activity and tolerates shoddiness in philosophy because it is an exalted activity will have neither good plumbing nor good philosophy. Neither its pipes nor its theories will hold water."

F. H. K. Green has recently been quoted[2] as saying, ". . . when the value of a treatment, new or old, is doubtful, there may be a higher moral obligation to test it critically than to continue to prescribe it year-in, year-out with the support merely of custom or of wishful thinking." I am encouraged to believe that we have arrived at a point in time when this moral obligation may be included as one of our clinical responsibilities.

We were required to consider our responsibility very closely in this regard about 8 years ago when confronted with

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the challenge of retrolental fibroplasia. As we watched the early vascular changes of this condition develop, we reasoned that these proliferating vessels might be halted by the then newly available hormone, adrenocorticotropin (ACTH). We gave this substance to an infant when, from the appearance of the ocular fundi, it was clear that the disease was progressing. The fundi of this infant returned to normal. This sequence of events was repeated following the treatment of many infants during the next year. At the end of this time we had a sufficient experience with the administration of ACTH to feel quite certain that there was an association between the use of this agent and the regression of the active process of retrolental fibroplasia. We had made a series of observations, but could not judge whether or not these were meaningful. Mr. Jackson, surgeon to the Birmingham Accident Hospital in England, has noted[3] that, ". . . research in medicine may take the form of observation or planned experiment . . . but experiment is a sharper tool—it has been compared to cross-examining Nature, rather than merely overhearing her."

It took only a short time by means of a planned trial to demonstrate that a high incidence of regression in retrolental fibroplasia was not significantly greater among those who received ACTH. This disease taught us many lessons.

As the role of oxygen in the pathogenesis of retrolental fibroplasia was revealed, we watched fascinated. The modern incubator made it possible with increasing precision to produce a micro-environment which was quite unlike any ever experienced by newborns on this planet. It was quite awesome to ponder this fact and to see the consequences which resulted from a change in only one of the ambient conditions.

These results recalled the studies of Blackfan and Yaglou made between 1926 and 1933[4] on the influence of varying conditions of environmental humidity upon the survival of premature infants. Under the limitations of the devices then available they found it impractical to explore the influence of humidities above 65% relative humidity, because the attendants were too uncomfortable in higher sticky atmospheres. Within the individual modern incubators, 90% relative humidity can be achieved without difficulty. High humidity was widely and uncritically adopted about 6 years ago on the presumption that infants with respiratory distress might resolve their pulmonary difficulty in such an environment. Water mists and detergent mists were suggested on rational theoretical grounds for the prevention and treatment of the respiratory-distress syndrome of the newborn.

These suggestions for altering the environment of the premature came at a time when we were particularly mindful of our clinical responsibilities and the lessons of retrolental fibroplasia were still ringing in our ears. Accordingly, we embarked upon a series of controlled clinical trials in the premature nursery of the Babies Hospital. This series, begun 5½ years ago, has not yet been completed. In the first of these trials, 200 premature infants were assigned in random order to one of two environmental conditions. In one of these conditions, which we arbitrarily designated as "Standard," the relative humidity was between 80% and 90%; Alevaire® mist was nebulized into the alternative incubators until the infants were 72 hours of age. At the conclusion of the trial it was shown that the two groups were reasonably similar except in the treatment on trial, the survival rates were essentially the same and the distributions of necropsy findings in those who succumbed were not significantly different.

We conducted a second trial in virtually the same manner as the first. The Standard condition was compared with nebulized water mist. Two hundred infants were enrolled in this trial. Again we were satisfied that the random method of assignment had resulted in two groups that were similar except for the treatment on trial. The survival rates were found to be essentially the

same. Respiratory performance, as judged by respiratory rate and retractions among those who survived and necropsy findings among those who succumbed, was not significantly different.

A third trial began in December, 1954. We were interested in bridging the gap between Blackfan and Yaglou's recommendation of 65% relative humidity and our recently adopted Standard condition. The actual ranges achieved were 30 to 60% versus 80 to 90% relative humidity. We were also influenced by the French experience[5] with hypothermia in premature infants and decided to conduct the third trial at an environmental temperature which was 5°F below that used in the first two. All incubators were set at the new air temperature of 84°F. In view of subsequent events, we have often speculated on what would have happened had we chosen to keep the bed temperature at 89°F, the level used in the previous two trials. One hundred and sixty individuals were assigned to the incubators at 30-60% relative humidity and 164 to the 80-90% condition. The conditions of this trial were maintained as prescribed until the infants were 120 hours of age. The survival rate during the trial period among infants who were in 80-90% relative humidity was significantly higher than the rate of the controls. In each birth-weight group the survival rate of infants in the more humid incubators was higher than that of the controls (Table I). However, it was not clear how this increased survival rate had been achieved. The frequency distributions of necropsy findings among those who died in the contrasting groups were essentially the same. The incidence of positive post-mortem cultures was not significantly different. The incidence and severity of respiratory distress were not different. Paradoxically, it seemed, the group which enjoyed the higher survival rate displayed higher respiratory rates.

TABLE I

SURVIVAL RATES BY BIRTH WEIGHT AT TWO CONDITIONS OF HUMIDITY

Air Temperature 84°F

Birth Weight	*80–90% R.H.*	*30–60% R.H.*	*Difference*
Above 1,500 gm			
(Number)	(71)	(70)	
% Survived	80%	74%	6%
1,001–1,500 gm			
(Number)	(73)	(71)	
% Survived	82%	65%	17%
Below 1,001 gm			
(Number)	(20)	(19)	
% Survived	55%	37%	18%

TABLE II

"AVERAGE" AXILLARY TEMPERATURE (°F) AT TWO CONDITIONS OF HUMIDITY

Air Temperature 84°F

Birth Weight	*80–90% R.H.*	*30–60% R.H.*	*Difference*
Above 1,500 gm			
(Number)	(80)	(77)	
Mean	94.8°	94.3°	0.5°
S.D.	±1.6	±1.9	
1,001–1,500 gm			
(Number)	(62)	(57)	
Mean	92.5°	91.2°	1.3°
S.D.	±1.7	±2.0	
Below 1,001 gm			
(Number)	(14)	(14)	
Mean	90.3°	87.9°	2.4°
S.D.	±1.8	±2.9	

From Blackfan and Yaglou's work we expected that at any given air temperature, infants in high humidity would lose less heat than those in low humidity. Therefore, we were not surprised to find that infants who spent their time in incubators at 80 to 90% relative humidity had higher average axillary temperatures than the controls. As can be seen in Table II, the magnitude of the difference between the means of axillary temperature was dependent upon birth-weight. The difference in the heaviest weight group was 0.5°F; in the lightest class, it was almost 2.5°F. The level

of body temperature at these environmental conditions was also weight dependent. The heaviest infants in both conditions of humidity were warmer than those in lighter birth-weight groups.

Did infants in the more humid incubators survive in greater numbers because they were warmer than their controls? Because we were unable to find any other clues, we formulated a working hypothesis to the effect that the seemingly beneficial influence of 80-90% relative humidity was in fact mediated through a reduction in the heat loss of prematures in the first 5 days of life. In essence, this was an extrapolation from the position of Blackfan and Yaglou 25 years ago.

The fourth in our series of trials was designed to evaluate the influence of an ambient temperature 5°F higher than the level chosen in the completed humidity study. The two contrasting air temperatures were 89°F (which we termed "normothermic") versus 84°F ("hypothermic"). The relative humidity was between 80 and 90% in both sets of incubators. There was, of course, a slight difference between the specific humidities, but in our judgment, this difference was too small to have any practical meaning. Ambient conditions of the trial were maintained until each infant reached the age of 120 hours.

A method of assignment by randomization was chosen to force equal representation with respect to birth weight and antibiotic administration, and this resulted in two groups that were essentially equal in many characteristics, but discrepant with respect to route and position at the time of delivery and age on admission to the nursery. When the net effect of these discrepancies was analyzed, it was found that the results remained unaltered.

We used a modification of the method of sequential analysis to evaluate the differences in survival under the two thermal conditions. This plan allowed a "running" analysis of "normothermic":"hypothermic" pairs of infants. These pairs were matched with respect to the antibiotic drugs which they received and with respect to their birth weights. The study was terminated when 91 pairs of infants (182 individuals) completed the trial. At this point a decision was reached to the effect that infants in "normothermic" incubators (89°F) enjoyed a significantly higher survival rate than their controls in "hypothermic" incubators (84°F).

Sixty-five of the pairs were considered "tied," in which both of the infants either lived (56 pairs) or died (9 pairs) (Table III). Only one of the pair lived in 26 "untied" pairs. Of these, 20 favored the "normothermic" hypothesis, since it was the "normothermic" member of the pair who survived. Six pairs were not favorable to the "normothermic" hypothesis; the individual in the "hypothermic" incubator was the sole survivor.

TABLE III

OUTCOME OF "PAIRS" AT TWO CONDITIONS OF AMBIENT TEMPERATURE

80–90% R.H.

		"Normothermic" Incubators		*"Hypothermic" Incubators*	*Number of Pairs*
"Tied" Pairs		Lived	:	Lived	56
		Died	:	Died	9
"Untied" Pairs	Favorable to "normothermic" hypothesis	Lived	:	Died	20
	Not favorable to "normothermic" hypothesis	Died	:	Lived	6

TABLE IV

SURVIVAL RATES BY BIRTH WEIGHT AT TWO CONDITIONS OF AMBIENT TEMPERATURE

80–90% R.H.

	"Normothermic" Incubator	*"Hypothermic" Incubator*	*Difference*
Entire series			
(Number)	(91)	(91)	
Survival rate	84%	68%	16%
Birth Weight			
Above 1,500 gm			
(Number)	(42)	(42)	
Survival rate	93%	79%	14%
1,001–1,500 gm			
(Number)	(35)	(35)	
Survival rate	86%	77%	9%
Below 1,001 gm			
(Number)	(14)	(14)	
Survival rate	50%	14%	36%

Eighty-four per cent of 91 infants who were placed in "normothermic" incubators survived the trial period, as compared with 68% survival in "hypothermic" incubators. In each birth-weight category in this study, the survival rate was greater among infants in "normothermic" incubators (Table IV). The levels of axilliary temperature reached by infants under these conditions were birth-weight dependent (Table V), as had been observed in the humidity study. The differences in mean axillary temperatures in the two groups varied from almost 3.5°F in the heaviest infants to almost 5°F among infants whose birth-weights were below 1,501 grams.

In this study, as in the humidity trial, we noted that warmer infants had more rapid respiratory rates than their cooler controls. These differences were small, but they were consistent when compared at equivalent age-intervals. Bacteriologic and pathologic evidence obtained from the infants who succumbed during the period of the temperature trial provided no satisfactory clues which might bear on the question of whether there was a unique cause of death in the cooler infants. We were interested to note that three cases of sclerema were encountered during the study, all in the "hypothermic" group. No conclusions concerning the significance of the latter association was possible from so small a contrast.

Thus we are left with more questions than answers. Our results lend support to the long held view that survival rates of premature infants can be improved by reducing their heat loss. In addition, our experience calls attention to such an influence during the first 5 days of life, when the risks to life are greatest. I do not believe that our results should be interpreted to indicate that the use of hypothermia in prematures, with artificial control of respiration and careful regulation of chemical changes in the blood, has been discredited. However, I should add that from the evidence available to my knowledge, it has not been satisfactorily established that the survival rates of premature infants can be improved by administering drugs to block homeothermic reflexes and by lowering ambient temperatures.

Our results do not permit us to give an opinion on whether the body temperature of the premature infant should be maintained at the intrauterine level. We did not achieve such a level, especially in the very

TABLE V

"AVERAGE" AXILLARY TEMPERATURES (°F) AT TWO CONDITIONS OF AMBIENT TEMPERATURE

Birth Weight	*"Normothermic" Incubator*	*"Hypothermic" Incubator*	*Difference*
Above 1,500 gm			
(Number)	(41)	(41)	
Mean	97.9°	94.5°	3.4°
S.D.	±0.7	±2.3	
1,001–1,500 gm			
(Number)	(35)	(35)	
Mean	96.8°	92.1°	4.7°
S.D.	±1.3	±2.0	
Below 1,001 gm			
(Number)	(12)	(14)	
Mean	92.7°	88.0°	4.7°
S.D.	±2.7	±2.3	

smallest premature infants. We have no assurance that the results obtained in trials conducted during the first 5 days of life may be applied to infants who are older.

We do not know whether survival is the best criterion for judging the ideal level of temperature of newborn premature infants. However, we must have a working definition of "optimum" level, for if we wait like the purist for every last bit of evidence, we shall be, in Greenwood's words,[6] ". . . no wiser than Horace's rustic waiting for the river to flow away." I should like, therefore, to propose the following, which has been modified from a definition made by Grison:[7] The optimum body temperature of the premature infant is the one which is associated with the highest rate of intact survival. I do not believe that we can state that the optimum thermal, or for that matter, any other, condition has been achieved until we are satisfied that the high rate of damage to the brain in the survivors of premature birth has also been influenced.

There are many other associated questions. Perhaps these may be summed up with the general question: How is the rate of morphologic and chemical maturation of the premature infant affected by thermal influences in the neonatal period?

Our immediate commitment to the topic of the physical environment and premature infants concerns another facet related to humidity. As I have stated, we observed a higher survival rate among infants under conditions of high humidity and have suggested that this beneficial influence was mediated through a reduction in heat loss. However, we have not excluded the possibility that there is an additional influence of high humidity over and above the thermal effect. We proposed to study the effect of two contrasting conditions of humidity on two groups of infants maintained at the same body temperature. This proposal required a new incubator design which was achieved through the long and devoted collaborative efforts of Mr. Samuel Y. Gibbon and Mr. Kenneth Richter of Air-Shields, Inc., and of Dr. Frederic J. Agate of Columbia University. In brief, this incubator permits us to set the infant's temperature at any desired level. Through a system of automatic controls, the supply of heat is turned on when the infant's temperature declines below a pre-set level, and heat is turned off when his temperature rises above the pre-set level. Thus, one level of body temperature is maintained, independent of birth weight or ambient humidity. When the results of these studies are available, we hope they will permit evaluation of a possible extra-thermal influence of ambient humidity upon the survival of these newborns.

We are also encouraged to hope that this incubator will permit us to approach the problem of determining the optimum conditions of the physical environment for the premature infant.

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