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A. Robert Bauer

Philip J. Howard

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RESPIRATION IN THE NEWBORN INFANT

A. ROBERT BAUER, M.D.* AND PHILIP J. HOWARD, M.D.**

During the last 30 years progress has been made in the study of respiration in the newborn infant, both from the standpoint of an understanding of the physiology involved and of the intelligent use of therapeutic measures which have been made available for respiratory difficulties. Since some of the pioneer work in that field was done at this hospital by Howard and myself, I would like to briefly summarize some of our results together with those of some other clinics.

Our first work was done with a body plethysmograph in which the infant's entire body was enclosed in a metal tank with the head protruding through a rubber collar similar to a Drinker respirator, allowing the patient to breathe room air. The air displaced inside the tank was equal to the amount of air taken into the respiratory tract, and by connecting a recording spirometer to the inside of the tank we were able to get faithful measurements of rate, tidal air and minute volume, and by placing inflated rubber tubing around the chest and abdomen we were able to get records of these movements at the same time. In another part of this experiment, we obtained tracings while administering varying concentrations of oxygen to the subject and making analyses of the respired mixture at one minute intervals with a Beckman oxygen analyser. As a result of these studies, we were able to show that low oxygen concentrations of 12% or less acted as a respiratory depressant in newborn infants, whereas concentrations of 40% or more were stimulating and resulted in increased minute volume. This was more or less true regardless of the pattern prior to the experiment; that is, if the respirations were regular and efficient in room air, the administration of 12% oxygen would convert them into an irregular inefficient type. On the other hand, if they were irregular and inefficient in room air, the administration of higher concentrations would make them regular and increased the minute volume in 7 out of 10 infants. These results were similar to those previously reported in premature by Wilson, Long and Howard.

The newborn infant's response to oxygen is almost the opposite to that found in adults who respond to low oxygen with hyperpnea and to high oxygen with a reduced respiratory effort. We found that at about 30 days of age the infant began to change over to the adult type of response. We were unable to demonstrate any pattern of coordination between chest and abdominal movements or that such lack of coordination contributed in any way to inefficient breathing. We felt that the breathing was chiefly abdominal and that the chest merely acted as a support for the pull of the diaphragm. At the end of each experiment, we administered 5% carbon dioxide in 95% oxygen and found it to be a most powerful stimulant in increasing minute volume.

Different explanations are offered for the peculiar newborn response. The most popular view at present is that the respiratory center is depressed by anoxia and does

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*Children's Hospital of Michigan, The Endocrine Clinic, Physician-in-Charge.
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not respond in its usual way to changes in carbon dioxide tension, and the chemoreceptors situated in the aorta and carotid arteries take over the control of respiration by responding to changes in oxygen tension. This would imply that the inefficient breathing was the cause of the anoxia which had depressed the respiratory center, and that the administration of oxygen relieved the anoxia and returned the center to a normal status so that it again responded to changes in carbon dioxide tension in the usual way. Cross and his associates in England have presented what they feel is very strong evidence to support this view.

Our explanation is somewhat at variance with theirs. We feel that this type of breathing is physiological for the newborn and simply represents his way of quantitating his relative oxygen and carbon dioxide tensions. It has been shown by Wilson and his group that the newborn has a low oxygen saturation and carbon dioxide tension, with a slight uncompensated acidosis which were interpreted to indicate a relatively anaerobic existence. It would seem to follow that if less oxygen were used in oxidative processes, there would be less carbon dioxide formed, since it is one of the end products of oxidation in the tissues. Because of the different solubility, diffusion and mixing characteristics of oxygen and carbon dioxide, shallow, irregular breathing with occasional periods of apnea tend to conserve carbon dioxide without proportionately diminishing oxygen intake. Since the relatively anaerobic existence and peculiar type of fetal hemoglobin offer some protection against anoxia, and the low carbon dioxide tension allows the infant to endure a greater retention of carbon dioxide without toxic effects, it would appear that both are some insurance against a prolonged interruption of oxygen and carbon dioxide exchanges which may occur during delivery or after delivery and before the infant's own respirations have been started.

Winterstein has advanced an interesting idea of respiratory control which he calls the "reaction theory". It proposes that all regulation is on the basis of pH change.

*Author's understanding of Winterstein's Reaction Theory:

Winterstein's explanation of how anoxia increases sensitivity of the respiratory center to CO₂ stimulation: Oxygen lack causes hyperpnea which reduces the numerator of the Henderson-Hasselbach equation by washing out CO₂ in the inspired air in a proportion of 3:1, the fraction becomes 3-1/60=2/60=1/15. Now, if because of anoxia, the absolute value of the fraction is reduced, that is, the hyperpnea washes out CO₂ reducing the numerator from 3 to 1 and the denominator is also reduced from 60 to 20 to preserve the 1/20 ratio by the action of kidneys and other buffer mechanisms; then if the same amount of CO₂ is added as mentioned above, the fraction would then be 1-1/20=1/20=1/15 which will give a lower pH than the 1/15 and hence a greater stimulation. Or stated another way, the same quantity of CO₂ will cause a greater stimulation of respiration in an individual whose absolute value of H⁺CO₃⁻/HCO₃⁻ has been reduced by acclimatization to anoxia. These figures were intentionally made simple and exaggerated. He also stated that this could be predicted mathematically from the Henderson ratio, but has also been reproduced experimentally, and that metabolism during anoxia is the same or even greater, producing as much or more CO₂.

NH₄Cl put into the blood causes it to shift strongly to the acid side, but the spinal fluid to the alkaline side and the increased ventilation is the algebraic sum of these two actions. This is the opposite to what Gessel found with NaHCO₃. The undissociated ammonia molecule (in the blood) appearing from the dissociation of the ammonium ion NH₄⁺=NH₃+H⁺, diffuses thru the barrier which is impervious to the ions. On the other side (spinal fluid) it again dissociates NH₃+H₂O=NH₄⁺+OH⁻ thus causing the alkalinity in the spinal fluid.

NaHCO₃—'The physicochemical process is obviously as follows: In the original solution the equation CO₃⁻=CO₂+OH⁻ gives the solution its alkaline properties. The CO₂ wanders thru the membrane to the other side, where it becomes CO₂+H₂O=HCO₃⁻=H⁺ thus giving an acid reaction'. The reaction H₂CO₃=CO₂+H₂O is a slow one, but is speeded up with carbonic anhydrase which is present inside the red blood cells.
whether in the respiratory center or in the chemoreceptors and also whether thru oxygen or carbon dioxide variation. In the case of carbon dioxide, the effect on the respiratory center can be direct thru the blood or indirect thru the spinal fluid. The amount of carbon dioxide in the blood changes the pH by dissociation of H ions from H2CO3, and as the blood bathes the center it is stimulated by these ions. In the spinal fluid these changes are brought about in quite a different way. Since the spinal fluid-blood barrier is impervious to ions, H ions cannot pass thru regardless of origin, but molecules such as carbon dioxide pass thru freely. Once in the spinal fluid the carbon dioxide forms carbonic acid which dissociates into H ions that are able to stimulate the center.

In the case of oxygen, he feels that the lack of it within the center or chemoreceptors gives rise to acid metabolic products which lower the pH and stimulate them from within. Paradoxically, the ensuing hyperpnea washes carbon dioxide out of the blood giving laboratory findings of a respiratory alkalosis at a time when the interior of the centers are in a state of relative acidosis. He also states that anoxia makes the respiratory center more sensitive to stimulation by carbon dioxide and explains it in this way: anoxia causes hyperpnea which washes carbon dioxide out of the blood, thereby reducing the numerator of the Henderson-Hasselbach equation from its usual 1/20-H2CO3/NaHCO3, and since the 1/20 ratio must be maintained the denominator is also reduced resulting in a total diminution of both. Consequently, a given quantity of carbon dioxide, either retained or administered will cause a greater increase in the numerator which reduces the pH and stimulates the respiratory center.

Miller and his group in Kansas City have done excellent work in this field and have concluded that the chemoreceptors are less sensitive in the newborn than in later life, in sharp disagreement with the stand taken by Cross and a little more in line with the view which we have taken. They also brought out an interesting point by allowing newborns to breathe a low concentration of oxygen, and then by giving 5% carbon dioxide in that atmosphere of low oxygen they were able to get a marked stimulation of breathing. This would seem to add some support to the idea of carbon dioxide primacy in the control of respiration in this age group. In their more recent work they have demonstrated an important correlation between respiratory rate and general prognosis. The infants studied were divided into three groups. Group I had the best prognosis and were those who had a respiratory rate of about 40/min. immediately after birth and continued with that rate. They showed a progressively increasing resting tidal volume and were normal, well babies. Those in Group II had an initially high rate but came down to around 40 sometime between 6 hours and several days. They also had a progressive increase in resting tidal volume and their prognosis was good. The infants in Group III started out with a normal rate, but increased up to 60/min. within 36 hours. These infants did not respond with an increasing resting tidal volume and had to meet their respiratory needs with an increase in rate. This was associated with a reduction in resting tidal volume, severe uncompensated respiratory acidosis and occasional hypoxia. This group had the poorest prognosis.
From the foregoing, it can be seen that there is some difference in opinion as to the interpretation of the different respiratory patterns. Our studies indicate that the decision to use oxygen therapy or other medicinal stimulants should be made on the basis of a general appraisal of such factors as cyanosis, feeble heart action, shock, weak cry and lack of response to stimulants in addition to the type and efficiency of respiration. This is becoming a matter of some importance for evidence is accumulating rapidly to indicate that especially in premature infants toxic results of oxygen administration such as retrolental fibroplasia and pulmonary irritation occur from concentrations higher than 40 to 50%.

For many years Johnston\textsuperscript{12} has been getting definite clinical improvement in bulbar polio patients with respiratory difficulty from the use of intravenous hypertonic glucose solution. He was anxious to see if we could show that improvement graphically by means of our respiratory tracings. We planned to make the study on actual polio cases, but since there were none in the hospital during that time it was done on unrelated cases. Tracings were made of the chest and abdominal movements on five children during the administration of 50cc of 25\% glucose solution over a 5 minute period. The excitement incident to the venapuncture did cause some stimulation of respiration which had to be considered in the final analysis of the results. However, there was one case in whom a previous cut-down made it possible to give the solution without disturbance. Two of the five responded with a stimulation of respiration, two got a sedative effect and one showed no change. From these few cases, we concluded that the beneficial effects of hypertonic glucose given intravenously were not immediately interpretable in our tracings so far as any consistent pattern was concerned. However, there was a measurable change noted in 80\% of the cases which was compatible with the clinical improvement observed, since an increased respiratory effort might be very helpful to one patient whereas a reduction in that effort could be the sign of improvement in another. A more definite trend might emerge from a larger series of cases.

While doing the plethysmograph studies on newborns, we wondered whether a study of the capillary blood flow as observed at the base of the finger or toe nail with a microscope would give information of value in conjunction with the former. There were many technical difficulties, as it was extremely important to get a sufficient fixation of the tiny finger or toe under the objective of the scope without constricting the normal flow. Even with several different plaster splints and a modern, powerful, dissecting microscope, the results were examination of the normal capillaries and did not add anything.

At present, we are working with a Woods’ oxymeter. It is a fine precision instrument with which one can get a continuous measurement of oxygen saturation by means of a photoelectric cell attached to the ear. Papers have appeared on its use in newborns, and the results seem to be well worth while. Kennedy and his group\textsuperscript{13} showed that oxygen saturation in the newborn averaged 67\% at birth, and rose to an average of 89\% in 17 minutes and 94\% in 2 hours. Miller\textsuperscript{14} used it in connection with his work on respiratory rate referred to above. He found that the infants in the more favorable groups had a consistently better oxygen saturation. This apparatus differs from those now in use in the Respiratory Center of this hospital, in that the
Bauer and Howard

ear piece is very small and was designed especially for newborn infants. Also, the percent saturation is expressed as an absolute figure without the usual gasometric test on a blood sample to establish a base line. The accuracy is within 3% at 90% saturation and 9% at 50% saturation. These features make it extremely valuable for work on the newborn as the saturation can be followed right from birth on, with practically no disturbance to the infant. We are joining with Churchill and Lafontaine to show some correlation between his electro encephalogram and neurological examinations and our respiratory studies and oxygen saturation. It is felt that such a program will add additional information on the etiology of some cases of cerebral palsy and mental deficiency.

15400 Glastonbury Road
Detroit 23, Michigan

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292