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George E. Becker
Yale University

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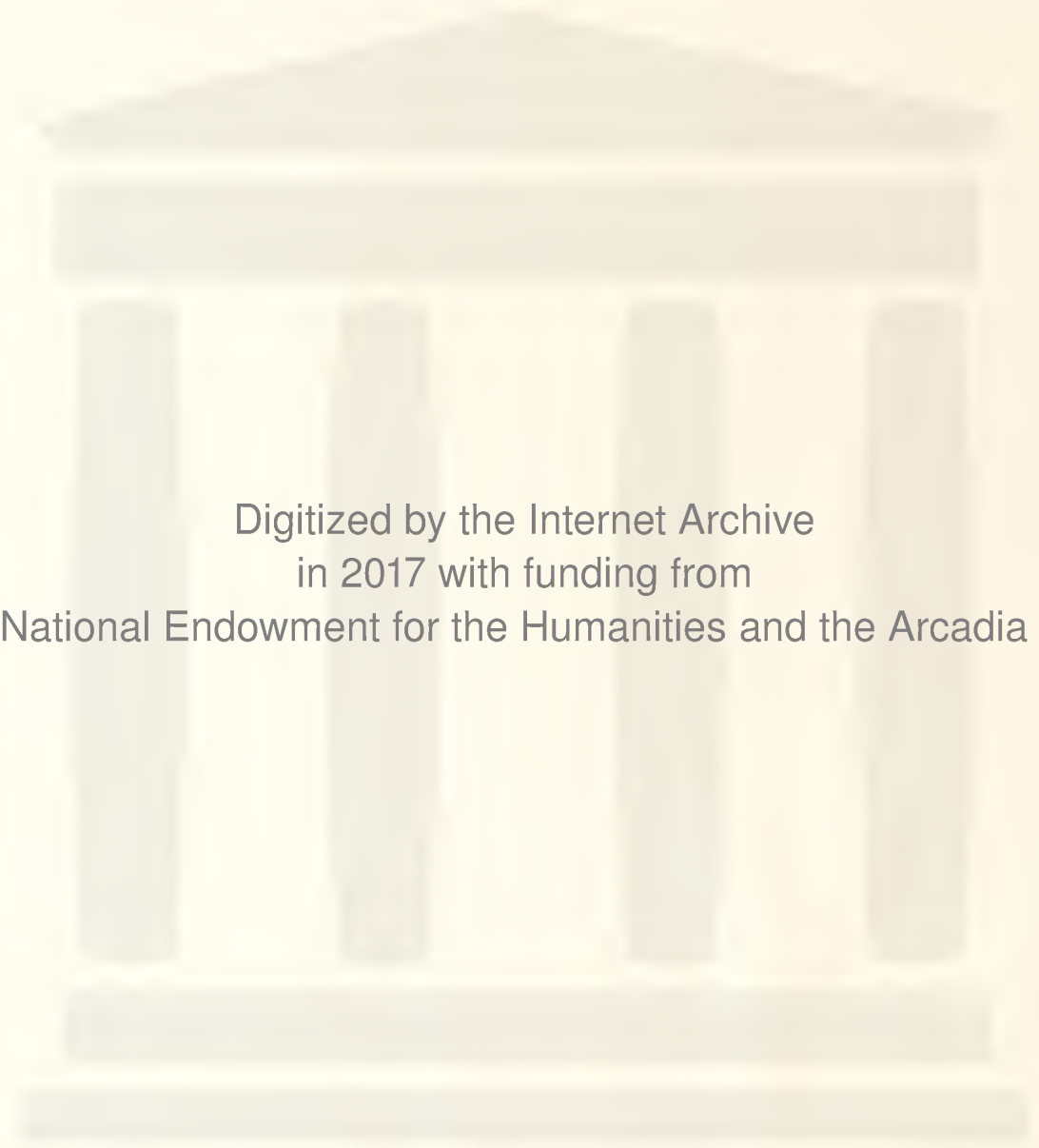

Some Studies Relating to Asphyxia Neonatorum and the Onset of Respiration in the Sheep

by

George E. Becker Jr.
B. S. Trinity College, 1951

A thesis submitted to the faculty of Yale University School of Medicine in candidacy for the degree of Doctor of Medicine

Department of Pediatrics

1955

Dedicated to Pat

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George E. Becker Jr.
New Haven, Connecticut
April 7, 1955

SOME STUDIES RELATING TO ASPHYXIA NEONATORUM AND THE ONSET OF RESPIRATION IN THE SHEEP

"When an animal is born and begins its struggle for an independent existence, its first efforts are those of breathing. Breathing is living; the onset of respiration is the beginning of life." (1) Barron

PURPOSE

Our purpose in these few experiments was really twofold: first, to shed further light on certain aspects of the problem of asphyxia neonatorum and second, to develop and evaluate certain techniques which could be used in pursuing further these investigations.

NATURE OF ASPHYXIA NEONATORUM

Several studies have been done on the nature of asphyxia neonatorum. Eastman (2) in 1932 wrote that the primary blood chemical change in (human) asphyxia neonatorum was a reduction in the oxygen content of fetal blood, in some cases to below 1 volume per cent. He also noted that the serum pH fell, in fatal cases, to below 7. His studies of mixed fetal blood supplying the brain showed elevated carbon dioxide tensions which, in his words, "... is difficult to reconcile with the apneic state of the fetus in utero and necessitates the assumption that the sensitivity of the fetal respiratory center, with respect to carbon dioxide, is definitely depressed." His conclusion was that CO_2 administered at this time was not only superfluous but harmful in that

it tended to aggravate an already existing acidosis and that, therefore, the chief therapeutic indication was for oxygen.

Barcroft (1) in his scholarly studies showed that, after ligation of the umbilical cord in sheep, there is a uniform and rapid rate of fall in oxygen concentration in the fetal blood (femoral artery) prior to the first respiratory gasp. In two minutes a level of 1 volume per cent was not unusual.

ANAEROBIC METABOLISM IN THE NEWBORN

Himwich and his workers (6) noted the extreme tolerance of newborn rats to hypoxia and anoxia and speculated that one of the possible factors making this possible was an anaerobic source of energy. (His other speculations: a low cerebral metabolic rate and poikilothermia.) In some very interesting studies (7) he found that infant rats survive some 50 minutes in a nitrogen atmosphere when sodium cyanide is injected (which has an inhibitory effect on the cytochrome-oxidase system of aerobic metabolism). (Adult rats survived only 10 minutes.) However, when iodoacetic acid is injected (which inhibits the conversion of triosephosphoric to phosphoglyceric acid in the anaerobic cleavage of glucose) the rats died promptly. He interprets this as proof of an anaerobic metabolism.

Wilson (8) discusses the possibility of anaerobic metabolism in the newborn (lost soon after birth) which reaches an endpoint in carbohydrate metabolism short of carbon dioxide and water. He suggests the probability "... that the acidosis of young infants indicated by carbon dioxide content and pH determinations is an indication of this anaerobic metabolism and of the production of an end product other than

carbonic acid such as lactic and pyruvic acid."

RESPIRATORY MOVEMENTS IN THE NEWBORN

Barcroft and Barron, in 1936, (9) discuss the genesis of respiratory movements in the sheep fetus. They observed rhythmic trunk movements associated with respiration in fetuses between the 38th and 49th days. During this stage asphyxial conditions of the cord will cause their cessation. However, after the 50th day, the rhythmic movements disappear as a spontaneous phenomenon but can be elicited by clamping the umbilical cord.

Davis and Potter (10), in injection studies with thorotrast in humans showed fetal motion in utero. They ventured the rather simple conjecture that "...at birth air is substituted for amniotic fluid."

Barcroft wrote with flavor in 1946 (11), after extensive work, as follows:

"... The effect of anoxia on the fully anesthetized sheep foetus is a simple gasp. I have been concerned with quite a number of gasps in my time; the picture is always the same.

"The distinguishing features of the gasp are 1) that it is a forced respiration involving much of the musculature of the body and 2) in its extreme form it is instantaneous, not involving any sustained movement. The gasp is therefore a medullary affair, and involves the severance of the medulla from the higher parts of the brain. The essence of asphyxia is that ... it 'knocks out' the centers of the brain from above downwards, the last to remain being the medullary

centers. At this stage any stimulus to the central nervous system, if it produces any effort at all, will produce a gasp. This is in fact what appears to happen; on the occlusion of the cord the gasp takes place after an interval of a minute (more or less) ... after a pause another gasp takes place, followed by others, and if all goes well these secure enough oxygen to bring the higher parts of the brain into action and a rhythm establishes itself. If the gasps do not achieve this result, they damp off and the foetus dies."

There have been other opinions. Eastman (12), studying blood drawn at the moment of respiratory onset in 7 normal infants, found relatively high oxygen concentrations in all, but carbon dioxide values "throughout the entire physiological range." He felt that a factor other than the carbon dioxide tension in fetal blood is dominant in starting respiration. Snyder (13) working with rabbits found that anoxemia always depressed fetal respiration. Increased carbon dioxide showed no effect on two-thirds of the little bunnies, but one-third of them showed stimulation. A low carbon dioxide invariably produced fetal apnea. He feels that oxygen above a critical level is an important stimulus to respiration. This view is quite at variance with Barcroft's. In the midst of the tussle Clement Smith (14) suggests that it may be unwarranted to expect a single principle to emerge from studies on different animals, with gestation periods varying from 32 to 147 days. Barcroft (14) does suggest, however, that animals in which respiratory movements cease during anoxia may have been somewhat asphyxiated to begin with. Hence, a slightly asphyxiated foetus, responding with respiratory activity, might cease to make such

movements under further asphyxia. He points out the obvious fact that a sufficiently asphyxiated foetus would be totally unresponsive.

RESUSCITATION OF ANOXEMIC NEWBORN

All investigators agree that the proper method of resuscitation is a matter for much further investigation. Eastman (2), as I have already mentioned, feels that the chief therapeutic indication in asphyxia neonatorum is for oxygen. Barcroft (1) has shown, however, that if oxygen is given to a lamb at birth during the first three minutes after cord ligation, the oxygen saturation of the fetal blood quickly reaches 100 %. He writes, "I have never been able to follow the reasoning which suggests that the administration of carbon dioxide can be of any particular benefit to a foetus so long as it is already overloaded with that material as the result of apnoea."

Concerning his own technique of resuscitation Barcroft (1) writes as follows:

"In the course of a long series of experiments I naturally have been confronted with a number of foetuses which showed little inclination to breathe even when the cord was ligated. In such cases ... (I direct a) stream of oxygen from a cylinder on to the foetus, more especially on to its face, nose, and mouth, once the air passages have been rid of mucus. I use the word 'stream' not 'trickle', because the current of oxygen should stimulate as large a surface as possible, and the atmosphere round the mouth and nose should be rich in that gas. The stream of oxygen should, in fact, be as vigorous as is deemed compatible with the welfare of the foetus, always bearing in mind that,

unless a foetus breathes it has no welfare. I mention this procedure because I have been occasionally surprised by the dramatic success which has followed it ... At a later stage, when the respiratory rhythm has been established, carbon dioxide in the oxygen is desirable.

Eastman (15) working with adult dogs in the presence of deep asphyxia, induced with nitrous oxide, found that using pure oxygen the restored respiration was normal in rate and amplitude. However, following resuscitation with carbon dioxide mixtures, the respiration tended to be convulsive and irregular. It frequently became shallow and further artificial respiration became necessary. His conclusion: pure oxygen is probably better in asphyxia neonatorum just as it is in experimental anoxemia.

At this point a word about the use of drugs to stimulate respiration is in order. Clement Smith writes (14) that they "offer some possibility of turning the tide by producing a few gasps or increasing those already produced ... their action is no more than that of a crank for starting an engine, they may turn the motor over once or twice and thereby induce a more normal mechanism to replace their effects." Such drugs include coramine, alpha-lobeline and caffeine.

ON TECHNIQUE AND ANIMALS

The manner in which the blood samples are drawn had a considerable effect on some of the work done by various investigators. Clement Smith (14) states that the specimens from the umbilical vessels varied in oxygen content depending on the degree of manipulation of the uterus and cord before and during the sampling. The faster and more gently they were obtained, the more consistent and the higher the

oxygen contents. Barcroft (1) has written at length on the technique of puncturing the umbilical vessels: "As term approaches, the umbilical vessels become much more likely to resent any sort of manipulation and to show their resentment by contraction. ...It may seem to the reader rather superfluous for me to give directions for the puncture of vessels so large and so obvious, yet such is their elusiveness and power of constriction that unless the samples ... can be taken before any narrowing takes place, (they) are worthless and the data derived from them are a definite menace in the notebook. The samples must, therefore, be obtained straight off, without the least bungling and with the minimal injury to the vessels." Barcroft also suggests the dropping of a small quantity of 4 per cent formalin on the cord, saying that, even in a term foetus, there is a wonderful effect in preventing constriction of the umbilical vessels.

Barcroft (16) points out that it is best, in his opinion, to work out the physiology of one species as completely as possible and mentions also that sheep have the advantage of being large enough to study with ease and they have a suitably "longish" period of gestation (147 days).

Finally, Barcroft offers these words of wisdom to the researcher: "Another point the worker in the field of foetal physiology must constantly battle against is the tendency to obtain more data from an experiment than he is justified in doing. It seems such a waste to do no more than obtain from a pregnant sheep a couple of samples of blood from some vessel, or a couple of blood pressure records or the like. When you have taken your samples or your records, vessels stare you in the face in all directions; why not take a sample from this

vessel, or that, or the other? It is easy to do, and a sheep costs so much and so forth, but if the procedures which you have undertaken have appreciably affected the composition of the blood in these alluring vessels, it is useless to push your needle into them; it is worse than useless, because as the result you will get data in your notebook which are wrong and which had better not be there."

Sir Joseph Barcroft closes his excellent volume on prenatal physiology (1) with this bit of inspiration: "Such, then, is the picture that I have drawn of the onset of respiration at birth. Perhaps it is too much to claim that it is even a picture; rather I regard it as a blocking out of one, for a lifetime might be spent in filling in the details."

METHODS OF ANALYSIS AND PLAN OF THE THREE EXPERIMENTS

The methods used in the analysis are the same as those described earlier by the laboratory of the Department of Pediatrics, Yale University School of Medicine, New Haven, Connecticut (17) except that sodium and potassium were determined on a Barklay internal standard flame photometer. Serum pH was determined on the Beckman pH meter at 38°C, using an anaerobic cell. Lactic acid was determined on serum, using the method of Barker and Summerson (18) and a lactic acid standard. Pyruvic acid was determined on serum, using the method of Friedmann (19) using a sodium pyruvate standard.

Briefly, the plan of the experiments was as follows:

1. To take a pregnant ewe at term.

2. Deliver the umbilical cord with the fetus still in utero.

3. Draw control samples of fetal arterial blood (through a polyethylene tube inserted through a 17 gauge, one and one half inch hypodermic needle in the umbilical artery, the tubing having been threaded well into the fetal arterial system).

4. Deliver the fetus (preventing respiratory movements with succinylcholine, a muscle relaxant, or with a mask, or both, or neither).

5. Draw more samples at suitable intervals.

6. To begin artificial respiration with air or oxygen at a suitable time and continue the sampling procedure.

Ideally such a technique would provide information about the blood chemical changes during induced asphyxia neonatorum and also during the phase of recovery from this asphyxia.

Since each of the experiments differed somewhat from the

other two, I shall describe them separately, in some detail. By and large, experiments two and three incorporated refinements in technique not considered before.

EXPERIMENT I

As in all three experiments, a term dorset ewe was anesthetized slowly with approximately 30cc. of isotonic sodium pentothal, given over a period of seven minutes, into the jugular vein. The animal was then laid on her back, a rapid midline incision made, sufficient for easy exposure of the pregnant uterus. Samples of uterine venous and arterial blood were taken (for another investigation) and the umbilical cord delivered through an incision in a relatively avascular portion of the uterus. Umbilical arterial and venous samples were taken, also for another study. Then 5 cc. of a 200 mgm. per cent solution of succinylcholine were injected into the umbilical vein, and immediately the cord was tied. As in the other experiments, the timing of samples was done from this moment. Considerable difficulty was encountered in puncturing the "resentful" umbilical artery but after six minutes a 17 gauge, one and one half inch hypodermic needle, through which had been threaded a polyethylene tube, was successfully introduced, close to the fetal umbilicus. The tubing was threaded for a distance of approximately eight inches, into the fetal arterial system. Blood samples for analysis were immediately drawn. The system was then washed out with heparin and samples taken as indicated in Chart II.

During this experiment, which was planned only as a "trial run" to test our techniques, and was therefore performed on an animal used for other study, we learned several important things.

1. The fetus made no attempts whatsoever at respiratory gasps.

2. There was considerable doubt as to when the fetal heart had stopped beating. Because of the thick fuzzy wool covering the fetus,

listening for the fetal heart with a stethoscope was unsatisfactory.

3. We confirmed Barcroft's findings that the fetal vessels were extremely elusive and that to obtain good results there "must be no bungling". Not only are the vessels extremely slippery, but also they are friable and it was found to be not at all difficult after getting into the umbilical artery, to go right through to the other side. (During one of the attempts, in fact, Dr. Barron's thumb was punctured by the operator, fortunately not deeply.)

4. Attempts at artificial respiration by thoracic compression and mouth to mouth breathing were totally unsuccessful, in that no oxygen was found in any of the samples drawn.

This experiment is presented stepwise in Charts I and II.

Chart I

Order of events - First experiment

Time	Event
10:16 - 10:23	30cc. isotonic pentothal given to ewe.
10:24	Midline abdominal incision.
10:25	Samples, uterine artery and vein.
10:26	Delivery of umbilical cord.
10:28	Samples, umbilical artery and vein and injection of 5cc. succinylcholine.
10:29	Umbilical cord ligated distal to cannulation site. Fetus delivered.
10:35	First samples.
10:37	Second samples.
10:44	Third samples.

Chart II

Values, First experiment

Time	Lactic	Pyruvic	CO_2	Na	Cl	pH	O_2	pCO_2
	γ/cc.	γ/cc.	meq./L.	meq./L.	meq./L.		vol.%	
9 min.	1250	11.8	19.8	133	110	6.67	0	94
11 min.	912	11.3	19.0	132	115	6.64	0	105
18 min.	1125	14.5	18.3	133	112	6.61	0	100

(cord delivery at time 0)

EXPERIMENT II

Pregnant term dorset ewe with anesthesia as before. The usual midline incision was made, the uterus opened and a section of the umbilical cord was delivered, arterial and venous blood samples were taken, and, in two minutes, the needle was inserted into the umbilical artery, the catheter threaded through to approximately seven inches and the system washed out with heparin. Then 10 mgm. of succinylcholine were injected as a 200 mgm. per cent solution into the umbilical vein. Initial arterial samples were drawn and, fifteen minutes after delivery of the cord, it was clamped. Further samples were timed from this moment, as indicated in Chart III.

During this experiment, positive pressure resuscitation was planned with pure oxygen delivered through a mask improvised from a glass funnel and a rubber glove, so cut that it fit snugly over the fetal head. However this attempt was unsuccessful, firstly, because the naso-oro pharynx was filled with thick, tenacious mucoid material, not easy to aspirate, and, secondly, because it was difficult to keep the lamb's mouth open and, hence, its airway clear. It was decided that we would do a tracheotomy on the third animal, in order to circumvent these problems.

An attempt was also made to make an electrocardiogram recording in order to follow accurately the status of the fetal heart throughout the sampling procedure. This was totally unsuccessful, however, for two reasons. Firstly, there was so much interference in the record from handling the fetus, etc., that these were all that could be seen, and, secondly, the use of the usual limb leads with plate electrodes and rubber straps did not provide a good conduction

medium, undoubtedly influenced by the masses of wet-matted wool on the fetal legs. It was decided to use toothed, sprung electric terminal clamps in the third experiment.

Since, in this experiment, the animal made no attempts at respiratory movement and was, by analysis, totally anoxemic, it was decided not to use succinylcholine, and to make a vigorous attempt at early resuscitation of the fetus.

This experiment is presented, stepwise, in Charts III and IV.

Chart III

Order of events - Second experiment

Time	Event
10:45 - 10:52	Anesthesia.
10:53	Abdominal incision. Cord delivered.
10:57	Samples, uterine vein.
11:03	Cannula in umbilical vein, heparin and succinylcholine injected.
11:04	Fetus delivered and masked.
11:05	Umbilical artery cannulated.
11:07	First samples.
11:08	Cord ligated.
11:10	Second samples.
11:12	Third samples.
11:15	Fourth samples.
11:18	Fifth samples.
11:20	Sixth samples.

Chart IV

Values, Second experiment

Time	Lactic	Pyruvic	CO_2	Na	K	Cl	pH	O_2	P	pCO_2
min.	γ/cc.	γ/cc.	meq./L.	meq./L.	meq./L.	meq./L.		vol.%	mgm.%	
14	1250	12.5	21.7	136	4.8	106	6.81	0	6.7	90
Cord clamped - - -										
17	1300	13.2	19.9	139	7.2	108	6.70	0	7.1	95
19	1120	11.5								
22	1400	14.7	22.2	135	5.8	112	6.59	0	6.6	123
25	1200	12.5		135	5.8		6.56	0	7.1	
27	1210	12.5	18.3	135	6.8	109	6.63	0	7.1	157

(cord delivery at time 0)

EXPERIMENT III

Animal and anesthesia as before. However, in this experiment a tracheotomy was performed (time, two minutes) and a cannula (connected to a clamped tube coming from a supply of pure oxygen) introduced and tied in place. The umbilical artery was cannulated with ease (no bungling this time). The electrocardiograph was connected with copper electric-terminal spring clamps, with sharp teeth, to the limbs and an excellent recording made. After the first samples had been obtained in the usual manner, positive pressure resuscitation was begun. Almost immediately the blood was visibly a brighter red.

The first fetal respiratory movements noted (see chart V) were isolated gasps, two or three per minute, involving mouth, diaphragm, thoracic and abdominal musculature. Caffeine injection (2 cc. ampule caffeine sodium benzoate containing gr. 7 1/2) produced, almost instantaneously, dramatic, deep gasps involving muscles of face, thorax, and abdomen. These lasted only 10 seconds, after which time there were no movements for several minutes. Toward the end of the experiment more gasps appeared, at increasingly long intervals, but of a very feeble nature.

Terminally, injections of saline and glucose were made, primarily to discover their effect, if any, on the heart. Positive pressure resuscitation was begun again for the same reason. The experiment is presented, stepwise, in Charts V, VI and VII. The latter gives electrocardiographic findings.

Chart V

Order of events - Third experiment

Time	Event
11:35 - 11:49	Anesthesia.
11:55	Samples, uterine vein.
12:02	Cord delivery and sampling.
12:03 - 12:05	Tracheotomy. EKG connected.
12:11	Umbilical artery cannula in place.
12:13	First samples.
12:15	Cord clamped. Oxygen started.
12:17	Second samples.
12:19	Third samples.
12:21	Fetal respiratory movements.
12:24	Fourth samples.
12:28	Fifth samples.
12:31	Oxygen stopped.
12:34	Oxygen started.
12:36	Sixth samples.
12:38	Oxygen stopped.
12:42	Caffeine injected. Dramatic respiratory gasps.
12:43	Seventh samples.
12:45	20cc. isotonic saline.
12:50	Eighth samples

Chart V (concluded)

Time	Event
12:53	40cc. 5 per cent glucose.
12:58	Ninth sample (Na and K only).
12:59	Positive pressure resuscitation.
1:00	Ninth sample (O_2 only).
1:00	Weak respiratory movements noted.
1:22	Ninth sample (organic acids, pH, electrolytes).

Chart VI - Values, Third experiment

Time	Lactic	Pyruvic	CO_2	Na	K	Cl	pH	O_2	Gluc.-mgm.	P	pCO_2	O_2 sat.
11	320	16.8	27.7	136	4	104	7.13	2.9	44	5.6	84	18
15	260	16.5	27.7	134	4.2	102	6.99	4	37	5.6	92	23
17	170	16.8	25.2	135	4.2	106	7	19.9	39	5.5	84	100
22	180	17.7	19.7	141	4.2	106	7.08	20.7	43	5.2	60	100
26	220	18.8	20.4	139	4.2	113	7.03	14.6	51	5.2	68	80
34	240	19	21.8	137	3.7	112	6.93	12.2	44	6	80	65
41	340	16.2	23.3	140	4.2	112	6.95	4.4	56	6.4	77	26
48	530	12.8	19.7	147	5.2	120	6.67	0.27	63	6.1	94	0
56				130	5.2	105		6.8		8.5		36
58				134	4.2							
80	980	10.5		134	3.2		6.56					

(cord delivery at time 0)

O_2 capacity on one sample - 18.6

Chart VII

Electrocardiographic findings, third experiment. Original tracing available from Dept. of Pediatrics. Sanborn Viso - Cardiette.

Time	Event
12:07	Initial tracing immediately after tracheotomy. Rate, 134; PR interval, .07 sec.; QT interval, .22 sec. (1.)
12:13	First samples. Rate, 168; PR, .06; QT, .20. T waves upright.
12:15	After cord clamping. Rate, 124; PR, .07; QT, .22. T waves deeply inverted with transition, in 3 seconds, to upright. (2.)
12:17	Second samples. O_2 saturation, 23 per cent. Rate, 104; PR, .06; QT, .22. T waves higher - U waves present.
12:19	Third samples. O_2 saturation, 100 per cent. Rate, 170; PR, .06. P waves the same.
12:21	First respiratory gasps. Rate, 170; PR, .06. Biphasic T wave, inverted.
12:22	Oxygen saturation, 100 per cent. Rate, 130; PR, .06; QT, .28.
12:30	Oxygen saturation, about 80 per cent. Rate, 116; PR, .06; QT, .32.

Chart VII (continued)

12:40 Oxygen saturation, about 65 per cent. Rate, 120; QT, .34; PR, .06. ST takeoff up slightly. May be anoxic change.

12:42 Respiratory movements following caffeine injection seen on EKG. (3.) Eighteen gasps in 11 seconds, then no more.

12:45 At injection of saline, 20cc. Rate, 172; slows in 3 secs. to 112. T wave high, upright to inverted, biphasic.

12:49 Oxygen saturation almost 0. Rate, 58; QT, .25. Apparently anoxic changes. (4.)

12:51 Rate, 48; QRS amplitude low. T waves isoelectric.

12:52 Rate, 60; T waves reappear. Glucose injection apparently had little demonstrable effect on EKG.

12:55 Further anoxemia. Rate, 40; PR, .13; QT, .42. T waves inverted.

12:58 Coupling occurs, 2.4 secs. between coupled beats. Sinus rhythm, P waves sometimes inverted, may be unusual focus in auricle. No QRS fragmentation. (5.)

12:59 Positive pressure started.

1:00 Rate, 105; PR, .13; QT, .34. QRS amp. 3 mm. ST take-off up 2 mm.

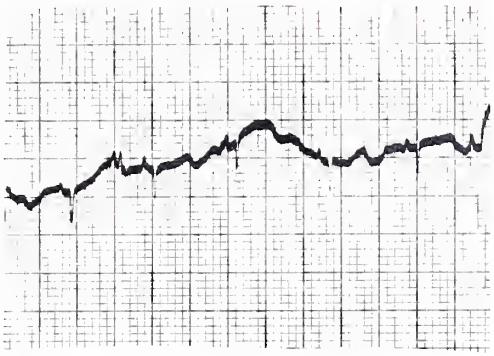
Chart VII (concluded)

1:30 Rate 105; PR, .13 (prolonged); QT, .34; QRS amplitude 3 mm. ST takeoff 2 mm. high.

Progressive slowing of heart until, with rectal temperature of 29° C. at

1:36 Rate, 32; PR, .17; QT, .34. Low QRS. Notched P wave. Inverted T wave. (7.)

Note: Numbers in brackets refer to portions of the electrocardiographic tracing reproduced herewith.



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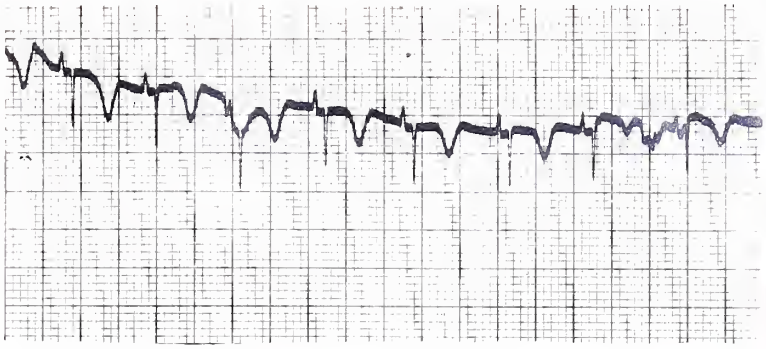

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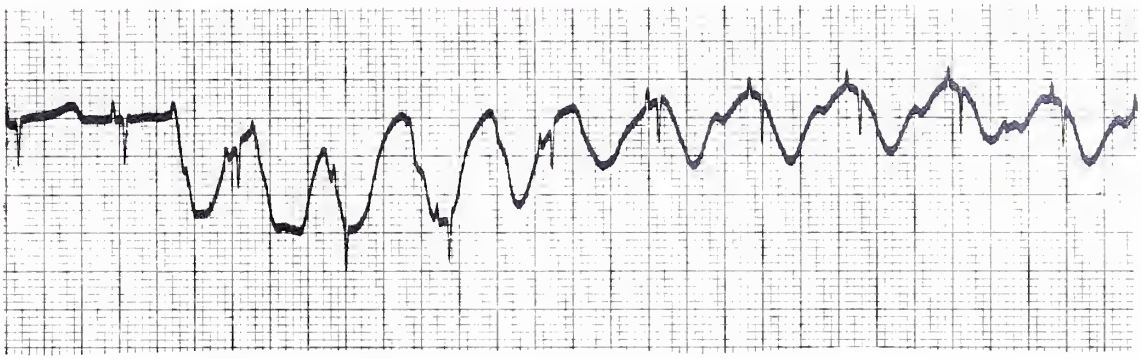

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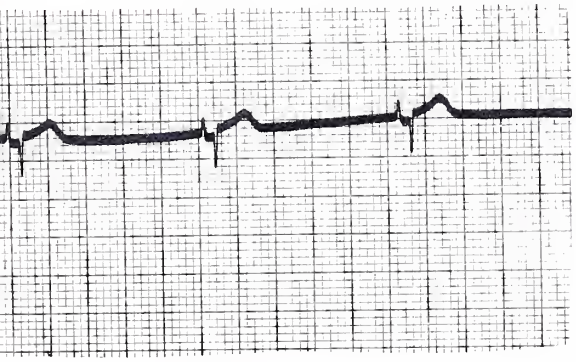

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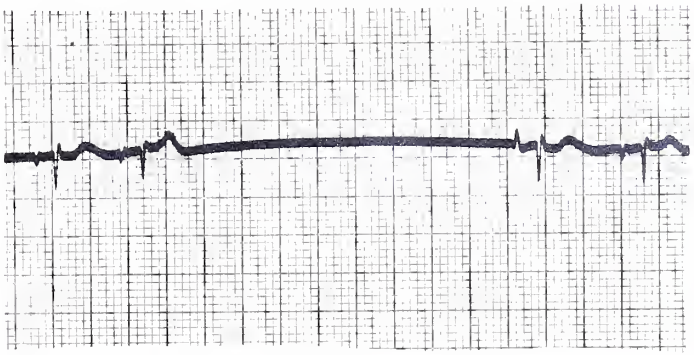
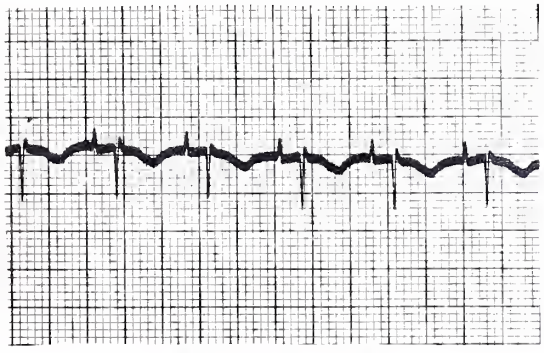
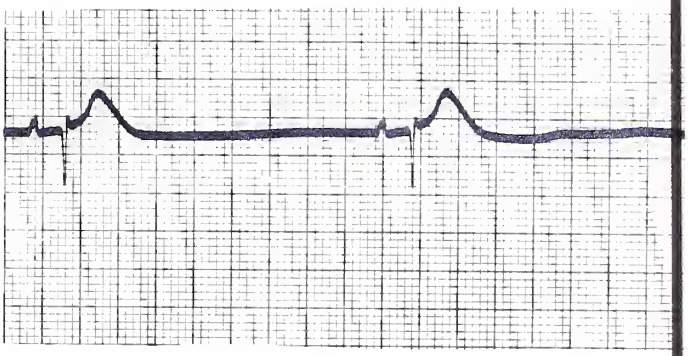


5. COUPLING



6. AFTER POSITIVE PRESSURE



DISCUSSION

It is obvious to the reader, I hope, that these experiments, because of their preliminary nature, should not be used as the basis for too many deductions. Their principal purpose was to serve as a proving ground for certain techniques - and as such they have been invaluable. There are, however, a few rather obvious findings in our mass of data which I shall point out, requesting that it be borne constantly in mind that these data, obtained as they were under constantly varying conditions, are, in the words of Barcroft, a "menace in the notebook". Some of the figures may be misleading, some of them may be correct; it is for further investigation to discover which are which. Feeling, however, that no investigation is totally worthless, I present these observations for what they may be worth.

1. The newborn lamb who does not breathe is severely oxygen deficient, indeed, sometimes the oxygen values in the arterial blood are so small as to be un-measureable by our techniques.

2. The anoxemia of asphyxia neonatorum is accompanied by a severe and ever progressive acidosis, as reflected by a falling blood pH, to values well below 7. This acidosis is due largely to two factors: the high pCO_2 values and the accumulation of high levels of lactic acid. Sodium and chloride levels remain largely stable and within physiological limits of normal, at least insofar as we know what normal is in the newborn lamb.

3. The anoxemia of asphyxia neonatorum is accompanied by a high level of serum lactic acid, at times well in excess of 1000 gamma per cc. A level of 1000 gamma per cc. is 100 mgm. per cent. These values compare more or less with those of Swann and Brucer who

found levels ranging from 75 mgm. per cent to 110 mgm. per cent in adult dogs after 5 minutes of anoxia. These animals had initial levels approaching 0.

4. The levels of pyruvic acid which we obtained at no time rose above 20 gamma per cc. (2 mgm. per cent).

5. With positive pressure oxygen, introduced directly into the trachea, within two minutes, 100 per cent blood oxygen saturation can be obtained.

6. In the face of high oxygen saturation the fetus maintains a high pCO_2, indicating, at best, minimal elimination of this gas. In view of the reports of other investigators finding significantly low levels of carbonic anhydrase in the newborn, it is interesting to speculate what relationship these two findings may bear to each other. Van Goor (3) in 1934 found the level of carbonic anhydrase in cord blood at birth to be only one half of its level in adult blood. Roughton (4) found levels in the goat fetus, depending on age, varying from .01 to 0.1 units per cubic millimeter, an increase of at least thirteen times being noted in the adult goat in which levels of 1.35 units per cubic millimeter were found. Stevenson (5), working with humans, found values of .8 units in the premature infant, 1.4 units in a term baby and 3.50 units in the adult. Of course it is known that catalysts are effective, often, in extremely minute amounts. No information is available as to the amount of anhydrase necessary to catalyse this reaction. Therein lies the crux of this matter.

7. Interestingly enough, the serum potassium levels fell within a normal physiological range (3.2 to 5.2). This surprised us greatly.

8. The electrocardiogram provided dramatic evidence of the ability of the fetal heart to withstand severe anoxemia, to fail and to recover again. In this experiment, the fetal heart continued beating for almost one and one-half hours after the initial period of asphyxia neonatorum.

9. The electrocardiogram recorded dramatically the effect of caffeine, a so-called respiratory stimulant, to act, as Smith says, like the "crank of and engine." This drug, in our hands, had an extremely transient effect.

10. The glucose levels tend to indicate that these animals continue mobilizing this chemical, so essential to their anaerobic metabolic pathways. Himwich (21) showed the remarkable effects of glucose in prolonging the survival time of 8 day old rats in a nitrogen atmosphere, as well as the effect of insulin in dramatically cutting the survival time of newborns when anoxic.

Such, then, were our findings. This experiment represents a mere scratching of the surface. It is hoped that future investigations will include a study of irreversible asphyxia neonatorum and, later, a study of resuscitative techniques. Projected research by this department includes: (a) cardiovascular - electrocardiogram, aortic blood pressure, cardiac output and measurements of blood and plasma volumes and distribution; (b) respiratory - spirometer tracings, possibly phrenic nerve and vagus recordings; (c) biochemical - arterial plasma and blood analyses, pH, electrolytes, organic acids including lactic and pyruvic, Kreb's cycle components, glucose utilization, blood gases, muscle, brain and heart tissue analyses; (d) cerebral - sagittal sinus plasma and blood analyses, possibly electroencephalograms;

(e) whole body function - response to stimulation, reflexes, body temperature (thermocouples).

The significance of research in the field of neonatal physiology cannot be overestimated. Too many infants die each year of "asphyxia neonatorum" - never having taken their first gasp. Another group, who survive, have permanent residua of neonatal asphyxia. A more complete understanding of this terribly critical period, the few minutes after birth, with its profound physiological changes, may lead to methods for the prevention of death and injury. Furthermore, this approach, working out fully the physiology of the lamb, offers the only objective method now available for the evaluation of resuscitative techniques since such experiments with humans by their very nature are obviously out of the question. When reading the literature on this subject, one is impressed with the vast number of opinions expressed and the dearth of facts available. In closing, it seems fitting to quote again the great physiologist, Sir Joseph Barcroft, who wrote:

"Such, then, is the picture that I have drawn of the onset of respiration at birth. Perhaps it is too much to claim even that it is a picture; rather I regard it as a blocking out of one, for a lifetime might be spent in filling in the details." (1)

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