Anesthesiology
V 38, No 4, April 1973

Reports of Scientific Meetings

Ellis N. Cohen, M.D., Editor

Sir Joseph Barcroft Centenary Symposium

Joseph Barcroft was born on July 26, 1872, in Newry, Ireland. He received his doctorate from King's College in 1896, became professor of physiology at Cambridge in 1926, and was knighted in 1935. Barcroft's classic studies of the oxygen-dissociation curve and differences between the affinities of hemoglobin of maternal and fetal blood led to the development of the new field of fetal physiology. Barcroft remained active in research until the last day of his life, in 1947.

To commemorate the centenary of Sir Joseph Barcroft's birth, a Symposium on Fetal Physiology was held in July 1972 at the Physiological Laboratory in Cambridge, where Barcroft worked for nearly half a century. About 250 scientists from all over the world were invited and for three days discussed subjects concerned with fetal development and fetal physiology.

The first session, on functional development of the nervous system in the fetus, was chaired by Sir Bryan Matthews, Barcroft's long-time colleague in physiology at Cambridge. During early gestation in lambs, cortical activity appears in a sequential fashion, with progressive activation of neurons from deeper to more superficial cortical areas. Membrane potential is surface-positive, but becomes more negative as gestation progresses. About the 125th day in the fetal lamb (full term is 147 days), membrane potential becomes similar to that of the adult sheep.

G. S. Dawes and associates (Oxford) observed that undisturbed fetal lambs have rapid-eye-movement (REM) sleep characterized by bursts of rapid low-voltage waves on the EEG. This appears in very early gestation, suggesting a subcortical function. Concomitant with REM sleep, rhythmic respiratory movements occur. Circadian rhythm is also present in the fetal lamb by the 110th day of gestation. Peak activity, including REM sleep, rhythmic breathing, and skeletal muscle activity, occurred about 9 P.M. in most fetal-lamb studies, and was independent of light or sound.

According to Hathorn (London), REM sleep also affects respiration in human newborn infants. During non-REM sleep, the newborn infant is flaccid, without skeletal-muscle activity, and breathing is slow and regular. During REM sleep, however, there are frequent movements of extremities and oral activity. Respiration is fast and irregular, and minute ventilation is significantly increased.

It has become apparent in recent years that observations must be made in intact chronic fetal preparations in order to understand the normal physiology of fetal life. Fetal lambs prepared according to a technique initiated by D. H. Barron and associates are now being utilized in many laboratories to produce important new information.

Using such chronic preparations, P. Johnson and co-workers (Oxford) found a unique reflex mechanism for respiratory control in fetal and newborn lambs. They discovered at the entrance to the larynx a chemoreceptor with the morphologic characteristics of taste buds which is innervated by the superior laryngeal nerve and stimulated only when the larynx comes in contact with specific fluids. When the upper airway was ligated above a tracheostomy, instillations of saline solution, amniotic fluid, or sheep milk into the larynx did not affect respiration; however, when water or cows' milk was instilled, rhythmic respiratory movements ceased abruptly and swallowing began. Apnea continued despite progressive asphyxia. Hyperpnea immediately followed replacement of the water with saline solution.

Chronic lamb preparations were also used by A. M. Rudolph and associates (San Francisco) to study fetal cardiac function. When heart rate was reduced by vagal stimulation, stroke volume changed little and cardiac output fell. This effect was probably related to poorly-developed sympathetic innervation in the fetal ventricle, since the tension–length relationship of the fetal myocardium is similar to that of the adult. In the adult heart, the two ventricles are in series, with a balance of output. In the fetal heart, the ventricles are in parallel and a

balancing mechanism does not exist. As a result, right ventricular output is twice left ventricular output. Approximately 10 per cent of right-heart output goes through the lungs, while the rest passes into the descending aorta via the ductus.

After the beginning of air breathing, the ductus arteriosus constricts as the result of an increase in P_{O_2}. Using a strip of guinea pig ductus, F. S. Fay (Worchester) demonstrated that high Pa_{O_2} was associated with an increase in tension on the ductus and an increase in cytochrome a_3 oxidation. Fay postulated that this increase in cytochrome a_3 oxidation accelerates oxidative phosphorylation, elevates cytoplasmic calcium ion, and thus causes contraction of the ductus.

According to M. A. Roach (London, Ontario), umbilical vessels in sheep and humans constrict with increased P_{O_2} by constricting circular muscles. An even more important mechanism for their closure at birth is the effect of physical stretch and/or decreased temperature. Contraction of the longitudinal and helical muscles of the umbilical vessels causes obliteration of their lumina more effectively than does contraction of the circular muscles.

Factors which affect placental blood flow and gas transfer were discussed in the session on placental function chaired by J. Metcalfe (Oregon). F. E. Forster (Philadelphia) pointed out that, unlike the lung, the placenta is a unique organ of gas transfer between two liquid compartments. It is more likely to be a concurrent system than a more efficient counter-current system. Shunts, including anatomic shunts and those due to uneven distribution of perfusion, exist within the placenta. The membranes separating the two capillary systems in the placenta are multilayered and may also influence placental gas transfer. However, inert gases, such as nitrogen and nitrous oxide, are completely equilibrated by the time the blood reaches the end of the capillary. The shift to the left of the fetal oxyhemoglobin-dissociation curve is not as advantageous as was previously assumed, since the lower capillary and tissue P_{O_2} levels may depress the activity of the cytochrome system. Furthermore, carbon dioxide in the fetal blood probably does not come into equilibrium with maternal carbon dioxide since it must diffuse against a bicarbonate gradient. The low level of carbonic anhydrase in fetal cells may accentuate the delay in CO_2 transfer.

There has been considerable doubt as to whether placental oxygen transfer in sheep is limited by diffusion. J. H. Rankin (Wisconsin) estimated the effectiveness of placental oxygen transfer in a concurrent system. His calculations indicated that the effectiveness of oxygen transfer decreases during maternal hypoxia and alkalosis, and that this decrease may account for the fetal hypoxia observed during maternal hyperventilation. An alternative explanation was presented by E. K. Motoyama (New Haven), who found that, in sheep, alkalosis is associated with increased vascular resistance in the umbilical circulation. This vasoconstriction is similar to that in the cerebral vascular bed, and the resulting placental hypoperfusion may contribute to fetal hypoxia.

Uterine blood flow in sheep is high in early pregnancy and diminishes by the 60–80th day of gestation coincident with an increase in progesterone and a decrease in estrogen/progesterone ratio. This decrease in flow was ascribed to a direct effect of progesterone on the uterine vascular bed by D. Caton (Gainesville). Administration of progesterone decreased uterine blood flow even in early pregnancy and in the nonpregnant ewe. Oxygen consumption by the uterus also decreased with progesterone. It was not clear whether this decrease was secondary to oxygen lack or changes in metabolism. Estrogens, on the other hand, increased uterine blood flow. Clinically, estrogens have been given to pregnant women with fetal distress in an attempt to increase fetal oxygen supply. However, according to N. W. Bruce (Oxford), estrogens in rabbits increase uterine blood flow by increasing myometrial and vaginal flow, but decrease maternal–placental flow.

The session on metabolism was chaired by R. A. McCance, another surviving colleague of Barcroft. At this session, D. Hull (London) presented a study of active fat in rabbits. In the newborn period, active fat is an "organ" of thermogenesis in response to cold. It is distinguishable from ordinary adipose tissue by its multilocular appearance and brown tinge. Distribution is characteristically localized in the lateral and posterior aspects of the neck. Distinction between active and white fat be-

comes more difficult during the neonatal period, as the former gradually loses its thermogenetic ability. Active fat is highly vascular, with a blood supply ten times greater than that of ordinary adipose tissue. Norepinephrine has a strong pyrogenic effect, producing a multifold increase in blood flow to active fat, while decreasing blood flow to white fat. Norepinephrine also increases the outflow of free fatty acids from active fat. The exact mechanism of thermogenesis and a possible role of the cytochrome enzyme system are yet to be explored. G. Alexander (N.S.W., Australia) and coworkers observed that newborn lambs delivered prematurely by injection of ACTH are incapable of increasing metabolic rate and heat production compared with full-term lambs. Metabolic rate often falls with the administration of norepinephrine, and may be associated with a lack of brown fat in the premature animals.

The session on parturition was chaired by D. H. Barron (Gainesville), Barcroft's longtime associate and the founder of the specialty of fetal physiology in the United States. Within the last several years, it has become evident that the fetus is actively participating in, if not actually controlling, the physiologic mechanism of labor and parturition. Based on studies in sheep and humans, Liggins (Auckland) hypothesized that at or near term, the fetal hypothalamus is activated by an unknown factor which stimulates fetal pituitary ACTH production. As a result, the fetal adrenal cortex is stimulated, resulting in an increase in glucocorticoids. These in turn increase levels of estrogens and prostaglandin $F_{2\alpha}$ and decrease progesterone in the placenta. An increase in estrogens, the estrogen/progesterone ratio, or $PGF_{2\alpha}$ decreases the threshold to oxytocin. Administration of ACTH and/or glucocorticoids to the fetus thereby produces premature parturition. Ablation of fetal pituitary or adrenal glands results in prolonged pregnancy.

The mechanism of parturition, however, is far from clear. R. B. Heap and co-workers (Edinburgh) and R. S. Comlin and associates (Cambridge) demonstrated striking species differences in the hormonal levels which control parturition. The human placenta produces progesterone, while the placentas of goats and sheep do not. In guinea pigs the plasma concentration of progesterone is elevtaed, not because of an increased production as in humans, but as a result of reduced clearance. In sows, estrogens increase before parturition, but progesterone does not decrease as it does in sheep. The plasma cortisol level increases in the fetal and neonatal lamb, but not in the calf or the foal. Common underlying factors which govern the mechanism of parturition among different mammalian species have yet to be demonstrated.

The closing session of the symposium was devoted to the study of pulmonary surfactant. Although the phospholipid component of surfactant had been studied extensively, little is known about the nature of the lipoprotein fraction. Through a complex extraction process, J. A. Clements and associates (San Francisco) have isolated a surface-active material (SAM) and found that 90 per cent of the lipid fraction was phosphatidyl choline (lecithin), while protein accounted for about 10 per cent of the SAM. Nearly two thirds of the lipoprotein fraction was found to be a unique protein with a molecular weight approximating 10,000. While the role of this protein component of surfactant remains unclear, it is possible to develop a specific immunoassay technique which may facilitate future study of the development and pathophysiology of surfactant.

L. Cluck (La Jolla) emphasized the importance of species differences in the study of surfactant. There are two major pathways for lecithin biosynthesis: 1) incorporation of diglycerides and CDP-choline; 2) N-transmethylation of phosphatidyl ethanolamine to lecithin. The latter pathway is present in human and primate fetuses, and surfactant appears in midgestation. In sheep and rabbits, the latter pathway may be insignificant during gestation, and surface activity does not appear until the last days of gestation. In the human fetus, surfactant is secreted into the alveolar fluid and expelled into the amniotic fluid. Measurement of the lecithin/sphingomyelin ratio in amniotic fluid has been utilized as a means of assessment of fetal lung maturation and possible development of RDS.

It has been found recently that maturation of the fetal lung can be accelerated by administration of glucocorticoids. The mechanism of accelerated maturation is not clear, but there is evidence for specific glucocorticoid receptors in the alveolar cells. The density of these re-

ceptors in the lung is greater than that of other organ cells. M. E. Avery (Montreal) studied the side-effects of corticosteroid administration upon the fetus. No abnormality was apparent during the postnatal growth of rabbits pretreated with glucocorticoids *in utero*. There was, however, a 12 per cent decrease in lung cell count in steroid-treated rabbits compared with their littermates, as determined by DNA and protein measurements. This decrease may indicate that accelerated differentiation during gestation is associated with a simultaneous decrease in multiplication. Clinically, administration of corticosteroids to human infants at the time of birth does not influence the incidence or time course of RDS.

G. C. Liggins (Auckland) has begun a clinical trial with glucocorticoids administered to parturients before premature delivery. In certain cases, delivery was delayed by the infusion of alcohol to allow the glucocorticoids time to affect the fetal lung. The results were impressive. When the infants were delivered two to seven days after the injection of glucocorticoids, there was a drastic decrease in the incidence and mortality of RDS among premature infants before 32 weeks of gestation. Extreme caution in undertaking such treatment, and a critical follow-up study of treated infants, were urged by the participants. As pointed out by Avery, injection of corticosteroids in the fetus may not be as innocuous at it appears.

ETSURO K. MOTOYAMA, M.D.
Associate Professor of Anesthesiology and Pediatrics
Yale University School of Medicine
New Haven, Connecticut

Literature Briefs

Myron B. Laver, M.D., Editor

Literature briefs were submitted by Drs. R. Clark, L. Cooperman, L. Cronau, B. Dalton, B. Das, A. Goldblatt, J. Harp, E. Lowenstein, L. Mark, H. Rackow, J. Reitan, and J. Ryan. Briefs appearing elsewhere in this issue are part of this column.

Circulation

CHEST X-RAY AND POISONING WITH INSECTICIDE The pulmonary radiologic findings in three cases of severe Parathion poisoning were shown to be remarkably similar. Fluffy perihilar infiltrates, present in the absence of vascular congestion and/or cardiomegaly, were noted to regress within hours of treatment with atropine and Protopam. All three patients were comatose or semicomatose, with copious secretions. The authors consider the radiographic findings diagnostic of pulmonary edema, although its nature (direct pulmonary capillary damage, left ventricular failure) is not defined. (*Bledsoe, F. H., and Seymour, E. Q.: Acute Pulmonary Edema Associated with Parathion Poisoning, Radiology 103: 53–56, 1972.*) EDITOR'S COMMENT: This article is of value because it describes one aspect of the clinical pattern seen to develop after organophosphate intoxication. Such descriptive exercises are of little further use when important clinical data, including arterial blood gases, are not included. It is quite important whether the level of arterial oxygenation is or is not consistent with the extensive radiologic changes in the chest x-ray.

Metabolism

CYANATE EFFECTS ON HEMOGLOBIN Urea may be useful in treatment and prevention of painful vaso-occlusive crises that occur in patients with sickle-cell anemia. In the body, urea is in equilibrium with ammonia and cyanate. Cyanate reacts with an α-amino group of hemoglobin (carbamylation), thereby diminishing the sickling phenomenon *in vitro*. Addition of cyanate did not affect glycolysis, ATP, 2,3-DPG stability, autohemolysis, or osmotic fragility. Potassium loss was less than in controlled cells and pyruvate kinase activity decreased, but other glycolytic enzymes were normally active. Oxygen affinity was increased, but the Bohr effect was unaltered. The authors conclude that their studies provide further support for the potential clinical use of cyanate in treating and preventing the anemia and painful crises of sickle-cell disease. (*DeFuria, S. G., and others: The Effects of Cyanate in Vitro on Red Blood Cell Metabolism and Function in Sickle Cell Anemia, J. Clin. Invest. 51: 566, 1972.*)