Physiologic Adjustments at Birth

Effects of Labor, Delivery and Anesthesia on the Newborn

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Intrauterine Environment. Some of the mystery and much of the controversy concerning the environment in which the fetus develops have been resolved following the development of techniques for implanting catheters into fetal and maternal vessels for prolonged periods of time without pregnancy being interrupted. These techniques have been successfully employed in both sheep and goats,[1] and more recently in the rhesus monkey,[2] enabling serial samples to be withdrawn from the unanesthetized mother and fetus. Although valuable data have been obtained from acute experiments in which the fetus is studied after removal from the uterus, the placental circulation being maintained, the normal functional relation between mother and fetus is considerably disturbed by this operative procedure and the anesthesia necessary for it.

As the fetus grows, the functional capacity of the placenta appears to increase to keep pace with his needs.[3] There are species variations in regard to the relative increase in weight of fetus and placenta as development proceeds, but in the human the placenta continues to grow and increase in weight to term.[4] The gradients for hydrogen ion and carbon dioxide tension across the placenta are small (approximately 0.05 *p*H units and 5 mm. of mercury respectively), so that the fetus is neither acidotic nor hypercapnic under normal conditions.[1,2] Although oxygen tension in fetal arterial blood is low by adult standards, oxygen consumption of the fetal lamb and goat (in ml./kg. of body weight per minute) is similar to the basal values obtained after birth and appears to remain constant during the third trimester.[1] Hemoglobin concentration and oxygen carrying capacity of fetal blood during the third trimester is similar to that of the adult animal and does not change as pregnancy advances unless the animal is subject to stress such as the operative procedure for insertion of the catheters. Adequate oxygenation of the tissues is probably maintained in the face of a relatively low arterial oxygen tension because of an umbilical vein saturation of 80–85 per cent together with high umbilical and systemic fetal blood flow rates. It should be noted that the use of oxygen tension gradient between mother and fetus as an index of oxygen availability is of little value in the absence of measurements of maternal and fetal blood flows or fetal oxygen consumption. When blood flow rates are high, large amounts of oxygen may be transferred into tissues at low partial pressures of oxygen.

Thus, the various lines of evidence responsible for the belief that the fetus has a limited control over its oxygen supply and lives under conditions of oxygen deprivation as term approaches can now largely be discounted. Even the higher oxygen affinity of fetal blood as an adaptive feature of life in utero has become a weaker argument since this is characteristic of early development in most forms of life from fish to man.

Acidosis of Birth Asphyxia. Oxygen levels in the umbilical arterial blood at birth range from 0 to nearly 70 per cent saturation in healthy infants, the average value being 22 per cent; in nearly one-quarter of these infants it is less than 10 per cent.[5] The relatively low

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oxygen levels are accompanied by varying degrees of hypercapnia and acidosis, average P_{CO_2} being 58 mm. of mercury and *p*H 7.28, lower *p*H and higher P_{CO_2} being associated with lower oxygen levels.[6]

These observations have suggested that the final stages of labor and delivery are associated with a reduction in exchange of oxygen and carbon dioxide across the placenta leading to various degrees of asphyxia at birth. Direct proof of this concept has been provided from the animal experiments described above and further from sampling of blood from the fetal scalp during labor.[7] This latter technique is an important advance in monitoring the condition of the fetus, and indicates that as labor advances the fetus gradually becomes more acidotic. The findings in cord blood at birth are therefore the result of a disturbance in the functional relationship between mother and fetus during labor and delivery, whether this be *per vaginam* or by cesarean section and do not reflect adaptations to an hypoxic environment *in utero*.

Several factors can disturb the normal functional relationship between fetal and maternal circulations and cause fetal acidosis. Blood flow through the intervillous space is reduced or may stop completely during strong uterine contractions[8]: it will also be reduced if the mother becomes hypotensive as the result of inferior vena caval or aortic compression by the uterus.[9, 10] Maternal alkalosis following excessive hyperventilation also appears to lead to a reduction in the intervillous flow and fetal acidosis.[11, 12] Since hydrogen ion is exchanged readily across the placenta, maternal acidosis will be reflected in the fetus; the mother may become acidotic as a result of excessive muscular activity or dehydration during prolonged labor, or as a result of depressant drugs and anesthesia. On the fetal side, cord compression occurs in approximately one-third of all deliveries and probably represents the most common mechanism interfering with transplacental exchange.[5]

These disturbances in the normal functional relationship between fetal and maternal circulations that inevitably occur during labor and delivery impose considerable limitations upon the interpretations of data relating to the composition of cord blood. This applies not only to respiratory gases but to all substances that are in continuous exchange between mother and fetus.

Achievement of Normal Acid-Base Balance Postnatally

During the first minutes after birth, *p*H continues to fall while lactate levels rise.[6, 13] This occurs even in the most vigorous infants in whom respiration is well established by one minute of age. Depressed infants are more acidotic initially and the fall in *p*H after birth is greater and of longer duration. By one hour of age, *p*H and lactate levels in healthy infants are near normal for the adult, but acidosis persists in the depressed low-score infants. Increase in acidosis immediately following birth is partly due to a rise in the concentration of oxyhemoglobin which dissociates more hydrogen ions than reduced hemoglobin; the concomitant rise in lactate concentration, however, indicates that influx of additional hydrogen ions, presumably from the intracellular compartment is taking place and is further evidence of oxygen lack during delivery.

Following lung expansion, arterial oxygen tension rises and P_{CO_2} falls rapidly, but a relatively normal acid-base state is not achieved before 1 to 3 hours. Recovery is accomplished primarily by pulmonary elimination of carbon dioxide and not by renal excretion of hydrogen ion. By 24 hours, the healthy newborn has reached the same acid-base state as the mother prior to labor.[14]

A number of factors influence the rate of recovery from birth asphyxia. Of these, analgesic and anesthetic drugs prior to delivery, and prematurity are the most important. Delay in recovery is also seen in the more aphyxiated infants, probably on the basis of circulatory impairment and central nervous system depression. This group includes infants who have aspirated meconium prior to delivery. They usually remain severely acidotic after resuscitation, low *p*H values being due primarily to accumulation of nonvolatile acids, as evidenced by base deficit values of up to 25 mEq./liter and lactate levels of up to 20 mEq./liter.[15] Occasionally retention of carbon dioxide is seen as well. However, this appears to be a less common complication than the metabolic acidosis and indicates circulatory impairment rather than an inability to excrete carbon dioxide.

A further factor influencing recovery is exposure of the naked newborn to normal room temperature.[16] Under these conditions oxygen consumption in the vigorous infant increases, metabolic acidosis persists and there is a further elevation in blood lactate concentration; a normal *p*H is achieved by increasing CO_2 elimination. The biochemical changes induced by cold stress in the depressed infants differ from those seen in the healthy ones in several respects; *p*H falls, there is a greater increase in base deficit, smaller increase in oxygen consumption and an increase in the ratio of lactate to pyruvate. These observations suggest that depressed infants have inadequate circulatory and respiratory responses to cold stress.

Several explanations for the low arterial P_{CO_2} (about 32 mm. of mercury) observed in healthy infants once normal acid-base balance has been achieved, have been offered. Hyperventilation due to anoxia or increased levels of organic acids due to anaerobic metabolism were first thought to be the cause.[17] It has been suggested that the sensitivity of the newborn's respiratory center to CO_2 is altered by progesterone.[18] It is also possible that the homeostatic responses of the newborn infant have been determined by the fetal environment where P_{CO_2} is low by adult standards.[14] Finally respiratory responses to mild cold stress noted above could be implicated, the infant gradually becoming "cold adapted" to his new environment.

The time of cord clamping, which will influence the quantity of additional blood from the placenta infused into the newborn infant, is thought by some to influence the neonatal readjustment.[19] This maneuver was not found to influence the acid-base readjustment in 20 randomly selected healthy infants delivered *per vaginam* who were compared with an equal number in whom the cord was clamped promptly after birth.[20] It should be pointed out that in studying the influence of placental transfusion the selection of cases can be easily biased, since the depressed and apneic infant requiring prompt resuscitation is more likely to have the cord clamped early.

Influence of Maternal Analgesia and Anesthesia on the Fetus and Newborn

Although most of the analgesic or anesthetic drugs administered to the mother readily cross the placenta there is not infrequently a lack of correlation between the dose of a particular drug administered to the mother and the condition of the baby at birth. A likely explanation for this lack of correlation is that the depressant effects of drugs or potent anesthetic agents is augmented or potentiated by varying degrees of asphyxia.[21]

It has also been difficult to explain the usually vigorous condition of the newborn infant in the presence of significant thiopental levels in umbilical vein blood, in contrast to the anesthetized state of the mother. In reinvestigating this problem it has been observed that while the barbiturate levels in the umbilical vein are high, the levels in the umbilical artery are low.[22] These findings suggest that the lack of depression in infants born vaginally following an induction dose of thiopental is due to very little barbiturate reaching arterial circulation and brain of the fetus. Relatively high levels in the umbilical vein only indicate that the drug readily crosses the placenta. Three factors could account for the lack of depression: cord compression, serial dilution of the drug as it passes through the fetal circulation, and accumulation of the drug in the liver.

The clinical condition and barbiturate levels in infants delivered by cesarean section have been compared with those in infants delivered vaginally. Similar doses of thiopental were given at comparable times prior to delivery in each group. The majority of infants delivered vaginally were vigorous while 5 of 6 delivered by cesarean section were severely depressed. It appears therefore that cord compression which is unlikely to be present at elective cesarean section, is the most important of the three possibilities. Uterine contractions themselves might reduce the amount of barbiturate that reaches the fetal circulation through their effect on maternal perfusion of the intervillous space.

The degree of ventilation of the anesthetized mother is also reflected in the fetus. Retention of carbon dioxide will occur if there is airway obstruction, an unduly large dead space, or hypoventilation. If severe it may lead to depression of the infant at birth. Unexpectedly, maternal hyperventilation has also been associated with depression of the newborn infant.[11] Experimental observations in pregnant guinea

pigs indicate that lowering the maternal arterial P_{CO_2} below 18 mm. of mercury together with the mechanical effects of hyperventilation, contribute to reducing the blood flow through the intervillous space [12, 23]; the newly born were hypercapnic and had a profound metabolic acidosis. One investigator has suggested that apnea at birth following maternal hyperventilation is due to low levels of carbon dioxide in the newborn infant.[24] Since neither *p*H nor P_{CO_2} were measured in the study, this explanation is conjectural and at variance with observations by others.

The danger from hyperventilation exists not for the conscious mother but for the unconscious patient who is artificially ventilated after receiving muscle relaxants. Severe alkalosis has been observed when the anesthesiologist has been attempting to maintain ventilation at a normal level.[12] It is possible that pregnant women might be more susceptible to the adverse effects of overventilation; the functional residual capacity of their lungs is less and arterial P_{CO_2} and alkali reserve decreased. Considerable caution should be exercised therefore in the ventilation of pregnant women undergoing cesarian section when muscle relaxants are being used; willful overventilation should be avoided.

Little is known of the relative susceptibilities of the fetus and the adult to a given drug, and inability to metabolize barbiturates has been reported in mice, guinea pigs and rabbits as a result of lack of development of certain enzyme systems.[25, 26] A hypersensitivity to *d*-tubocurarine chloride has also been proposed for human newborns,[27] the response resembling that of a myasthenic patient. Response of the fetus to ataractic drugs administered to the mother is also of importance since the maintenance of fetal blood pressure is essential for adequate placental perfusion. Since the fetus can now be studied directly through chronic indwelling catheters,[1, 2] the next few years should see considerable advances in our knowledge in this field.

An uncommon cause of severe neonatal depression is the accidental injection of local anesthetic agent into the fetus during attempted caudal anesthesia. The infant remains hypotonic and continues to have bradycardia after ventilation, and convulsions occur as soon as the infant is oxygenated. Pupils are dilated.[28, 29] Two infants have survived such an accident following prompt exchange transfusions; gastric lavage also appears helpful in removing the local anesthetic agent. It seems likely that the danger of this mishap is greater if caudal anesthesia is attempted late in labor when the fetal head is low in the pelvis. It has not been reported previously, but may have passed unnoticed due to delay in resuscitation or inadequate ventilation of the apneic infant. Convulsions, which are one of the cardinal signs of overdose with local anesthetic agents, only appeared after the newborn infants had been well oxygenated.

The Onset of Breathing

Because birth is accompanied by marked changes in fetal arterial oxygen tension, acid base state, as well as the thermal environment and tactile, auditory and visual stimuli to which the newborn infant is exposed, elucidation of a proprioceptive stimulus for the first breath has been difficult. It is unlikely that a single impulse would serve to initiate this important process.

Among the stimuli that have been implicated, asphyxia holds a favored position as the principal driving force.[5] There is little doubt that a fall in arterial oxygen tension and *p*H accompanied by a rise in carbon dioxide tension induce gasping in utero as well as after birth. Rhythmic breathing may ensue possibly as a result of improving oxygenation and normalization of acid-base state. The respiratory drive during asphyxia depends upon the presence of carotid and aortic chemo-receptors, which are known to be functional in the newborn period at least in the rabbit.[30] However, neither hypoxia nor hypercapnia alone (in the presence of normal *p*H) initiates breathing. Respiratory activity is not observed when the fetal oxygen tension has fallen to values as low as 2.5 mm. of mercury or when carbon dioxide rises to above 50 mm. of mercury.[31] These findings suggest two possibilities: either chemo-receptors of the fetus do not respond to hypoxia in the presence of a normal *p*H and carbon dioxide tension, or the state of activity of the respiratory neurones is such that the afferent stimuli from the carotid and aortic

chemo-receptors do not lead to sufficient efferent discharge.

The time interval between birth and the first breath is normally short, being only a few seconds. This favors excitation of the respiratory center by neurally transmitted impulses from peripherally located receptors which are not dependent upon the slower changes in blood composition. Thermal stimuli appear to be of particular significance. The rate of fall of skin temperature in the first minutes of extrauterine life indicates that the infant is losing about 600 cal./minute.

Occlusion of the umbilical cord, which causes a prompt though transient rise in blood pressure is considered by some to be of cardinal importance in initiating respiration. However, breathing can occur in the presence of intact umbilical circulation in the laboratory animal and in the human being, both *in utero* and after delivery. Tactile stimuli appear to be of secondary importance. Although strong stimulation of the fetal lamb produces gasping, rhythmic breathing is not initiated.

Respiratory Responses During and Following Asphyxia

Recently it has been found that cardiovascular, respiratory and biochemical changes occurring during asphyxia under controlled conditions are predictable. Information on this subject is most complete in the newborn monkey. During the initial phase of asphyxia of the unanesthetized newborn animal, respiratory efforts increase in depth and frequency for up to 3 minutes. This period which is called primary hyperpnea is followed by primary apnea lasting for approximately one minute. Rhythmic gasping then begins and is maintained at a fairly constant rate of about 6 gasps per minute for several minutes. The gasps finally become weaker and slower. Their cessation marks the beginning of secondary apnea.

There is some variation in the duration of gasping (time to last gasp) in different species, depending on the initial acid base state, drugs given to the mother and environmental temperature. At a given environmental temperature the principal determinant of duration of gasping in the nonanesthetized animal is the initial arterial *p*H.[32] Narcotics and systemic anesthetic agents administered to the mother can abolish the period of primary hyperpnea and prolong primary apnea; large doses can suppress all respiratory efforts. Gasping is prolonged if body temperature is lowered.

During primary apnea a variety of stimuli can initiate gasping (such as pain, cold and analeptics).[33] Once the stage of secondary apnea has been reached, however, these stimuli are without effect. Artificial ventilation or rapid correction of *p*H by infusion of base, if given soon enough after the "last gasp," are the only ways presently known by which gasping can be reinitiated.

There is a linear relation between the duration of aspyhxia and the recovery of respiratory function after resuscitation.[34] In newborn monkeys, for each minute after the last gasp that artificial ventilation is delayed, there is a further delay of 2 minutes before gasping begins again, and 4 minutes before rhythmic breathing is established. This indicates that the longer artificial ventilation is delayed during secondary apnea the longer will it take to resuscitate the infant.

In newborn monkeys asphyxiated beyond the last gasp, and then resuscitated, measurable oxygen uptake may be delayed as long as 3 minutes although the lungs are being ventilated with 100 per cent oxygen.[34] The delay is greatest in animals requiring cardiac massage to restore heart rate and blood pressure. This is most probably the result of low pulmonary vascular resistance and right-to-left shunting through the foramen ovale and ductus arteriosus. Thus asphyxia does not necessarily end with the onset of ventilation.

Asphyxia and Brain Damage

Maintenance of a normal *p*H during asphyxia by rapid intravenous infusion of base together with glucose prolongs gasping, delays cardiovascular collapse, and shortens the time for gasping to return and spontaneous breathing to be established after the animal has been resuscitated.[35] Furthermore the rapid correction or maintenance of *p*H in the presence of hyperglycemia during asphyxia can reduce or prevent morphologically detectable brain damage.[36] It has been proposed that the beneficial effects of *p*H correction are derived from prolongation and acceleration of anaerobic glyco-

lysis, restitution of oxygen carrying capacity of hemoglobin and responsiveness of cardiovascular muscle to sympathomimetic amines and fall in pulmonary vascular resistance due to reduction in carbon dioxide tension.

Asphyxiated newborn monkeys resuscitated before the last gasp (that is within 8.4 minutes) show little or no permanent cerebral damage. On the other hand, prolongation of asphyxia for 4 minutes beyond the last gasp is accompanied by widespread tissue damage and abnormal behavior in surviving animals. Thus a relatively brief delay in resuscitation can have serious sequelae. For the newborn monkey the "safe" period of asphyxia is quite short if functional integrity is to be maintained.

The question arises how long the asphyxiated human infant can remain apneic without suffering permanent damage to the brain. Until it is possible to evaluate the duration of asphyxia before birth and to know whether the nonbreathing infant is in primary or secondary apnea, and until it is known whether or not drugs given to the mother have a protective action against asphyxia, an answer cannot be provided. Mere survival is not enough. The high instance of neurologic impairment in survivors reflects the ignorance on this subject.

Circulatory Readjustments After Birth

Cineradiographic studies on the fetal lamb [37] have shown that arterialized blood from the placenta flows into the fetus through the umbilical vein, passes rapidly through the liver into the inferior vena cava via the ductus venosus and from there into the left atrium, soon to appear in the aorta and the arteries of the head. When dye is injected into the abdominal inferior vena cava or the superior vena cava, it passes into the right atrium, right ventricle and then into the descending aorta via the pulmonary artery and ductus arteriosus. Only a small portion of blood appears to circulate through the lungs. The crista dividens appears to separate the inferior vena caval flow into two streams before the atria are reached, the stream from the ductus venosus being guided largely into the left atrium.

The development of high fidelity electromagnetic flow meters has made it possible to study the regional blood flow of the fetus in a more precise fashion.[38] Earlier estimates of flow [39] have been confirmed, 55 per cent of the combined ventricular output returning to the placenta, 35 per cent flowing through the tissues and the remaining 10 per cent flowing through the lungs. Pulmonary blood flow is not constant, however, and can be increased up to fivefold by injection of acetylcholine or histamine in μg. quantities into the pulmonary artery.[38] The degree of oxygenation of the fetus also influences pulmonary vascular resistance, a rise in fetal arterial oxygen saturation brought about by administration of 100 per cent oxygen to the ewe doubling the pulmonary arterial flow in the presence of an essentially unchanged perfusion pressure. Acute aspyhxia of the fetus produces intense pulmonary vasoconstriction. Of interest is the observation that considerable fluctuations in fetal pulmonary blood flow occur under apparently steady state conditions, suggesting participation of autonomic nervous system control.

With the onset of respiration and lung expansion the pulmonary vascular resistance falls. This appears to be largely due to the direct effect of oxygen and carbon dioxide on the blood vessels, resistance decreasing as oxygen tension rises and carbon dioxide tension falls.[40] Lung expansion alone also contributes to lowering of the pulmonary vascular resistance.

In fetal life the foramen ovale and ductus arteriosus act as bypass channels allowing a large proportion of the combined cardiac output to return to the placenta without flowing through the lungs. It is uncertain that the ductus venosus has any important function in the latter part of fetal life. In the piglet, lamb and monkey it is a minute structure at term, and in the horse it is occluded before birth.

Transition from the fetal to adult type of circulation is not an abrupt process, the foramen ovale and ductus arteriosus remaining open for varying lengths of time. The pulmonary arterial pressure remains high for several hours.[41-44] This is not unexpected because the lumens of the pulmonary arterioles and elastic arteries increase only gradually.[45] As the pulmonary vascular resistance falls, the direction of blood flow through the ductus arteriosus reverses.[16] In the first hours of extrauterine life the flow is bidirectional.[47, 48] The shunt eventually becomes entirely left-to-right and by 15 hours of age is functionally insignificant.[43]

The pressure in the left atrium falls in the first few hours of life to levels below those in the normal adult; by 24 hours it may be less than 1 mm. of mercury above that in the right atrium.[49] This small pressure difference probably accounts for the persistence of a right-to-left shunt through the foramen ovale for 24 hours or longer.

The ductus arteriosus constricts in response to an increase in arterial oxygen tension.[50] Sympathomimetic amines also cause it to constrict.[50] Hypoxemia can cause a constricted ductus to reopen[51] and at the same time may also re-establish the fetal pattern of circulation by increasing the pulmonary vascular resistance.[52] This response of the ductus arteriosus to oxygen or hypoxia is thus opposite that of the pulmonary arterioles, enabling the right ventricle to contribute a variable fraction of its output to placental perfusion during fetal life. The different reactivity of these vessels during hypoxia although an asset to the fetus becomes a liability for the newborn infant. Hypoxic episodes in early neonatal life can lead to a rise in pulmonary vascular resistance and opening of the ductus arteriosus, increasing any residual right-to-left shunt. The reasons for the different responses of these vessels to hypoxia have not so far been determined.

The ductus is widely patent in infants suffering from respiratory distress syndrome and serial dye-dilution curves in both human infants and newborn lambs reveal that shunting may occur at the level of both foramen ovale and ductus arteriosus.[53, 54] In severely ill infants there is usually a bidirectional shunt through the ductus. A right-to-left shunt at the foramen ovale is also frequently present, depending upon the volume of left-to-right shunt at the ductus level. If the latter is large, pressure in the left atrium is high and shunting at the foramen ovale level small or not present. Recovery in both lambs and babies is accompanied by a rising systemic pressure and a predominantly left-to-right shunt that diminishes as the ductus closes. Deterioration is accompanied by a fall in systemic pressure and large bidirectional shunting.

Summary

Contrary to earlier beliefs the fetus does not develop under conditions of oxygen deprivation; its acid-base state is similar to that of the mother. During labor and delivery the fetus becomes acidotic as result of a variable reduction and exchange of oxygen and CO_2 across the placenta. In healthy vigorous infants recovery after birth is rapid and depends upon the prompt establishment of pulmonary function.

Depression and apnea at birth is most commonly caused by drugs or anesthesia given to the mother during labor and delivery. Their effect may be augmented or potentiated by varying degrees of asphyxia.

Cardiovascular, respiratory and biochemical changes occurring during asphyxia under controlled conditions are predictable, and a linear relationship exists between the duration of asphyxia and recovery of respiratory function after resuscitation.

Transition from the fetal to the adult type of circulation is a gradual process and can be reversed under conditions of hypoxia.

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HEMOLYSIS Hemodiluents, pumps, suckers, and cardiotomy systems used in intracardiac manipulations play only a minor part in the production of free plasma hemoglobin. The major source of free plasma hemoglobin has been from the hemolysis of blood spilled into the pericardial cavity. Blood in the pleural cavity also contained a high level of free plasma hemoglobin but it has not been demonstrated whether the hemolysis of this blood occurred in the pleural cavity or in the pericardial cavity into which it was first spilled. The surgeon must be prepared to discard all blood that is spilled into these cavities. Thus, more blood is required during the operation. (*Morris, K. N., and others: Hemolysis of Blood in the Pericardium: The Major Source of Plasma Hemoglobin During Total Body Perfusion, J. Thor. Cardiov. Surg. 49: 250 (Feb.) 1965.*)

PERFUSION Reduction of homologous blood requirements in high flow extracorporeal circulation has been accomplished by perfusate dilution up to 58 per cent of total volume. Immediate postperfusion overinfusion was required for all groups and reflected probable loss of diluent from the intravascular space. Electrolytes, P_{O_2}, and P_{CO_2} were normal during and after perfusion. Pulmonary and metabolic complications have been less than in patients receiving whole blood. Probably high flow rates compensate for the reduced oxygen-carrying capacity of the diluted blood. (*Litwak, R. S., and others: High Flow Total Body Perfusion Utilizing Diluted Perfusate in a Large Prime System, J. Thor. Cardiov. Surg. 49: 74 (Jan.) 1965.*)