

CONVULSIONS PRODUCED BY FETAL ANOXIA; EXPERIMENTAL STUDY *

FREDERICK A. FENDER, M.D., WILLIAM B. NEFF, M.D., AND
GRACE BINGER, M.D.

San Francisco, Calif.

OUR interest in the possible relation between anoxia and the convulsive state began with our observation that many patients who presented themselves for investigation of their convulsions had complicated birth histories. A review of the literature revealed many publications on this subject.

Much of our present understanding of the physiology and pathology of respiratory processes, effects upon the organism of the inhalation of various gases, and methods of study of these phenomena, is derived from the publications of pioneers in this field: Barcroft (1), Henderson (2), Haldane (3), and Peters and van Slyke (4). The effects of experimental anoxia have been investigated by Yant and coworkers (5), Himwich and associates (6), Windle and Becker (7), Kabat (8), and Yaskin and Thorner (9). It is believed that even more significant information may become available when the results of investigations carried out during wartime are released to the entire profession.

The central nervous system demands a great amount of oxygen for normal function. Metabolism is more active in the cerebrum than in any other "organ" of the body, and the rate of vascular irrigation of the brain is tremendous. Conversely, nervous tissue is more sensitive to lack of oxygen than any other type of tissue, corresponding to the following gradient: the grey matter of the cerebrum and cerebellum, as pointed out by Yaskin, requires the most oxygen, the white matter less, and the spinal cord least of all. This conforms with Drinker's table showing survival time, under conditions of anoxia, of cells in various portions of the central nervous system (10). Given in minutes, it reads: cerebrum, small pyramidal cells, eight; cerebellum, Purkinje's cells, thirteen; medullary centers, twenty to thirty; spinal cord, forty-five to sixty; sympathetic ganglia, sixty; myenteric plexus, one hundred eighty. Rough confirmation is found in the careful work of Yant (5) and others who studied the pathologic changes produced by anoxia in dogs. Various alterations—chromatolysis, distortion of nuclei, vascular stasis, vacuolization and fragmentation of cells, perineural edema and so on—tend to be most marked at the highest neurologic levels: the

* From the Department of Surgery and the Division of Anesthesia of the Department of Surgery, Stanford University School of Medicine, San Francisco, California.

cortex, thalamus and corpus striatum. In the brain stem, spinal cord, and at lower levels, changes were less extensive.

The implication is that levels believed to be responsible for convulsions or "epilepsy" are seriously affected by anoxia of even brief duration, whereas lower centers, less damaged by the same influence, allow survival to be maintained at a reflex or vegetative plane.

In 1938, Frederic Schreiber (11, 12) published two articles that contributed much to focus attention on the dangers of anoxia. After the eighty-year silence that followed Little's original warning (13), Schreiber was sufficiently articulate in regard to the birth histories of his patients who exhibited neurologic defects to provoke a series of inquiries by other investigators. These concerned chiefly delivery: anesthesia, analgesia, preoperative and postoperative medication, difficulties encountered at or immediately following birth, etc.

We have chosen to deal with anoxia in a broader sense. In an attempt more closely to approximate a clinical correlation, we subjected the animal fetus to deprivation of the normal amount of oxygen by limiting, for a short time, the oxygen supplied to the prospective mother. It was our intention to use a method that might provoke certain states simulating those occurring in fetal life and birth which we believe to be associated with deprivation of oxygen to the fetus.

EXPERIMENTAL MATERIAL

Pregnant bitches, whenever possible within the last week of pregnancy, were subjected to an atmosphere in which the oxygen content was lowered to as little as 4 per cent. The experiment lasted between twenty and thirty minutes. Carbon dioxide was not allowed to accumulate, and in all samples ran less than 1 per cent. A separate port in the tank allowed frequent sampling for such determinations. The equilibrium of the atmosphere was controlled so the animal could be observed.

The average experiment progressed as follows. The animal was placed in the tank and nitrogen was turned on. The next step was determined by her clinical condition, the aim being to keep her barely alive during the twenty to thirty minutes. At the end of this period the animal was returned to room air. After a short interval, during which defecation, urination, and inability to stand followed by an ataxic gait were noted, she returned to a normal state if she survived.

One bitch aborted the evening of the experiment and ate her young. Twenty-five pups, born from twenty-four to seventy-two hours after the experiment—the majority within the first forty-eight hours—died during the first few weeks. Three survived without apparent neurologic involvement, and were returned to stock.

Since there could be no proper control for this series, a word is in order regarding the animals that did not survive. No epidemic disease was in progress among our laboratory animals at the time,

earlier or later. Those deaths that could be investigated by necropsy were carefully studied. No cause for death was found. None suffered from distemper. Other pups, born at the same time and under the same conditions, survived and were lusty.

Hence, it seems possible to state definitely that the pups in this experiment which died shortly after birth did so because of the anoxia to which they had been subjected through their mothers.

Of the 5 surviving animals, 2—the first from a litter of 2, and the second from a litter of 3—developed status epilepticus at five and six weeks, respectively. The first was killed after twenty-four hours to terminate its state, and the second survived for three days during which seizures were almost constant. Motion pictures were made of these convulsions. Microscopic study of the brains revealed no significant departure from normal. There was no evidence of distemper in complete general necropsies. There was no infestation by worms.

Following is a typical protocol.

TABLE 1

ANOXIA BITCH 8: 7/24/41

3:48:15	In tank. Nitrogen on.
3:50:45	Movement within uterus. Inspirations deeper.
3:52:25	Sniffs around box. Pupils smaller. Yawns. Breasts cyanotic.
3:56:20	Unable to stand. Sample showed 12 per cent oxygen.
3:57:15	Tremor of jaw. Tongue cyanotic. Yawns. Sample showed 6 per cent oxygen.
4:00:00	Rapid (about 140), very shallow breathing. Unconscious.
4:00:30	Oxygen added. No change.
4:05:44	Breasts pale.
4:07:45	No change. Sample showed 8 per cent oxygen.
4:10:20	Semiconscious. Does not hold up head or move. Sample showed 8 per cent oxygen.
4:11:30	Oxygen added.
4:12:20	Jaw muscles twitch bilaterally.
4:14:00	Animal more alert. Sample showed 10 per cent oxygen.
4:22:50	Convulsive movements of face. Sample showed 7 per cent oxygen. After sample had been taken, animal was removed from cage. Apparent recovery followed within 10 minutes after involuntary defecation, a period of inability to stand, gross ataxia. Two pups were born 8/4/41. One survived and was returned to stock. The other died 9/20/41 after three days of almost constant convulsions.

Windle and Becker (7) noted a convulsive state following the interruption of arterial blood supply to the fetus. It is our impression that the refinement of our approach made possible more accurate measurements of the degree of oxygen deprivation.

In regard to the use of the expressions "convulsions" and "convulsive movements," it would appear timely to clarify our position. A variety of phenomena has been included under these names. Our experience (14) in producing convulsions experimentally leads us to believe that such phenomena as periodic rigidity, muscle twitchings, etc., should not be called convulsions, but that this term should be reserved for episodes more closely resembling the state seen clinically. In the cases of the 2 pups cited previously, genuine convulsions seemed to occur.

Convulsions occur spontaneously in dogs on rare occasions. In twenty years, no such incident has taken place in our laboratory. Moreover, the fact that 25 pups born after the experiment did not survive, and that 2 of the subsisting 5 animals developed convulsions, seems to place the experimental results well beyond the limits of chance.

The clinical background for this work is to be reported independently. We believe a significant percentage of patients who suffer from convulsions for which no obvious cause can be ascribed have histories of complicated fetal life or birth. These comprise incidents that may be due to anoxia.

SUMMARY

Nervous tissue is more sensitive to oxygen deprivation than any other type of body tissue. This tends to be most marked at the highest neurologic levels.

Cases are reported of 2 pups born of mothers which had been deprived of normal oxygen supply shortly before delivery. Both pups developed a convulsive state, 1 five and 1 six weeks after birth. It is felt that anoxia played a role in the development of this state.

It is further believed that fetal and neonatal anoxia in humans may play a major part in the development of epilepsy.

REFERENCES

1. Barcroft, J.: *Architecture of Physiological Function*, New York, The Macmillan Company, 1934.
2. Henderson, Y.: *Fundamentals of Asphyxia*, J. A. M. A. 101: 261-266 (July 22) 1933.
3. Haldane, J. S., and Priestly, J. G.: *Respiration*, Ed. 2, New Haven, Yale University Press,
4. Peters, J. P., and van Slyke, D. D.: *Quantitative Clinical Chemistry* Baltimore, Williams & Wilkins Company, 1: 868-1018, 1931.
5. Yant, W. P.; Chornyak, J.; Schrenk, H. H.; Patty, F. A., and Sayers, R. R.: *Pub. Health Bull.* 211. *Studies in Asphyxia*. U. S. Treasury Dept., August 1934.
6. Himwich, H. E.; Fazekas, J. F., and Homberger, E.: *Effect of Hypoglycemia and Anoxia on Survival Period of Infant and Adult Rats and Cats*, *Endocrinology* 33: 96-101 (Aug.) 1943.
7. Windle, W. F., and Becker, R. F.: *Experimental Study of Asphyxia Neonatorum in Guinea Pig*, *Am. J. Obst. & Gynec.* 45: 183-200 (Feb.) 1943.
8. Kabat, H.: *Greater Resistance of Very Young Animals to Arrest of Brain Circulation*, *Am. J. Physiol.* 130: 588-599 (Sept.) 1940.
9. Yaskin, J. C., and Thorner, M. W.: *Effects upon Cerebral Cortex of Altitude Chamber Anoxia*, *Tr. Am. Neurol. A.* 69: 88, 1943.
10. Drinker, C. K.: *Carbon Monoxide Asphyxia*, New York, Oxford University Press, 1938.
11. Schreiber, F., and Gates, N.: *Cerebral Injury in Newborn due to Anoxia at Birth*. *J. Michigan M. Soc.*, 37: 145-150 (Feb.) 1938.
12. Schreiber, F.: *Apnea of Newborn and Associated Cerebral Injury*, *J. A. M. A.* 111: 1263-1269 (Oct.) 1938.
13. Little, W. J.: *Influence of Abnormal Parturition, Difficult Labors, Premature Birth and Asphyxia Neonatorum on Mental and Physical Condition of Child, Especially in Relation to Deformities*, *Tr. Obst. Soc., Lond.*, 1861, 3: 293-344, 1862.
14. Fender, F. A.: *Convulsive Phenomena Produced by New Method of Remote Excitation*, *Arch. Neurol. & Psychiat.* 45: 617-632 (April) 1941.
15. van Liere, E. J.: *Anoxia, Its Effect on the Body*, Chicago, University of Chicago Press, 1942.