CEREBRAL MANIFESTATIONS OF ANOXIA

A Review of the Literature

PART I

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The dangers of anoxia have been apparent since long before the discovery of surgical anesthesia. The immediate consequences of oxygen deprivation are sufficiently violent and spectacular to elicit prompt recognition and corrective measures. Asphyxial phenomena are associated with situations other than anesthesia in so many ways that not only the medical profession but the general reading public is constantly made aware of its dangers. Entire societies have been formed to teach the preventive and corrective measures necessary in accidental asphyxiation.

Smoke, poisons, gases other than anesthetics, drowning, varying atmospheric pressures, suffocation, diseases, and shock are among the multitude of causes of anoxia. The results of studies made in all of these phases of asphyxial incidents may be of value to the anesthetist in the specific study of anoxia associated with anesthesia. Particularly, the studies of anoxia in relation to aviation are of interest because from them the modifications of asphyxial signs that occur as the result of anesthesia may be determined.

Experimental Studies with Animals

Experimental studies of anoxia and its effect on the cerebral cortex produced a wealth of information, some of it contradictory. Yant et al. studied the neuropathy associated with carbon monoxide, carbon dioxide, and oxygen-deficient atmospheres. Dogs and rats were studied in atmospheres containing from 2.26 per cent to 8 per cent of oxygen for from eleven to twenty-five minutes (dogs) and twenty-four to seventy-two minutes (rats). There was marked difference in the susceptibility of the nerve cells to deprivation of oxygen; the cells of the cortex of the brain were most sensitive. Dogs asphyxiated by atmospheres deficient in oxygen died in less than thirty minutes.

Weinberger et al. found that following temporary arrest of circulation of the central nervous system, pathologic lesions were evident in animals after three minutes and ten seconds. Necrosis and softening of the cortex were followed by more severe damage as the time increased, liquefaction resulting after seven minutes.

Hartman, in considering the etiologic factors in cerebral anoxia, concluded that all lesions of the cerebral cortex, whether the cause is shock, sedation, or fever, are rather uniform when all factors are considered.

Gomez and Pike ligated the carotid and subclavian arteries of animals and found that "with the return of the circulation, dilatation of the pericellular lymph space and slight swelling of the cell body occurs, disappearing as recovery prog-
resses. Chromatolysis . . . induced by anemia is not necessarily fatal. . . . Neurones from different regions as well as neurones of the same regions differ in degree of resistance to anemia. . . . Failure to resuscitate animals after anemia of the central nervous system is probably due to the destruction of many of the cells of the vital centers (vaso-motor and respiratory) which do not have histological peculiarities by which they may be defined. Death, however, of a few cells of any center does not necessarily mean the total loss of function of that center since the remaining cells may be sufficient to discharge the functions of the center."

Gildea and Cobb, also studying the effects of anemia on the cerebral cortex in experiments on cats, found indications that periods of anemia of not more than ten minutes result in permanent injury to the cortex and not uncommonly in changes that end in death from convulsions or failure of the respiratory center.

Kessler et al., who studied the effect of anoxic anoxia on the central nervous system in rats, concluded that the effects were pharmacologic rather than physiologic. Thorner and Lewy produced repeated sublethal anoxia in guinea pigs and cats. They concluded that irreversible, summative lowering of the cerebral reserve followed repeated episodes of anoxia. Using pure nitrogen in their experiments they concluded that guinea pigs, immersed in an atmosphere deficient in oxygen, "behave in a somewhat stereotyped manner. There is usually an almost immediate increase in the respiratory rate. In from ten and fifteen seconds the animal becomes very active, in another 20 seconds the animal shows some arching of the neck and then slumps to the floor of the container. The retinal light reflex, ear, tongue and mucous membranes appear cyanotic. Spasmodic movements may be seen, varying from isolated chronic twitching to generalized convulsions. If the animal is immersed for more than one minute, it is usually apneic when removed and must be given artificial respiration. . . . Exposures to sublethal periods of pure anoxia lead to vascular and degenerative changes in the brains of guinea pigs and cats. Some of these changes are irreversible and become summated in animals repeatedly subjected to anoxia."

Weinberger et al., studying the effects of temporary arrest of the circulation of cats, found that, following three minutes and ten seconds or less of circulatory arrest, there were no obvious neurologic disturbances. After the circulation was arrested for three minutes and twenty-five seconds, alterations in behavior and psychic functions resulted. After six minutes' arrest, evidence of disturbances of vision and sensation of permanent nature resulted. Seven minutes and thirty-six seconds of circulatory arrest produced permanent and practically complete dementia: blindness, sensory, and auditory defects, motor and postural defects, and reflex abnormalities. When the arrest of circulation was prolonged to eight minutes and forty-five seconds, life could not be restored for more than a few hours.

**Experimental Studies in Human Subjects**

Haldane in 1919 discussed the symptoms, causes, and prevention of anoxemia. He concluded that "whenever a comparatively slight anoxaemia . . . is continued for several hours, the common result is
nausea, headache and general depression. . . . When the anoxaemia is more severe, the evidence of progressive damage becomes more and more marked, so that even when the cause of anoxaemia is completely removed grave symptoms may remain." This is only one of many discussions of the anoxic phenomena that have resulted from studies of oxygen deprivation in aviation.

McFarland102 (1932) studied air squadrons at partial pressures equivalent to altitudes of 17,000 to 28,000 feet. He found that simple sensory and motor responses were not seriously impaired until collapse. Choice reactions were impaired when oxygen was reduced to 11.43 per cent. Neuromuscular control was lost before capacity. Tremors and twitchings occurred. Memory was impaired at an average of 9.05 per cent oxygen and was in proportion to the extent of deprivation. Attention was greatly affected. Higher mental processes were affected; ideas became irrational or fixed and capacity for judgment and self criticism was lost. Slight oxygen deprivation produced stimulation of moods, followed by sleepiness, lethargy, and indifference. At 9.05 per cent, loss of ethical and moral habits occurred. Hysterical laughter, anger, or sleep was common. These reactions were compared to phases of alcoholism. These studies "tend to show the importance of one's basic physiological make-up in the formation of one's personality."

Actual cases of oxygen deprivation during flight have been reported. Among these are the report by Ward and Olson147 of a 21 year old aviator who was found unconscious and apneic after being deprived of oxygen at an altitude of 25,000 feet for thirty-nine minutes and at an altitude of 12,000 feet for an additional sixteen minutes. For eighteen hours after resuscitation he remained in coma. He then became alert, elated, and talkative. Logic, judgment, and memory were poor. On the second day he vomited. His mental state remained the same as the previous day. After seven weeks the mental state was entirely normal. Titrud and Haymaker144 reported three cases of oxygen deprivation during flight. A 21 year old aviator was found unconscious after a flight at 20,000 feet. Oxygen and artificial respiration were administered. Convulsions and delirium developed. Death occurred forty-eight hours later. Study of the brain showed widespread necrosis of ganglion cells. Damage was of such extent as to equal decerebration. A second incident involved a 22 year old aviator who was deprived of oxygen for a period of ten minutes during a flight at 24,000 feet. Oxygen and artificial respiration were administered. Convulsions developed on the ninth day. Death occurred on the twenty-first day after the episode of anoxia. Examination of the brain showed extensive damage. A third young man who was deprived of oxygen during combat was discovered one and one-half hours later, cyanotic and delirious. He recovered, but when he was transferred from the hospital three weeks later, he was severely retarded both physically and mentally.

Anoxia and Anesthesia

Cyanosis, asphyxia, and anoxia have been subjects of interest since before the discovery of anesthetics. Following the idea through examples of thought as they appear in the literature, wavering near and often far from the idea, the thread of the effects of anoxia during
anesthesia can be traced from the first publications on the subject of anesthesia.

W. T. G. Morton\textsuperscript{108} in his "Remarks on the proper mode of administering sulphuric ether by inhalation," published in 1847, said: "The vapor of sulphuric ether, as is well known, will not support life in its pure and unmixed state, being destitute of oxygen; and fears were entertained, when it was first applied to its present use, that, unless extreme care was taken to supply the patient with a large amount of atmospheric air, not enough oxygen would enter the lungs to decarboxylize the blood and change it from venous to arterial; venous blood would then be sent to the brain, and the patient die from asphyxia, in the same manner as when deprived of oxygen by immersion in water, or from any other cause." The subject was even part of the controversy. In his Memoir on Sulphuric Ether, also published in 1847, Morton\textsuperscript{108} wrote: "On that day [January 2, 1847], he [Jackson] called at the hospital with some oxygen gas as an antidote for asphyxia, which he heard was produced by the ether."

Snow\textsuperscript{146} in his book published in 1847 referred to stertorous breathing and commented that "I have, however, never known it to leave any cerebral symptoms afterward." He also presented a case of a man, 49 years of age, who developed spectral illusions for a week or two after operation. He had been given ether twice within twenty minutes. Snow had "not heard of anything of the kind after ether in any other case."

In 1887 Buxton\textsuperscript{18}, outlining the physiologic action of nitrous oxide gas, commented: "Whatever may be the saving of gas brought about by employing supplemental bags wherein the nitrous oxide is collected and re-inspired again and again, the patient suffers by their use from the double evil of breathing diluted and impure nitrous oxide, and further, is not favourably placed for exhaling the refuse of the lungs. I should incline to attribute to this method the cases one occasionally meets with of severe headache, vertigo, dizziness and other untoward symptoms consecutive upon nitrous oxide inhalation." He experimented on dogs whose brains during oxygen deprivation were observed through trephine openings.

Jackson\textsuperscript{81} (1894) conducted experiments on dogs to determine the cause of the intensification of lateral deviation of the eyes in a case of hemiplegia during chloroform anesthesia. He concluded that the phenomenon was the result of insufficient circulatory compensation of the brain.

Buxton\textsuperscript{18} (1897), reporting the death of a nurse during nitrous oxide and ether anesthesia for the extraction of teeth, warned of the dangers of oxygen deprivation and asphyxia. He made an additional observation that is still pertinent today: The accidents that occur during anesthesia often appear "in press but not in professional journals."

Hewitt\textsuperscript{74} (1899), in discussing deaths during nitrous oxide anesthesia, said that almost always deaths from asphyxia were the result of obstruction. He observed that "when nitrous oxide is administered free from oxygen, asphyxiial phenomena arise; obstructive stertor, convulsive muscular movement and cyanosis."

King\textsuperscript{87} (1904), following the recovery of two patients after apparent death under chloroform, concluded that deaths under chloroform
were not, as was usually thought, the result of cardiac failure but were respiratory in nature.

Miller\textsuperscript{104} (1912) investigated postoperative mortality from anesthetics and said that “Death during or following an operation is due to the anesthetic if the death would not have occurred under an ideal anesthetic.”

Warner\textsuperscript{148} (1915) pointed out that “perfectly normal color can be maintained while the patient is presenting all symptoms of asphyxia including convulsions.”

Barcroft\textsuperscript{7} (1920) said: “No degree of anoxaemia which produces a less effect than that of complete unconsciousness leaves anything more than the most transient effects; if the anoxaemia be pushed to the point at which the subject is within a measurable distance of death, the results may take days or weeks to get over, but only in the case of elderly or unsound persons is the machine wrecked beyond repair. . . . Just as acute anoxaemia simulates drunkenness chronic anoxaemia simulates fatigue. Another symptom frequently associated with mental fatigue is irritability.”

Grant\textsuperscript{69} (1923) after experiments concluded that anoxemia plays no part in the causation of tetany during hyperpnea.

Henderson\textsuperscript{72} and many others have persistently preached the doctrine of asphyxial phenomena and their prevention.

Others have explored the postanesthetic phenomena, often approaching but also often overlooking the role of anoxia (Kaye\textsuperscript{84,\textsuperscript{85} Miller,\textsuperscript{108} Nelson\textsuperscript{111,\textsuperscript{112}}).

Macklin\textsuperscript{97} (1931) concluded that “neither practically nor theoretically can a carefully controlled anoxaemia be regarded as a contra-indication to [the use of nitrous oxide].”

Moore\textsuperscript{107} (1934) stated that the presence of cyanosis “is no indication of actual danger, nor is its absence a sign of entire safety.”

Raginsky and Bourne\textsuperscript{121} (1934) expressed the opinion that the 80:20 mixture of nitrous oxide and oxygen is insufficient for some human beings.

Flagg\textsuperscript{41} has been among a group of persistent writers on the subject of prevention of asphyxia.

Harris\textsuperscript{69} (1937), as well as others, made a vigorous statement in behalf of adequate oxygenation. “Anoxia, employed in anaesthesia can only be looked upon as an additional burden thrown upon the tissues of the body already subjected to the unphysiological strain of the anaesthetic agent. One must therefore conclude that the use of anoxia as an adjuvant in anaesthesia is unsound, while the Secondary Saturation of McKesson is to be heartily condemned.”

Lawrence\textsuperscript{100} in 1937 suggested that percentages of oxygen sufficient to meet metabolic requirements were necessary to safe nitrous oxide anesthesia.

Bennett and Seevers\textsuperscript{117} (1937), studying anoxia in human subjects, concluded that “Experimental studies . . . substantiate the common clinical observation that anoxia is a necessary accompaniment of deep anesthesia with nitrous oxide in the subject who has not received previous depressant drug medication.”

The specific designation of the role of anoxia in cerebral damage following anesthesia was brought to the attention of anesthetists in 1936 in a monograph by Courville.\textsuperscript{26} In the introduction he stated: “On the basis of the evidence at hand, it seems evident, therefore, that varying degrees of anoxemia do exist and are necessary in the production of anesthesia with nitrous oxide and
that cellular asphyxia strongly reinforces any direct narcotic action of the gas. As the higher concentrations of nitrous oxide are reached, there always exists the danger of irrevocable damage to the brain. Should even a transient respiratory and circulatory failure occur under anesthesia, asphyxia of the cortical nerve cells occurs after the utilization of the small amount of available oxygen." Continued evidence seems to indicate that the foregoing statement could be modified to include other anesthetics.

Gellhorn⁶⁰ (1937) reported experiments on the effects of anoxia. "Systematic investigations were carried out in which the influence of oxygen deficiency, excess of carbon dioxide and voluntary heavy breathing (hyperpnea) were studied in relation to various sensory functions, motor coordination, psychic processes, and subcortical reflexes. As to the sensory functions which were mediated by the cortex, it was found that auditory acuity and visual intensity discrimination were greatly decreased under all three conditions. Similar results were obtained with respect to visual after-images. Various psychic processes, such as formation of associations, the cancellation of a number (Bourdon's test), the addition of two digits (Kraepelin's Test), were investigated with respect to the effects of the three factors mentioned above, and here it was found again that under all three conditions the psychic processes were influenced in a similar fashion. There were only quantitative differences, the changes produced by oxygen deficiency being most severe. . . . All the phenomena were, in most cases, more or less immediately reversible upon readmission of air. . . . In contradistinction to these results it was found that the physiologic processes involving the lower part of the brain (brain stem) and not the cortex, showed a different reaction. . . . These investigations seem to indicate that the psychic processes are cortical phenomena which depend on and are modified by the same physiologic factors which influence ordinary physiologic processes."

In discussing cerebral anoxemia Soley and Jump¹⁸⁸ (1939) stated: "Judging from the usual pre-operative case history . . . it is not generally considered important to question the patient as to incidents which could have resulted in anatomical changes due to asphyxia . . . Even though one were to attempt to elicit a history of asphyxia from a patient, it would be difficult to be sure that the history was reliable."

Behrend and Riggs¹⁰ (1940) discussed predisposing factors, prevention, and treatment of cerebral complications following operation. "In the cases studied by us, anoxia was usually secondary to acute general circulatory collapse precipitated by administration of an anesthetic plus the trauma of operation in patients whose margin of circulatory reserve had been reduced."

Wynne¹⁶⁰ (1940) studied the relation of cyanosis and anoxemia and prepared a chart showing the relation of blood components to cyanosis.

Some authorities maintain that undesirable effects of nitrous oxide anesthesia are a manifestation of a toxic action of nitrous oxide, while others contend that such effects are the result of anoxia. Murphy¹¹⁰ (1940) affirmed the latter opinion: "It has been accepted by clinical anesthetists . . . that nitrous oxide is neither toxic, in the ordinary sense, nor is it irritating to the tissue. . . . The abandonment of the secondary saturation techniques, the
promiscuous use of nitrous oxide by unskilled attendants . . . and the 'pushing' of nitrous oxide in surgical cases, will soon prove that asphyxiation not anesthesia with nitrous oxide is responsible for the untoward effects which recently have been receiving attention."

The work of Waters\textsuperscript{155} (1940) (1944) exemplified the increasing interest and concern of anesthetists in the subject of anoxia in relation to anesthesia. McCarthy,\textsuperscript{99,100} (1941) (1942) also emphasized the interest in the dangers and prevention of anoxia. "There is a real danger that serious complications may be produced by anoxia incident to nitrous oxide anesthesia. This is always an indication of technical error that may be avoided by proper care in administration and by close observation of the patient for signs of oxygen want."

Batten\textsuperscript{8} (1942) in discussing the hazards of hypoxia suggested that: (1) the avoidance of the promiscuous use of respiratory depressant drugs, (2) administration of not less than 20 per cent oxygen with nitrous oxide, (3) maintenance of normal levels of respiration, pulse, and blood pressure, (4) postanesthetic care, (5) oxygen inhalations when signs of hypoxia appear, and (6) curtailment of the use of spinal anesthetics would reduce the dangers.

Horvath et al\textsuperscript{177} (1943), in studying schizophrenic patients subjected to reduced oxygen concentrations to the point of unconsciousness, concluded that "anoxia severe enough to produce brief periods of unconsciousness has no lasting harmful effects on the central nervous system."

**Postoperative Psychosis**

The search for the cause of the cerebral sequelae of operations has included study of factors other than anesthesia. Postoperative psychosis has been recognized as a complication of operations since before the discovery of surgical anesthesia. Ambrose Paré mentioned the occurrence of mental symptoms after operations.

Some of the causes of psychotic episodes have been variously stated as familial tendencies, drug allergy, fever, fear, worry, epilepsy, sepsis, senility, and hysteria.\textsuperscript{3,123} Psychoses are known to have followed the use of many drugs without the addition of surgical intervention. Among the many drugs known to have produced such episodes are a group often used in treating conditions before or during anesthesia. Gage-Day\textsuperscript{46} (1909) listed among other drugs which caused acute toxic insanities, chloral, morphine, alcohol, chloroform, ether, and paraldehyde. Danziger\textsuperscript{26} (1945) listed the compounds that have been known to cause symptoms of mental disorders in man. He stated: "It is suggested that anoxia is a sufficient and perhaps a necessary condition for the development of abnormal behavior."

Da Costa\textsuperscript{25} (1910) included among other causes of postoperative psychoses the possibilities that the "anesthetic may poison" the patient and that disturbances of cerebral circulation may occur.

Woltman\textsuperscript{157} (1939) in commenting on postoperative neurologic complications said: "Immediately, or several days after operation, lead-pipe rigidity may develop in the patient. It is a serious omen that some patients slip into this state and out of it again and recover. . . . A somewhat similar condition, but resembling decerebrate rigidity, has been observed after spinal anesthesia in which the usual dose has been administered to a patient who has profound anemia. . . . [The com-
monest type of psychosis] does not begin immediately after operation but begins after an interval of about five days and lasts for about two weeks. . . . It seems significant that when the psychosis is a "postoperative psychosis" in the restricted sense of the term, anesthesia is almost always by inhalation and usually includes ether. . . . Most postoperative mental disorders . . . belong to the restricted group of postoperative psychoses. Next in frequency is the group which may safely be called toxic-infective-exhaustive psychoses, in which the psychoses immediately preceding and following operations usually are included. These in turn are followed by the deficiencies, the manic-depressive group and finally by the senile, schizoid, epileptoid, mentally unstable and other groups."

Doyle, 82 (1928), in reporting twenty-eight cases of postoperative psychosis, suggested that the term "post-anesthetic psychosis" be used for disturbed mental conditions which immediately follow operation and that the term "postoperative psychosis" be used for mental disturbances which occur after a normal interval has followed the operation.

That anoxia as the cause of cerebral damage is not accepted unequivocally is attested by the number of cases reported in which causes other than anoxia are given for various sequelae of anesthesia. This is probably as it should be, for it is apparent in reading large series of articles that authors are often so engrossed in riding a special hobby, propounding a favorite theory, or expounding the merits of certain drugs or methods that they are carried away from the real import of the events which they are recording. Because of the recent emphasis on anoxia, it requires courage to mention factors other than anoxia in reporting unusual postoperative complications.

Edwards and Warrick, 85 (1947) cautioned against overemphasis of anoxia. "True coma may occur after an anaesthetic in which anoxia has been present. . . . It is necessary to recognize the occasional occurrence of functional cases, as energetic physical treatment, so important in the curable cases of organic lesions, is likely to do the patient more harm than good."

An incident reported by Belinkoff, 11 (1949) illustrates this point. A child, aged 5, was given avertin and ether-oxygen in preparation for bronchography. A convulsion preceded the operation. It was relieved by 4 cc. of 2½ per cent pentothal sodium. One hour and forty minutes later she seemed to be awake but was screaming and throwing her head against the pillow. "This was of great concern to the attending physicians, who thought her condition resembled that of a decerebrate and permanent brain damage from the convulsion and associated anoxia might have occurred. However, reassurance from the nurses and family that this was merely the reaction of a spoiled child led [the physicians] to leave her completely alone. After several hours of studious neglect, she quieted down to normal. Her family stated that she was perfectly normal and that they could notice no personality changes."

Another case in point is that of Hirshfeld, 78 (1941): "It is only quite recently that attention has been focused on cerebral damage from anesthesia as a possible cause of post-operative mortality. Before the anesthetic itself can be denounced as the cause of post-surgical coma, the more common renal, metabolic and pulmonary
complications must be excluded. . . .” In a case of coma following a period of respiratory arrest during nitrous oxide-oxygen anesthesia, amphetamine was administered after other therapeutic measures had failed to rouse the patient. “Forty-eight hours after the institution of therapy, she responded rationally to conversation. . . . The patient went on to an uneventful recovery. No neurological or cerebral sequelae manifested themselves after the disappearance of the coma. . . . Seven weeks after operation, the patient was completely symptom-free and revealed no sign of any cerebral damage.”

Adams, in 1894 concluded that idiosyncrasy to nitrous oxide was the cause of a death. The brain did not reveal abnormalities of the cerebral substance. Status thymico-lymphaticus (Davies), thymus (Owens), status epilepticus (Healy), chronic encephalitis (Ginker and Walker), carotid sinus (Downs), and acidosis (Ross) are among the causes ascribed by the authors to episodes that might well be placed in the category of anoxic phenomena. Uremia, senility, diabetes, and other diagnoses have been made in cases of postoperative coma and psychosis.

As the concept of cerebral damage from anoxia became clearer, there began to appear a series of reports discussing the phenomena, experiments specifically designed to study them, and reports of cases. Cases previously reported were reclassified. From the time of Courville’s monograph in 1936, in which he reported incidents accompanying nitrous oxide anesthesia, reports have been made that incriminate most of the anesthetic agents being used.

A chronological listing of these reports is made to show the development of the concept. Articles are reported here without attempt to categorize them according to anesthetic agent or to separate discussions from case reports. Pertinent comments were often included with case reports. Since some of the cases of convulsions during anesthesia present a clinical picture comparable to those classified under anoxic sequelae, these have also been included in this sequence.

Among the early reports is one case which may have been the result of oxygen deprivation. Stanley, (1842) reported a case in which, after ten inspirations of nitrous oxide, a young man experienced only slight effect. He again breathed gas, and a series of violent muscular motions resulted which lasted for ten minutes. Alternate violent muscular exertions and intermissions continued for one half hour. He recovered in a day or two during which he had throbbing sensations in the forehead. Stanley reasoned that impure gas had been made and was the cause of the difficulty.

Ashford reported an incident in which a young woman was unconscious for two hours following nitrous oxide anesthesia for a dental extraction. Headache persisted but the patient started for home. She became faint and dizzy and recalled nothing further until the following day when she found her left arm useless. Pain in her head continued, and at times she was delirious. There were motor and sensory changes involving the left part of the face, tongue, and upper and lower extremities. Later typhoid fever developed. The patient recovered. The author questioned whether the nitrous oxide might have produced “congestion
of the brain and diffusion into its ventricles or tissues," or whether this case might verify the truth of the contention that "typhoid fever is essentially a nervous fever." Four months after the anesthetic the patient walked with ease, her face was unaffected, and headache had disappeared.

Warner149 (1882) reported a case of twitching at the right angle of the mouth and of the hand of a patient during nitrous oxide anesthesia for dental extraction. The patient regained consciousness quickly.

Buxton14 (1887), experimenting on human beings to determine the cause of ankle clonus during nitrous oxide anesthesia, concluded that: "Whatever view we adopt with regard to ankle clonus, we have to further explain how, under nitrous oxide the cerebral-spinal axis, the peripheral nerves, or the muscles, become so altered that this phenomena can appear and vanish with recovery from brief narcosis. . . . Rhythmic jerkations attend nitrous oxide administration in a certain number of cases. The clonic and tonic contractions, it should be observed, so occurring are quite different from the irregular convulsions, the result of stimulation, brought about by asphyxia. . . . Ankle-clonus . . . is dependent upon changes, probably of an irritative character, occurring in hypertonic muscle, and brought about by like changes in the whole nervous system."

Savage128 (1887) discussed postoperative insanities. He outlined the course of the disorder in the following manner: "Any cause which will give rise to delirium may set up a more chronic form of mental disorder quite apart from any febrile disturbance. (a) The most common form of mental disorder which comes on in such cases is of the type of acute delirious mania; (b) though such mental disorder is generally of a temporary character, it may pass into a chronic weak-mindedness, or it may pass into (c) progressive dementia which cannot be distinguished from general paralysis of the insane." In addition he reported that he had seen cases of insanity after all anesthetics. He reported five cases, three of which could probably be included in the group under consideration:

Case 1.—A man, aged 26, with a family history that included nervousness and insanity and who had an alcoholic tendency, developed an acute mania. He was given chloroform for examination of an injured hand. An acute manic episode followed his recovery from anesthesia. He recovered.

Case 2.—A woman, aged 21, with an acquired neurosis had had one acute maniacal episode from which she recovered. Chloroform was administered for an examination. Acute insanity followed.

Case 3.—An elderly man was given an ether anesthetic during which no unusual episode occurred. When he recovered, his mind was affected. He acted "half-drunk." He eventually recovered and became mentally alert.

Case 4.—A young woman, after transfusion and stimulants after the birth of a child ten years previously, had developed hysterical attacks and a tendency to use alcohol excessively. She had had one acute attack of dementia. Nitrous oxide was given for dental extraction. A maniacal outbreak followed the recovery. She never regained her senses or recognized her friends. She became "silly and fat."

Case 5.—A woman was aneste-
tized (agent was not mentioned) for removal of a simple breast tumor. "At once after the operation she was noticed to be changed in character, irritable and exciting, unstable, with weakened control and loss of memory." Tremors, hesitant speech, defective memory, and unequal pupils persisted until death five months later. The post-mortem examination showed "wasting of brain, with excessive fluid, adhesions of membranes to the cortex." The author mentioned that another such patient was under his care.

Homans (1889) reported two cases of dementia following ether anesthesia for amputation of the breast, the patients being ages 35 and 50. The symptoms in each patient were the same. After operation a period of "euthanasia" existed for two days; on the third day the patients became excited; the mind wandered. This state persisted until the fifth day when it appeared that the "mind was gone." Excited babbling and delirium lasted for one week. Both patients were "well mentally thereafter." Both were from nervous families.

Gorton (1889-90) reported two cases. A boy, aged 14, of good mental capacity became maniacal following tardy recovery from ether which was administered for extraction of teeth. There had been no episode of unusual nature during the course of anesthesia. Later it was reported that he "did not appear like himself." Eventually he became somewhat "demented." The second case was of a woman, aged 22, of good intelligence. Ether was administered for dental extraction. More than two hours elapsed before she recovered. After wakening she became dull and indifferent. Later she became irritable, self conscious, and "dramatic" in her actions. Fourteen months later she became hysterical and maniacal. This acute phase gradually subsided.

De Forest (1897) reported the case of a woman, aged 51, who was given ether for the removal of a lump from the breast. The evening after operation the left arm and leg could not be used. She could speak only with difficulty. She became progressively worse until death on the sixth day. The rectal temperature rose to 103 F.

Garrigues (1897) in discussing paralyses that followed anesthesia reported four cases of lameness. He said: "Anaesthesia-paralysis of central origin is much rarer than that of peripheral origin and is rather obscure. It may be due to cerebral apoplexy or emboli; either of which would produce ischaemia in the surroundings and secondary softening of the brain." He mentioned the case of an old woman who was given chloroform for one hour. Acute mania followed. The author recommended avoidance of operation on the aged and avoidance of prolonged operation to prevent this complication.

Green (1901) reported an incident in which gas was administered, using Barth's inhaler and allowing plenty of air. A few minutes after the patient recovered consciousness, numbness of the hands, legs, and feet was experienced. The hands were pronated, the fingers slightly flexed, and the thumb adducted. Respirations were rapid and stridorous. His color was excellent; he was restless and unable to articulate. These symptoms continued for more than twenty minutes. The man was not hysterical.

Lamb (1903) reported a case of respiratory arrest during chloro-
form anesthesia lasting one and one-fourth hours. An "intracranial condition being suspected," and a trephine exploration of the cerebellum was made with negative findings. The patient began to breathe after vigorous treatment including tracheotomy and galvanic current. The respiratory arrest recurred thirty hours later. The postmortem examination disclosed a "small cerebellar abscess."

Gabriel\(^\text{45}\) (1905) reported a case of paralysis of the soft palate with swallowing difficulty following nitrous oxide anesthesia.

East\(^\text{83}\) (1908) recorded a case of a patient, aged 21, with no history of previous mental instability who was given ether for forty minutes for extraction of teeth. Mania immediately upon recovery was followed by sleep. Upon awakening the maniacal state recurred. The temperature was elevated to 102 F. On the fourth day after the episode, he was quieter. Recovery was uneventful.

Ross\(^\text{125}\) (1921), in discussing acidosis following operation, briefly outlined the clinical picture presented by these patients "which varies in severity from those showing rather prolonged nausea and vomiting, headache, and slight restlessness, to those cases in which the patient rouses from the anesthetic only to lapse into a rapidly deepening coma, with rising temperature, pulse and respiration rates and with death supervening within twenty-four to forty-eight hours."

Caine\(^\text{47}\) (1932) reported four cases, one patient dying on the operating table. Three survived for varying periods. A woman, aged 39, became apneic during nitrous oxide anesthesia. The saturation technic was used. Cardiac failure occurred; resustitutive measures produced resumption of cardiac and respiratory function. The patient responded without regaining full consciousness but died during the first day. A second patient, a woman, aged 58, was anesthetized by the saturation technic with nitrous oxide and oxygen. Cardiac failure was overcome by cardiac massage. She recovered six hours after operation. Visual disturbances, vomiting, and restlessness were present. The course was progressively downward until her death two months later. The third case was of a woman, aged 37, in whom respiratory and cardiac failure occurred during a laparotomy under nitrous oxide-oxygen-ether anesthesia. After three years she could speak unintelligibly; blindness and paralysis persisted beyond six years. In commenting on these cases the author said: "Restoration of the heart’s action and respiration does not mean that the patient is all right, but there are likely to be degenerative changes in the brain that are irreparable. Restoration of consciousness and apparent normality after the heart has stopped under these circumstances does not mean that there is no permanent damage to the brain that will be manifested later. The human brain cannot stand the suspension of circulation and return to normal as can the brain of the dog."

Atkeisson\(^\text{5}\) (1923) reported one case of a woman, aged 25, who was anesthetized with nitrous oxide and oxygen for an examination six weeks after an accident and delivery of a premature baby. During the course of anesthesia, respiration ceased for fifteen minutes. She wakened in delirium and remained incoherent, mumbling, and crying until death twenty-four hours later. Examination of the brain was not done.
McCordie and Featherstone\(^{88}\) (1926) reported two incidents that occurred in the same operating room, the patients dying within an hour of each other. The first was a woman, aged 60, who was given \(E_2C_1\) mixture with a “little ethyl chloride” for amputation of a breast. After twenty-five minutes of anesthesia, respiration ceased. Respirations became spontaneous fifteen minutes later. She did not recover from the anesthetic and died twenty hours later without regaining consciousness. The temperature was 106 F. Postmortem examination showed cerebral softening—thrombosis of basilar arteries and the sylvian arteries. Metastatic lesions and recent hemorrhage involved the right half of the cerebellum. The second patient, a man, aged 48, was anesthetized following perforation of a duodenal ulcer. \(E_2C_1\) mixture was used for the induction during which the patient struggled for four minutes. Oxygen was administered because of cyanosis. Twenty minutes after induction the color was improved, but the respirations were jerky and then ceased. Heart action ceased. Artificial respiration, cardiac massage, and intraventricular injection of adrenalin resulted in return of cardiac and respiratory function three or four minutes later. Respirations remained spasmodic for an hour and twenty minutes. Diagnosis of hemorrhage in the area of the pons varolii was made. Death occurred five and one-half hours after restoration of respiration. Postmortem examination showed the brain to be edematous; vessels of the pons and the floor of the sylvian aqueduct were congested.

Glynn\(^{88}\) (1926) reported one case: “An apparently healthy lad was anaesthetized with nitrous oxide and the stump of a molar tooth extracted. He never recovered consciousness and died in thirty-seven hours. . . . The administration of the anaesthetic and the extraction took a minute, or slightly more. The patient began to recover, . . . but soon went ‘nasty color, then black’ and collapsed. [Convulsions began several hours later. The necropsy revealed that] the brain was congested and contained a few punctiform hemorrhages; . . . the lungs showed moderately extensive lobar pneumonia.”

Clement\(^{18}\) (1926) reported three cases in which convulsions followed periods of anoxemia after anesthesia. He advanced the opinion that so-called ether convulsions are probably due to anoxemia. A young man had convulsions after an anesthetic of nitrous oxide, ethylene, and oxygen. Percentage of oxygen had been low (4-6 per cent). He recovered. A child, aged 7, had convulsions during anesthesia; oxygen was given, and the child recovered. A child had convulsions during nitrous oxide anesthesia; frequent additions of oxygen controlled the convulsions, but at the close of the procedure, in spite of oxygen, convulsions became so severe as to interfere with breathing. Bromides and atropine were administered; the child recovered.

Evans\(^{38}\) (1928) reported seventeen cases of anoxemia in which inhalations of oxygen overcame the difficulties except in three of the patients who did not recover.

Weber\(^{151}\) (1931) reported a case of a boy, aged 14, who could not see or hear in a conscious way. A diagnosis of decerebrate automatism was made. At the age of 2 years the child had convulsions during ether anesthesia given for appendectomy. The child had been normal before
the operation. The convulsions lasted for twenty hours and thereafter occurred at frequent intervals. In commenting on this case the author said: "It seems as if the nerve cells of the whole cerebral cortex that are concerned in the voluntary movements and conscious perception of all kinds have been selectively destroyed in a way analogous to that in which the glandular cells of the whole liver have sometimes been more or less selectively destroyed in cases of acute hepatic atrophy following chloroform anaesthesia. It is just possible that, with the convulsions there may have been a diffuse bilateral sudden haemorrhage to the cerebral cortex."

Yaskin\textsuperscript{182} (1931) recorded an incident in which "immediately after an instrumental delivery a previously healthy woman presented an acute and diffuse involvement of many regions of the brain, particularly striking was the involvement of the supranuclear structures concerned with articulation and swallowing, disturbances of consciousness, transient blindness, general increased tonus in the musculature with increased reflexes, myoclonic movements of the extremities and transient weakness of the extra-ocular muscles. These phenomena were accompanied by a febrile course and a serious constitutional reaction with no evidence of meningitis. There followed a rapid recession of symptoms with residues pointing to a slight but permanent damage to the extrapyramidal system." Nitrous oxide was used. The baby appeared normal in color.

Landau and Wooley\textsuperscript{89} (1934) reported a case in which restlessness, giddiness, spots before the eyes, and photophobia followed evipal gas-oxygen anesthesia. On the fifth day headache, nystagmus, and vomiting developed. The symptoms cleared on the eighth day, and recovery thereafter was uninterrupted.

Quaste\textsuperscript{119} (1934) studied the effects of oxygen deficiencies and remarked that "the similarity between the psychological reactions following oxygen want and those found in light narcosis, and the resemblance of these to the reactions found in certain types of mental disorders have attracted a number of investigators. It has become a likely hypothesis that certain forms of mental disorders may find their origin in a physiological state corresponding to anoxaemia."

Lennox et al\textsuperscript{92} (1935) concluded: "Neither sleep nor epileptic seizures are due to reduction in the total cerebral circulation. . . . In man unconsciousness supervenes if the oxygen supply to the brain is suddenly reduced to such an extent that the oxygen saturation of the blood in the internal jugular vein falls to 24 per cent or below."

Courville\textsuperscript{50,22} (1936) (1939) reported thirteen cases, in nine of which the condition was fatal. The case summaries are quoted:


"Case 3. Convulsive seizures and coma following administration of nitrous oxide anesthesia for extraction of teeth. Death after two and a half days."

* * *


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"Case 5. Respiratory failure under nitrous oxide-oxygen anesthesia for curettage of chronic osteomyelitic focus of right tibia. Residual coma and generalized muscular twitching with decerebrate rigidity. Death after four days and seven hours."

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"Case 9. Extraction of teeth under nitrous oxide-oxygen anesthesia. Transient respiratory failure followed by convulsions and coma for 24 hours. Improvement in mental status for several days. Complete blindness followed by deep coma and death in 26 days after onset."

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"Case 11. Residual lenticular syndrome in a patient surviving an anoxemic episode after nitrous oxide anesthesia eight years before."

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A review of the subject of asphyxia following nitrous oxide anesthesia, extensive discussion of the pathologic changes in the brain, and case histories make up a monograph of which the summary is quoted here:

"This study is concerned with the problem of cerebral asphyxia or anoxia as a result of nitrous oxide anesthesia. It is based upon clinical and pathologic observations in a series of 13 cases, 9 of which terminated fatally. In all the fatal cases an autopsy was obtained and
a more or less critical examination of the cerebral tissues was made.

"Cerebral manifestations following inhalation of nitrous oxide have been recognized for almost a hundred years. The immediate nervous manifestations usually consist of generalized convulsive seizures, muscular rigidity and persistent coma, at times terminating fatally with signs of 'decerebrate rigidity.' Delayed symptoms may occur in the form of a psychosis, a parkinsonian symptom-complex or disturbances of special sensation, particularly in the form of a partial or complete amaurosis. The patient may recover entirely after an anoxemic episode, may survive for a variable period with residual symptoms or may die within a few days. In fatal cases, death usually occurs within 2 to 7 days, but may occur only after an interval of weeks or months. Examples of each of these variations are to be found in the series of cases described herewith.

"Anoxemia following administration of nitrous oxide may be the result of an impure gas, a faulty apparatus, or a preexisting or suddenly developed pulmonary lesion. The possibility of faulty administration of the anesthetic and of individual idiosyncracy to this gas are also to be considered. Several factors may be present in a single case, all contributing to production of the cerebral lesion. Regardless of the exact source of the trouble, the clinical symptoms and the pathologic findings are the effect of asphyxia and are not due to any toxic effect of nitrous oxide itself.

"The mechanism in most instances seems to be one of two types,—(a) sudden circulatory and/or respiratory failure with consequent cerebral damage due to the immediate utilization of the remaining small amounts of available oxygen or (b) prolonged exposure of the brain to a dangerous degree of oxygen want.

"The resulting cortical lesion necessarily depends upon the degree of anoxemia and its duration. There may be (a) a sclerosis of scattered pyramidal cells, (b) an occurrence of discrete pale areas (Herde) in the cortex, (c) a patchy necrosis of superficial, intermediate or deep, or all cortical layers, (d) a subtotal destruction of the cortex, or if the patient survives for a sufficient interval, (e) a vascular scar may result due to the formation of new blood vessels. Changes in the nerve cells may be described as (a) sclerotic, (b) acute degenerative, (c) ischemic, and in chronic cases (d) 'calcified' nerve cells. Lipoidal degeneration (e) is also a common form of cellular change. The microglia develop into compound granular corpuscles in the presence of necrosis. The astrocytes adjacent to the necrotic areas undergo proliferation to aid in the formation of the astro-vascular scar. The oligodendroglia undergo acute swelling and variable degrees of proliferation, particularly in the subcortical white substance. The arachnoid and pia may show cellular proliferation, and adhesions between these two membranes may take place.

"The lenticular nucleus seems to be affected to about the same degree as the cerebral cortex, and essentially the same architectural and cellular changes are found. Small globules of calcium are commonly observed in the small blood vessels in this structure similar to those found in carbon monoxide poisoning. The Purkinje cells of the cerebellar cortex are quite markedly altered.
"A study of the brain in fatal cases discloses several interesting facts. Not all portions of the cortex are uniformly or symmetrically involved. This no doubt explains the variable clinical picture found in those cases surviving for several weeks or more. While it is possible to predicate the character of the lesion from the clinical history, one cannot always be sure of the severity of cortical damage. This is due to the great difficulty in evaluating all the possible causative factors. The earliest lesions are found about the pericellular and pericapillary spaces, which would suggest that the injury is a result of 'tissue respiration',—a disturbed carbon dioxide-oxygen exchange between the tissue fluids and the cellular elements.

"This condition, hitherto not critically studied from a clinical and pathologic standpoint, demands further investigation. A careful analysis of all possible factors should be made at the time an accident occurs under nitrous oxide anesthesia to determine if possible the cause of the trouble. A detailed study of the brain should be made in every fatal case. The ultimate changes taking place in the brain after prolonged survival period are as yet unknown."

Courville21 (1936) reported on one of the cases from his previous study in which the patient with residual lenticular syndrome continued to improve three years after the former report.

Lowenberg et al195,96 (1936) (1938) reported three cases of cerebral cortical and basal ganglion destruction and an additional case in which clinical evidence of a similar process was apparent. In one case after ten minutes of respiratory arrest rigidity and tremor occurred. Continued unconsciousness, pyrexia, loss of tendon reflexes, rigidity, and tremor progressed until death sixty hours after the onset. Necropsy disclosed severe injury of the cerebral cortex, basal ganglion, and midbrain. A second patient, in whom respiratory arrest occurred during nitrous oxide anesthesia, died seventy-two hours after the episode. Examination of the brain showed severe damage of the cerebral cortex and basal ganglions. In case 3 cardiac and respiratory arrest occurred after one hour of nitrous oxide anesthesia. Pyrexia, twitchings of the left hand, rigidity, and coma lasted until death 119 hours later. The brain showed damage similar to that in the preceding cases. The fourth patient had similar symptoms several hours after operation. He recovered. Six and one-half years later there were signs of residual neurologic damage. There was no impairment of mentality. The author's comment was: "The histologic picture suggested that the destruction of the brain is due to the toxic action of nitrous oxide on the parenchyma. A definite selective destruction is noted, the cortex and the basal ganglion being much more severely damaged than the brain stem and the cerebellum, resulting in a clinical picture of decortication. Destruction of this type is frequently a toxic manifestation and similar findings have been noted in the cases of poisoning by excessive doses of pantopon, morphine, and ergoapiol. Therefore, death may be due to extensive destruction of the cortex and basal ganglia rather than to involvement of the respiratory area per se."

Ford et al144 (1937) reported one case of extensive injury to the cerebral cortex.

O'Brien and Steegman118 (1938)
reported one case in which death occurred sixteen months after the administration of nitrous oxide anesthesia. During those months there was never a return to the conscious type of mental activity. Marked degenerative changes in the brain were evident.

Gebauer and Coleman (1938): A woman, aged 29, was anesthetized with cyclopropane by the carbon dioxide absorption technic for two hours and thirty-five minutes. Moderate shock developed. She was stuporous four hours after operation. Thirty-six hours postoperatively mild convulsions, coma, and cyanosis developed. There were no definite neurologic findings. Muscle rigidity was apparent on the fifth day. She remained unconscious until death on the seventh postoperative day. Autopsy showed "extensive degenerative process of the cerebral cortex."

Abbott and Courville (1938) reported an episode in which a woman, aged 37, was given nitrous oxide and oxygen for fifteen minutes, then ethylene, oxygen, and ether. There was marked cyanosis at the time the anesthetic agents were changed, and irregular respirations for the remaining forty-five minutes. Very little ethylene was given. Coma persisted for two days postoperatively. Retardation of voluntary speech, frontal headache, faintness, and disorientation developed later. She died on the forty-second day. Following autopsy the authors commented it seemed that the "globus pallidus of the lenticular nuclei is the most sensitive part of the brain to the effects of asphyxia."

Stewart (1938) presented a case "in which apnea occurred during nitrous-oxide and oxygen anesthesia, causing widespread destruc-
probably as a result of an asphyxial episode associated with the administration of an anesthetic agent. Some of these patients had been given a general, spinal or local anesthetic for relief of pain during a surgical procedure. Others had been anesthetized through the placental circulation, the mother receiving anesthesia to abolish the pain of childbearing. Most of the cases in which severe neurological symptoms appeared following anesthesia were thought to fall into the anoxic anoxia group. . . . Unless the anesthetist can recognize cerebral asphyxia in the absence of cyanosis and remedy the situation, the consequences may be grave. . . . While the neuropathologist can report only what he sees under the microscope, it is most significant that in those cases in which death has been delayed a few hours or more following nitrous oxide asphyxia, there can be demonstrated a diffuse degeneration of the brain tissue. The determination of the etiology of this brain change must be left to the clinician who observes these cases while still living and is familiar with all the circumstances of the individual case. . . . A catabolic type of anoxic anoxia also plays an important part in cerebral alterations associated with anesthesia. Although the oxygen supply may be normal, intrinsic or extrinsic factors may increase the demand of the tissues to the point where this demand cannot be fulfilled. In these cases, drugs which depress the respiratory mechanism are thought to inhibit the integration between increased oxygen demand and the available oxygen supply. . . . For every degree of fever there is a corresponding increase of at least 7 per cent in oxygen demand. Several of the cases under discussion were children with high temperatures at the time of operation who began having generalized convulsions immediately following operation or on the operating table during nitrous oxide-oxygen-ether or ether anesthesia. . . . It is of utmost importance to keep up the blood volume during operative procedures in order to avoid anoxic brain changes. In the integration necessary for adaptation to lowered blood volume and anemia . . . the amount of oxygen supplied with the anesthetic must be increased to meet the changing conditions in the patient’s internal environment or cerebral tissue will succumb. . . . Excessive preoperative medication may set the stage for cerebral anoxia because the respiratory and cardiac centers, depressed by drugs, cannot function properly to meet varying oxygen demands of cerebral tissue during anesthesia. . . . Any imbalance in the neurohumoral chemistry of cerebral cells must be taken into account. . . . Dehydration, hypoglycemia or hyperglycemia, deficiencies in calcium, potassium, or phosphorus can inhibit the ability of the cell to utilize oxygen and in this way initiate a destructive anoxia. . . . In 5 patients with cerebral changes following spinal anesthesia, . . . large doses of pre-operative medication had been given in each instance. . . . It appears that in rare cases even local anesthesia may set up a histotoxic anoxia, leaving cerebral devastation in its wake.”

Steegman138 (1939) reported four cases, in the first of which a man, aged 37, was given avertin (100 mg. per kg.) in preparation for encephalography. Collapse was followed by a twenty-four hour period of restlessness. Spasticity developed. He remained unconscious until death ninety-six hours after the episode. Extensive diffuse defects and degenerative
changes in the ganglion cells, proliferative reaction of the neuroglia, and cells in a state of dissolution were reported after autopsy. The second case had previously been reported (Gebauer and Coleman 48). The third, a man, aged 30, received nitrous oxide and oxygen anesthesia for repair of an injury of a finger. After a few breaths of pure nitrous oxide, cyanosis developed. Oxygen 12 per cent, then 20 per cent, did not improve the color. A small amount of ether was given. Respiratory arrest ensued. This was corrected by artificial respiration. Consciousness was regained slowly. Convulsions and clouded sensorium were apparent upon recovery. On the second postoperative day the patient became noisy and restless; the third day visual disturbances were noted. The patient left the hospital on the fourth day, apparently normal. Tremor and convulsions returned. On the fifth day spastic gait, hypertonicity of the left arm and leg, and progressive paralysis developed. He became stuporous and restless, and twitchings were noted until death on the twelfth postoperative day. Examination of the brain showed a degenerative process. The fourth case had previously been reported (O'Brien and Steegman 118).

McClure et al. 101 (1939) reported four cases. Case 1.—Following an anoxic episode, the patient died in the operating room. Case 2.—Following an operation which lasted three and one-half hours, the patient continued in a drowsy state. Speech and swallowing difficulties were noticed as well as left facial paralysis and mental confusion. The anesthetic was not specified. The patient was “discharged.” Case 3.—Avertin, nitrous oxide-oxygen were administered following which the patient remained unconscious for five days; later he was mentally confused. Case 4.—Following ethylene-oxygen-ether anesthesia a patient did not regain consciousness. Four and one-half months later the speech was unintelligible and hemiplegia persisted.

Dawkins 28 (1940) reported 2,406 anesthesias with vinethene of which nine were attended by convulsions, none fatal. Of 196 in-patients, four had convulsions. Of 2,210 out-patients, five had convulsions. The in-patients had convulsions similar to those seen with deep ether anesthesia during the close of operations. The out-patients were children between the ages of 3 and 9, and in each instance the convulsions came on “after the anesthetic was concluded. Anesthesia was normal in each case and the child was then removed to the recovery room, where it recovered consciousness sufficiently to start spitting out, twitching of the facial muscles then began, and soon all the muscles of the body were involved. The child would then become unconscious and cyanosed, and would cease breathing.... Artificial respiration was employed and preparations were made to give evipan; but in each case respiration restarted before evipan was given, and the convulsions gradually ceased. The colour returned to normal and the child would then sleep for about an hour. If awakened before this it would get up and run about the room, banging its head on the walls and appearing completely incoordinated.... Those who were allowed to sleep during the cessation of convulsions awoke normally in about an hour.... The mental symptoms would appear to indicate some form of cerebral damage, fortunately not of a permanent nature.”

Batten and Courville 9 (1940) re-
ported ten cases, the first five having been previously reported.

Case 6.—A woman, aged 27, was delivered of a normal child under nitrous oxide and oxygen anesthesia. She remained unconscious for thirty-five hours. During this period she talked and repeatedly asked about the condition of her child. When consciousness returned she had blurring in the left visual field, thickness of speech, difficulty in swallowing, jerking movements of both arms, and marked paresis of all extremities. These symptoms persisted for one month. During the next three months she was easily fatigued, emotionally unstable, had a feeling of inadequacy, and loss of interest in her work, social contacts, and music. Her memory was poor, and it was difficult for her to concentrate. Three years later she was still somewhat unstable; when fatigued her hands were unsteady; her interests in avocations had not entirely returned. "This 'flattening of the emotional curve' seems to be one of the persistent residual characteristics of the anoxicemic states provoked by nitrous-oxide oxygen anesthesia."

Case 7.—A woman, aged 30, had a precipitate delivery. Nitrous oxide-oxygen-ether anesthesia was given for repair of a lacerated perineum. After a short period of time respirations became labored, then ceased. They were re-established within a few minutes upon administration of oxygen. She remained comatose, and convulsions, restlessness, and delirium developed. Her mental condition improved. Examination four days after the episode found her rational; there were apraxia of the right hand and limitation of vision to the lower quadrants of the visual fields. Five weeks later she appeared to be perfectly normal. "The period of respiratory failure was very short and this probably accounts for the lack of permanent mental symptoms."

Case 8.—A woman, aged 28, following an incomplete abortion, had a dilatation and curettage done under nitrous oxide-oxygen anesthesia. Cyanosis and rigidity developed, but there were no cardiac or respiratory irregularities. When she was removed from operating table, she screamed in a hysterical manner. This continued until she was quieted with paraldehyde. One hour later restless stupor and purposeless movements of the extremities developed. She could not be aroused. Later in the day she became quieter. The next day she seemed quite normal mentally. Nine days later there were no residual symptoms. "The peculiar staring silent gaze . . . seems to be one of the immediate residual characteristics of the condition."

Case 9.—A woman, aged 26, whose hemoglobin was 50 per cent, did not recover promptly following nitrous oxide-oxygen anesthesia. She appeared to be very dull, unable to comprehend, would sit upright in bed staring wide-eyed, and ask questions in an idiotic manner. She appeared to be distressed mentally, moaned, and moved her arms in an aimless manner. Oxygen inhalations and transfusion were given, and she became quiet. The next morning she was somewhat obtuse mentally but understood what was said to her and talked in a rational manner. There was amnesia for events of the previous day. From then on there was an uneventful postanesthetic course. She was perfectly normal mentally fourteen days later.

Case 10.—A boy, aged 5, had eight teeth removed under nitrous
oxide-oxygen anesthesia. He was never cyanotic but once "caught his breath." He slept for two hours and when roused cried out in a hysterical manner. He did not recognize his mother. Later he cried incoherently and was unco-operative. There was advanced defect in sight and hearing. The next morning he had entirely recovered.

Monroe and Benjamin\(^{106}\) (1941) reported a case of convulsions in which some of the symptoms of acute anoxia were evident. Following a convulsion that occurred after seventy-three minutes of anesthesia, the patient died on the seventh postoperative day. "A neurological examination ... was made 36 hours after the onset of convulsions. The patient was in profound stupor, there was no response to pin pricks. The ankle jerks were present and about equal; the knee jerks were present and very brisk. ... No pathologic reflexes were present. The cremasteric and abdominal reflexes were absent. No facial asymmetry was present; the patient did not respond to external stimuli. ... Necropsy was performed four hours after death. ... The essential anatomic diagnosis was: Bilateral confluent broncho-pneumonia; unresolved pneumonia with beginning cunnification; necrotic hemorrhagic infarct of the left upper pulmonary lobe; pulmonary thrombosis; dilatation of the right heart; mild diffuse hemorrhages of the pia-arachnoid; edema and perivascular hemorrhages of the brain; hypoplasia of the aorta; involution of the thymus; atrophy of thyroid. ... The severe generalized ganglion-cell degeneration found as a result of heat stroke or hyperthermia was not observed."

Courville\(^{24}\) (1941) studied cerebral anoxia and ether anesthesia. He reported two cases and commented:

"The relatively high mortality of cases with ether convulsions ... about 18% ... clearly indicates that we are not dealing with an ordinary convulsive state but one symptomatic of a more lethal background. ... More to the point in the possible connection of ether complications with true asphyxia are those instances in which death is delayed for a variable interval of time, or in which permanent or transitory neurologic or psychiatric manifestations betoken serious or minor disturbances of the gray matter of the brain. ... Case 1, Ethyl chloride ether anesthesia. ... Cyanosis and cardiac failure under anesthesia, successful resuscitation but persistent coma after operation, decerebrate rigidity and blindness as residuals. Alive, completely blind, and spastic ten months later. ... Case 2, Ether anesthesia. ... Respiratory failure necessitating artificial respiration and administration of stimulants. Recovery followed by psychosis and spasticity. Gradual recovery, death two years later of alcoholism."

Johnston\(^{82}\) (1941) reported five cases in one of which a man, aged 40, who died seven hours after operation (anesthetic agent was not reported) had symptoms suggestive of cerebral damage.

Schnedorf et al\(^{130}\) reported two cases and experiments on two dogs and reviewed the literature. The first of the cases was of a man, aged 58, who was given 100 mg. procaine hydrochloride and 5 mg. pontocaine intraspinally in the third lumbar space. Anesthesia was to the fourth thoracic level. Anesthesia was supplemented with inhalations of nitrous oxide and oxygen in a 50:50 per cent mixture. Shock developed. Blood pressure was undetectable, and respiration ceased.
With resuscitative procedures, respirations became spontaneous after twenty-five minutes. The patient reacted the following day but remained comatose for several days. He remained irrational until death twenty-one days later. Extensive cerebral damage, typical of anoxia, was shown at autopsy. The second patient was a boy, aged 3, who did not react for several hours after ether anesthesia. Lateral horizontal nystagmus and twitching of facial muscles were noted. Spasms of the upper extremities progressed to generalized convulsions, cyanosis, and death fourteen hours later. Postmortem examination showed involvement of the brain cortex and brain stem, vascularization of white matter with extravasation of blood, and degeneration of brain cells. Two dogs were subjected to conditions simulating those that existed during the anesthetics. The brains showed the same changes as those present in the patients.

Lorhan et al.\textsuperscript{184} (1941) studied the histopathologic changes in rats following administration of pentothenal sodium and sulfanilamide. They found that "Sulfanilamide in doses of 0.6 to 1.0 Gm. per Kg. produces toxic effects which render white rats more susceptible to pentothenal sodium. With a dosage of 1.0 Gm. per Kg. marked neurological symptoms are observed."

Ingleby et al.\textsuperscript{185} (1941) made comparative autopsy studies of eighteen dogs after anesthesia. Barbiturates, ethyl ether, and cyclopropane with oxygen were the agents used in the studies. They found that "in the brain, the cortex was most affected. Each anesthetic used caused varying degrees of Nissl's acute degeneration. In the cyclopropane-oxygen group the cerebral lesions were definitely more severe. All of this group showed some neuronophagia, the extent did not depend on the number of administrations. In interpreting these findings we consider that the acute degeneration was due to the lethal dose of the anesthetic. Neuronophagia and glial changes indicate a longer standing lesion, and are probably the consequence of previous administrations of the anesthetic. If this be so, it would indicate that cyclopropane-oxygen is definitely more toxic to nerve cells than the barbiturates or ether. When brains and livers from the first few dogs were examined it was thought that there might be some correlation between liver and brain damage. However, careful comparison of sections from the whole series showed that this was not so. . . . Two points seemed to emerge; the first is that the clinician's fear of damage to the liver as a result of anesthesia is well founded; the second is that the effects of cyclopropane-oxygen on the central nervous system will bear watching."

Turino and Merwarth\textsuperscript{145} (1941) reported an incident in which a woman, aged 31, was given gas-oxygen anesthesia for the delivery of a stillborn baby. Ether was added to produce complete anesthesia. "As the head was being delivered with forceps . . . the patient's respiration became irregular, shallow, and slowed to less than 8 per minute. The pulse of poor quality became momentarily imperceptible, and then quickened to 144 per minute. . . . Approximately one hour following delivery of the fetus, there occurred muscular twitching of the face, first involving the left and later both sides, extreme restlessness and unintelligible jabbering sounds. The eyes remained open and staring, the pupils were dilated, and the lower
extremities were spastic. Five hours after delivery the upper extremities became rigid. The patient tossed her head from side to side, cried out loudly, and threshed around so much that restraint was necessary. The facial grimaces continued. . . . The clinical picture forty-eight hours later was that of widespread decortication. . . . Death occurred . . . three and one-half months after the anoxic episode. . . . Grossly scattered minute areas of necrosis were found in the gray and white matter of the cortex and the gray matter of the base of the brain. . . . Factors which may be responsible for anoxia have been traced to faulty gas machines, impurities of the gas, alcoholism on the part of the patient, or the unskilled anesthetist.

White et al\textsuperscript{153} (1942) studied changes in brain volume during anesthesia, anoxia, and hypercapnia. Swelling of the brain occurred during exploration for an hypophyseal adenoma under local anesthesia supplemented with nitrous oxide and oxygen. Minor cyanosis produced swelling of the brain. In experiments on cats, during barbiturate or ether anesthesia, no swelling occurred when the airway was unobstructed. Anoxia, however, caused an increase in intercellular or intracellular fluid, or both.

Tye\textsuperscript{146} (1942) reported five cases of convulsions of anesthesia with two deaths and three recoveries. One of the patients died during the convolution; the other patient who died lived twenty-nine days in a state of decerebrate rigidity without ever regaining consciousness.

Ray and Marshall\textsuperscript{122} reported twelve cases of convulsions that occurred during general anesthesia. The nine patients who survived showed delayed recovery from anesthesia or late sequelae, or both.

The ages ranged from 2 to 44 years. Three children were given ether, six of the group received closed-mask ether with nitrous oxide-oxygen, two had ethylene-ether-oxygen, and one had cyclopropane-oxygen-ether. The authors thought that a contributing cause was the inhibition of the ability of cells of the brain to utilize oxygen. "One patient has what appears to be permanent changes in temperament and personality while another has residual hemiparesis. . . . In four of the seven patients subjected to electroencephalography at varying periods after their operations, there were pathologic changes recorded."

Suggs\textsuperscript{142} (1943) reported a case in which a woman, aged 32, was given nitrous oxide and oxygen for fifteen minutes. The induction was "stormy." Respiratory arrest occurred although there was no cyanosis (hemoglobin 66 per cent) or pallor. Artificial respiration, oxygen inhalation, and stimulants were given. An hour elapsed before voluntary respirations returned. Three hours later spastic convulsions began; these recurred at varying intervals. Consciousness never returned. She lived in a static state for forty-one days. The postmortem examination showed "Degenerative lesions of the ganglion cells varying in severity with different regions of the cortex, being most prominent in the parietal lobes. Basal ganglia and midbrain are only moderately involved. The cerebellum reveals extensive degeneration of Purkinje cells. The Ammon's horn shows only few scattered degenerative ganglion cells."

Woodhall and Goodman\textsuperscript{138} (1943), reporting the use of pentothal sodium in neurologic surgery, cited five cases in which complications developed, two of which are pertinent.
Case 1.—A woman, aged 23, received 2.9 Gm. pentothal sodium in seventy-five minutes for repair of median and ulnar nerves. She reacted in two hours, became maniacal for four hours. She was drowsy for twenty-four hours. "The influence of the anesthetic agent in this reaction was not clear."

Case 2.—A woman, aged 35, was given 1.45 Gm. pentothal sodium for section of the sensory root of the fifth nerve by the subtemporal approach. After recovery two hours later, she became maniacal and remained so for the next twenty-four hours.

Aageson\(^1\) (1944) reported a case of a girl, aged 12, who was anesthetized with nitrous oxide-oxygen-ether for an appendectomy. There was normal return of consciousness. Deafness was noted two days after operation. Dizziness to the point of falling developed after the child had left the hospital. This symptom disappeared two weeks later. The deafness persisted. In commenting on the case the author said, "the lesion appears organic in nature and the outlook for further recovery seems doubtful."

Fletcher\(^2\) (1945) reported in detail eight of twenty-nine cases that had come to his attention.

Case 1.—A woman, aged 60, had nitrous oxide administered for dental extraction at the age of 29 years. An episode of difficulty during the anesthesia had occurred. After thirty years there were apparent residual neurologic signs.

Case 2.—A woman, aged 35, a daughter of the patient previously described, had no difficulty following nitrous oxide anesthesia given for the delivery of her child. Nitrous oxide was given for short periods at ten different times for dental work. Residual signs of personality disintegration were apparent two years later. These were interpreted as the accumulated effect of many anesthetics. The occurrence of similar reactions in mother and daughter was suggestive of a predisposition to anoxia.

Case 3.—A man, aged 21, was given nitrous oxide on nineteen different occasions for dental work. One year later, residual neurologic signs were apparent.

Case 4.—A woman, aged 42, had been anesthetized for tonsillectomy at the age of 12. (The agent was not recorded.) Following the anesthesia she was lethargic for a week, and persistent headaches developed. At the age of 19, she was given chloroform during the delivery of a child. The baby was critically ill for five weeks after birth. At the age of 22, the patient had ether anesthesia, and at 24, during nitrous oxide-oxygen-ether anesthesia, she had an episode of respiratory difficulty. Several months later, residual symptoms persisted. At the age of 32, she had a nervous breakdown and psychotic signs after nitrous oxide anesthesia for dental work. At age 35, a series of nitrous oxide anesthetics were given for treatment of furuncles. There were flare-ups of the mental condition. Four times nitrous oxide was given for dental treatment with mental flare-ups after each.

Case 5.—A boy, aged 6, was given nitrous oxide-oxygen anesthesia for tonsillectomy. No untoward incident occurred. There was a decline in his mental state. Two years later he began to show marked improvement.

Case 6.—A man, aged 20, was unconscious after nitrous oxide-oxygen-ether anesthesia for seven hours. Mild persistent residual signs were evident.

Case 7.—A man, aged 22, had nitrous oxide-oxygen-ether anesthe-
sia for appendectomy. There was no episode of difficulty. One year later cerebral disturbances were manifested. After another year he was improving.

Case 8.—A man, aged 20, had a toe nail removed under nitrous oxide-oxygen anesthesia. Nervous instability that had existed before the operation was enhanced by the anesthetic.

Pisetsky (1945) reported a case in which the patient, a man, when 33 years of age had ether for ninety-five minutes for a mastoidectomy. There were no complications during or immediately following operation. He was a "heavy drinker." The day after operation left hemiplegia was noticed. The condition became permanent. Six months later, while intoxicated, the patient was anesthetized for one hour for appendectomy. The anesthesia was "difficult." Three hours after operation he was restless and cyanotic. He was aphasic and had swallowing difficulty and continued restlessness. He was restrained. There was gradual improvement. He was discharged on the twenty-first postoperative day.

Barach and Rovenstine (1945) reported a case of a boy, aged 13, who became markedly cyanotic after one half hour of nitrous oxide anesthesia for reduction of a fractured femur. Oxygen restored the color to normal. The child died on the fifth day without regaining consciousness in a completely decerebrate state.

Hamilton (1945) reported a case of ether convulsions. A boy, aged 9 years and 10 months, was given ethyl chloride and ether for an appendectomy. Convulsions started soon after the ether was added. Anesthesia was deepened, oxygen and chloroform, carbogen, coramine, luminal, atropine, calcium gluconate, and saline solution were used in attempts to control the convulsions. The following day he was still unconscious. On the second day, while he was still unconscious, the arms were stiff. The next day he made mumbling responses to questions. Convulsions continued. Magnesium sulfate, enemas, phenobarbital, and insulin with glucose were tried at various times. Three weeks after the operation there was increased spasticity. An extension frame and physical therapy were used to combat contractures that were developing. About six weeks after operation the spastic condition became less severe. There was gross wasting of muscles. The boy spoke a few words and had the mentality of a young child. "It is suggested that the condition could be accounted for by thrombosis of the superior longitudinal sinus, and it appears unlikely that a complete recovery can be expected."

Among others, Feldman (1945) suggested the use of from 40 to 50 per cent oxygen in dental anesthesia to prevent oxygen want.

Schmidt (1945) in discussing respiratory physiology said: "Direct study of the oxygen consumption of the brain in situ has shown that cerebral metabolic activity runs parallel to cerebral functional activity and that convulsions may lead to cerebral anoxia (with all its consequences) because they increase the oxygen demand beyond the available supply."

Wilson (1946) gave a soldier 0.7 Gm. pentothal sodium in preparation for dental extraction (which was not done). Cyanosis and respiratory arrest were treated with oxygen, carbon dioxide, and artificial respiration. Spontaneous breathing began one hour after cessation. The patient was semiconscious. Violent "jactitation" oc-
curred. The next morning he was drowsy and blind. Seven days later “pins and needles” in the right hand and tremors with spasmodic contractions of the flexors of the forearm developed. The contractions extended to the left arm and left leg. Sixty-seven days later his eyes had improved to “slightly short of normal.”

Lenahan and Reed (1947) reported a case of apparent decerebrate rigidity. “The patient, a forty-seven year old white male, entered [the hospital] at 4:30 p.m., October 26, 1944, for repair of a right indirect inguinal hernia. There was an alcohol odor on his breath. . . . His history was negative except for an attack of acute anterior poliomyelitis twenty-seven years earlier, which left no residual damage. . . . Anesthesia was induced with 2.5 per cent of sodium pentothal and supplemented with cyclopropane-oxygen. Induction was difficult and 38 cc. of pentothal was necessary before unconsciousness resulted and cyclopropane-oxygen was given. Throughout the forty-five minutes of actual operation, anesthesia was maintained on cyclopropane 150 cc. and oxygen 300 cc. per minute. Supplementary pentothal was not required during operation. An airway was introduced soon after anesthesia had become established. When the patient left the operating room, his pharyngeal reflexes had returned and the airway was removed. . . . On the way to his room the patient stopped breathing and became very cyanotic. The cessation of breathing with cyanosis lasted about two or three minutes. Artificial respiration was begun at the end of one minute and continued while the patient was being removed from the stretcher cart and after he was put in bed. Administration of oxygen by nasal catheter was begun immediately, together with intravenous saline solution and artificial respiration by the Schaefer prone method continued for ten minutes. The airway was open and a good exchange of air was maintained. In addition to manual resuscitation and the administration of oxygen, 2 cc. each of coramine and metrazol were given intravenously five minutes apart. Plasma was used to replace the saline solution. The patient now began a labored type of breathing. . . . Due to rigidity of the patient’s neck and inability properly to visualize the larynx, intubation was not successful. . . . Shortly afterward the patient began to have convulsions which were characterized by aimless movements of the arms and legs. . . . The eyeballs were roving as in anesthesia of the second or early third stage. Profuse diaphoresis was observed, the patient’s body feeling cold and clammy. A nasopharyngeal tube was introduced. . . . The tonic and clonic movements continued without ceasing and at the end of one hour 100 mg. of curare . . . was given slowly by the intravenous route. This stopped the convulsions and for the next thirteen and one-half hours curare was given intermittently in sufficient amounts to control them. . . . A Magill intratracheal tube was then inserted.

“Continuous oxygen was administered through the intratracheal tube. . . . Because of the large doses of curare that were necessary to control the convulsions, active breathing was sometimes halted and it was necessary to resort to passive respiration for a few minutes until normal respiration was again established. . . . About sixteen hours after he was returned from surgery, the patient began to respond when spoken to and to complain about the intratracheal tube. It was removed
and a nasal catheter inserted. Twenty-four hours postoperatively the patient was able to void voluntarily, expel flatus, and ask for a cigarette. His speech was thick and slow; his stretch reflexes were hyperactive, but the pathological reflexes were absent. For the edema of the brain cells the neurological consultant prescribed 50 cc. of 50 per cent glucose to be given intravenously every eight hours for six doses. . . . The temperature rose steadily to a peak of 104°F. at 2 a.m. on the first postoperative day, then dropped slowly to normal by the third postoperative day. Thereafter recovery was more or less uneventful.” The patient returned to a responsible position. After two years he showed no mental impairment.

Ruzicka and Nicholson126 (1947), in commenting on cardiac arrest under anesthesia, said: “The revival of cardiac and respiratory activity does not mean that the eventual recovery of these patients is assured. . . . In the presence of clinical signs of severe damage to the brain, abnormalities in the brain usually are not discovered at necropsy. Those patients who recover have a constant loss of memory for events twenty-four hours previous to operation.”

Woolmer159 (1948) reported an instance involving accidental injection of procaine. “Cisternal myelography was to be performed on a woman of 39 suffering from a tumor of the cervical cord. As a result of confusing two similar syringes, 3 c.c.m. of 2% procaine (60 mg.) was inadvertently injected into the cisterna magna instead of opaque oil, while the patient was sitting upright in a chair. Within a few seconds of the injection the patient complained that her head felt hot. She lost consciousness during the second minute after the injection. Respiration ceased about a minute later, and remained in abeyance for 45 minutes. All reflexes were abolished and there was a profound flaccid paralysis, but no marked cardiovascular depression. There was extreme cyanosis from the onset of respiratory paralysis until effective artificial respiration was established 5-10 minutes later, and the pulse became feeble towards the end of this period, but regained a satisfactory volume when the anoxaemia was corrected.

“Artificial respiration was maintained by rhythmic insufflation of oxygen through an endotracheal tube, and the patient’s condition remained fairly good, in spite of the profound flaccidity. Spontaneous respiration began to return 45 minutes after it had ceased, and was fully re-established in a few minutes. The laryngeal reflex became active ten minutes later. The patient did not regain consciousness, however, and during the next three hours she had a series of convulsions. From then, until she died six days later, the clinical picture was typical of grave neuronal damage following cerebral anoxia, with unconsciousness, convulsions, rigidity, mask-like facies and profound dementia. The histological findings were complicated by the presence of a malignant tumor occupying much of the cord and extending into the brain stem. . . . The tumor may have rendered the neurones abnormally sensitive, but it is clear from a study of Courville’s cases that the oxygen lack to which they were subjected could have caused similar damage in healthy neurones. In short, the supposition is that this dose of procaine intra-cisternally was enough to cause profound, but reversible, respiratory paralysis. The irreversible changes which
killed the patient were due to anoxaemia."

In the "Queries and Minor Notes" section of the Journal of the American Medical Association (1948) a pertinent question is asked and answered:\textsuperscript{120}:

"To the Editor:—What are the references to literature regarding cerebral cortical changes that may take place with drop in blood pressure following spinal anesthesia with subsequent acute collapse and cardiac and respiratory failure? The patient recovers after a few minutes; begins to breathe and to have normal heart beat and blood pressure. Is there evidence indicating that such persons through deprivation of oxygen to cortical cells will subsequently lead a vegetative existence without normal consciousness? . . ."

"Answer.—Reference has been made many times in the literature to damage to the brain which followed use of various kinds of anesthetics and which resulted from a variety of conditions during anesthesia. . . A variety of results have been observed. In some cases the patient never regains consciousness and dies ten to twenty hours after resumption of breathing and after the return of pulse rate and blood pressure to satisfactory levels. Also, partial recovery, as well as full recovery, may occur."

Etsten and Himwich\textsuperscript{37} (1948) determined the degree of oxygenation of the blood during pentothal sodium anesthesia, "determinations which are to serve as a guideline to the limits of safety. . . . A 1 per cent solution of pentothal sodium was administered intravenously to non-premedicated and non-operative subjects. . . . Arterial blood samples were drawn from the femoral artery while the patient was in the resting state and during the various stages and planes of anesthesia. . . . Thirty-eight observations were made on eleven patients. . . . The intravenous administration of sodium pentothal produces anoxia and an increase of carbon dioxide content in the blood during moderate surgical anesthesia and deep surgical planes of anesthesia. The institution of oxygen therapy by insufflation is insufficient to correct the depletion of accumulation of the blood gases during the deep planes of anesthesia. Supplemental respiration technic of oxygen therapy is the most efficient method that can be instituted during pentothal anesthesia to avoid anoxia and hypercapnia."

Strohl and Sarver\textsuperscript{141} (1948) reported a case of a girl, aged 7, who was given cyclopropane for appendectomy. Twenty minutes after the incision was made, it was noticed that clonic movements of the face, arms, legs, and abdominal muscle were present. One grain (0.064 Gm.) of phenobarbital was given intramuscularly. Convulsive movements became more pronounced and persisted for fifteen minutes. At this time cyanosis developed and respirations stopped. Spontaneous respirations started after ninety seconds of artificial respiration. The rectal temperature was 106 F. Convulsions recurred intermittently for forty-eight hours. Alternate coma and excitation continued for nine days. Mental evaluation tests, three months after operation, showed an estimated age of five to ten months. "Movements were uncoordinated and characterized by coarseness, spasticity, cog-wheel rigidity and weakness. The child could not stand or walk. She was discharged one hundred and thirty-six days after the onset of illness."

In addition to the cases included in the preceding sequence, there are, among several newspaper ac-
counts of accidents occurring during anesthesia, two which seem to belong in the group under discussion and which have not yet been identified with cases reported in medical journals.

A law suit was brought against a doctor by the husband of a patient, aged 33. She had been "rendered permanently unconscious by an operation" almost two years before. Ever since the operation she "neither sees, nor feels, nor understands." Pentothal sodium was used as the anesthetic. In the suit the husband claimed that "an air bubble entering the blood-stream...caused anoxemic damage to the nervous system and degeneration of the brain tissue."

In another newspaper account microscopic tests were to be made to determine the cause of death of a woman, aged 38, "who had been unconscious for six weeks after being given an intravenous anesthetic preliminary to a facial operation."

Sodium nembutal was used intravenously as a preliminary anesthetic, and 60 units of curare was given to relax the muscles of the throat. "However, a spasm of the larynx occurred and the operation was interrupted twice for administration of oxygen."

In other newspaper accounts of deaths during anesthesia, incidents similar to those recounted in medical journals are common. Details are not sufficient to warrant including them in the present review.

In summarizing their cases, Batten and Courville (1940) have stated the conclusion which may well be drawn for the entire series. "The residual, mental and emotional symptoms vary considerably as to their nature, severity and persistence. Disturbances of consciousness, as coma or stupor, are invariably present. This state is followed by delirium, transitory or recurrent hysterical outbursts, emotional instability, hallucinatory or cataleptic states or mental confusion. In patients who survive, progressive dementia has been reported, although improvement even after weeks or months has also been observed. Psychotic states may be (1) transitory and followed by more or less complete recovery, (2) recurrent, often resulting in more serious demented states or deaths, or (3) progressively downward leading to more or less complete dementia. After the period of anesthesia, irritative motor phenomena (convulsive, muscular twitchings or carphologia) often accompany the mental disturbances. In patients who survive for days or weeks or who live with persistent mental or emotional changes, signs indicative of lenticular damage (athetosis, choreiform movements and muscular rigidity) are commonly seen. Alcoholism seems to predispose to cortical damage, resulting in the development of serious, often persistent, nervous or mental states, possibly due to the preliminary interference with cellular respiration. It is likely that cerebral and lenticular damage are due to the accompanying asphyxia (anoxic anoxemia) and not to the toxic effects of nitrous oxide itself. In patients who die within a few days or weeks, patchy necrosis or subtotal destruction of the cerebral cortex is found, often associated with necrosis of the lenticular nuclei. Similar but less extensive changes are found in the brain of individuals who survive for a longer interval."

Comment

Having read the summaries of these reports totaling more than 170 cases (in which accurate counts
were given), it becomes apparent that the problem of anoxia during anesthesia is one with which every anesthetist must become familiar. That no such case has occurred in the experience of any one anesthetist is either a case of failure to recognize the condition or extreme good fortune. It is imperative that every person administering anesthetics know every sign of oxygen want and do everything possible to prevent its occurrence. If, in spite of every precaution, anoxic manifestations do appear, immediate corrective measures must be instituted.

False security will be the result of placing confidence in any agent or method on the assumption that anoxia does not exist with its use. In the reported cases, the agents, nitrous oxide, chloroform, ether, ethyl chloride, ether-chloroform mixtures (E₄C₁), ethylene, vinylene, cyclopropane, nembutal, pentothal sodium, avertin, procaine, nupercaine; and the methods, open, semi-open, carbon dioxide absorption, rectal, intravenous, spinal, and combinations thereof have been used.

The common factor seems to be anoxia, the least serious consequence of which it is wise to avoid, and to the more serious consequences of which no person would, for lack of knowledge, risk having contributed.

This review has been prepared with the object of emphasizing a great danger inherent in the practice of anesthesia and of economizing the time and efforts of those who wish to learn more about this phase of the complex science of anesthesia. Additional references will be added in a subsequent report that will also include the reports of anoxia in relation to fetal and postnatal life.

**Summary**

A review has been made of the literature pertaining to the cerebral effects of anoxia, with emphasis on their occurrence during anesthesia. The deleterious effects of oxygen deprivation were recognized long before the mechanisms were understood. The acceleration of interest during the last fifteen years is a healthy trend. The appalling consequences of anoxia are such that there cannot be overemphasis of the problem in any of its phases.

Note: In attempting to review the cases, it became apparent that true evaluations of the incidence of any complication cannot be made. The report of a single case, without indicating the total experience of the author or the percentage incidence of the episode within his experience, makes it impossible to correlate the facts properly. If a code—e.g., \(x\), representing the number of cases reported; \(y\), representing the number of the same type of anesthetic; and \(z\), representing the total number of cases in the experience of the author, as \((1/421)/10,000\)—could be used in all case reports, eventually the relative importance of any factor could be established.
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