

4-1948

Cerebral Anoxia and Its Residuals: IV. The Asphyxial Syndromes - Acute, Subacute, and Chronic

Cyril B. Courville
College of Medical Evangelists

Follow this and additional works at: <http://scholarsrepository.llu.edu/medartssciences>



Part of the [Life Sciences Commons](#), and the [Medicine and Health Sciences Commons](#)

Recommended Citation

Courville, Cyril B. (1948) "Cerebral Anoxia and Its Residuals: IV. The Asphyxial Syndromes - Acute, Subacute, and Chronic," *Medical Arts and Sciences: A Scientific Journal of the College of Medical Evangelists*: Vol. 2: No. 2, Article 5.
Available at: <http://scholarsrepository.llu.edu/medartssciences/vol2/iss2/5>

This Article is brought to you for free and open access by the Loma Linda University Publications at TheScholarsRepository@LLU: Digital Archive of Research, Scholarship & Creative Works. It has been accepted for inclusion in Medical Arts and Sciences: A Scientific Journal of the College of Medical Evangelists by an authorized administrator of TheScholarsRepository@LLU: Digital Archive of Research, Scholarship & Creative Works. For more information, please contact scholarsrepository@llu.edu.

CEREBRAL ANOXIA AND ITS RESIDUALS*

IV. THE ASPHYXIAL SYNDROMES—ACUTE, SUBACUTE, AND CHRONIC

CYRIL B. COURVILLE, M.D.

In dealing with the clinical aspects of asphyxia we are necessarily concerned with the responsible etiologic factors. Since there is some variation, at times considerable, in the resultant clinical syndrome after the more common mechanisms of asphyxia, it seems worth while to discuss each type separately. On this basis we shall deal with (1) the acute, subacute, and chronic manifestations of asphyxia of the newborn, (2) asphyxia after exposure to carbon monoxide, (3) the anoxic states after anesthesia, (4) the residuals after mechanical obstruction of the air passages, (5) the acute and chronic manifestations of anoxemia incident to high altitudes, and some attention will be given as well to (6) the acute effects of some of the lesser anoxemic episodes which accompany acute exsanguination and the anemias. Finally, brief attention will be given to (7) the possible association of certain chronic nervous diseases, both functional and structural, with antecedent minor anoxic episodes.

NEONATAL ASPHYXIA

The consequences of neonatal asphyxia, particularly acute death under these circumstances, have been recognized for some time. And yet there still remains much confusion as to the relationship existing between minor degrees of anoxia at birth and certain struc-

tural residuals which are discovered by pneumo-encephalography, at operation, or at autopsy some months or years later. This situation is to be attributed to the fact that the original anoxic episode has been either overlooked or forgotten and that the nature and course of the anoxial lesion of the encephalic gray matter have not been fully understood.

Be all this as it may, we have to deal in this condition with a most serious situation. It has been estimated that 30,000 infants die of asphyxia neonatorum annually in these United States. This condition therefore constitutes a problem of major proportions, one to which our best attention should be directed.

When Little reported his findings in various deformities of the extremities (1843, 1853, 1861), he pointed out that the common spastic states of childhood were to be explained on the basis of asphyxia at the time of birth. In succeeding years there arose a school of thought which postulated some physical injury of the brain as the cause of these conditions. McNutt (1885) seems to have been the first to suggest meningeal hemorrhage at birth as the cause of such spasticities, a theory which, with the support of Osler (1889), came to be widely accepted. Other investigators, including Freud (1897), fell in line, and it came to be accepted as an established fact that subdural or subarachnoid hemorrhage at birth was the cause of such lesions. Some fifty years after McNutt's postulate appeared, the question was raised (Courville [1937]) as to the mechanism of production of the ultimate lesions, and in particular what happened to the subdural membrane if subdural hemorrhage was the actual cause of the cerebral lesion. The clue came a few years thereafter, when the cerebral lesions in two cases of lobar atrophy of childhood (ulegyria) were investigated histologically and found to present evidence suggestive of anoxia at birth as their cause

* From the Department of Nervous Diseases, College of Medical Evangelists, and the Cajal Laboratory of Neuropathology, Los Angeles County Hospital, Los Angeles, California.

(Friedman and Courville [1941]). A further study of a number of other lesions hitherto assumed to be congenital or the result of hemorrhage at birth led to the conclusion that they are actually the end-results of asphyxia (Courville and Marsh [1944]). From an experimental viewpoint, the recent work on the production of cerebral changes by anoxia at birth has further contributed to our knowledge of both the symptoms and signs of this condition (Windle [1944, 1945]; Windle and Becker [1942, 1943]; Windle, Becker, and Weil [1944]).

The clinical course of instances of asphyxia neonatorum may be divided into three phases—the immediate effects, the interval picture, and the ultimate manifestations. The *immediate effects*, of course, include the anoxial episode itself, which assumes some embarrassment of respiration, often with complete cessation of thoracic movements (asphyxia livida). At times, however, there is an associated cardiac standstill, so that what little oxygen there is in the blood stream is almost immediately consumed. This type (asphyxia pallida) is obviously a much more serious situation. It must be remembered, moreover, that a serious degree of cerebral anoxia can take place without any evident postnatal respiratory embarrassment, the damage having been done progressively *in utero* as a result of placental infarction, partial strangulation through mechanical interference with the circulation in the cord, or imperfect oxygenation of the mother's blood. Of course, prolonged and undue compression of the fetal head in its passage through the birth canal incident to disproportion or to excessive physical force by means of forceps constitutes the major cause of neonatal asphyxia. However, other factors aside from those purely mechanical at times play an important etiologic role, oversedation of the mother being one of them (Schreiber and Gates [1938], Schreiber [1939], Cunningham [1945]).

Following the asphyxial episode other signs may betoken the occurrence of cerebral anoxia. Persistent or fluctuating episodes of blueness of the skin and mucous membranes,

convulsive seizures or muscular twitchings, a depression of spontaneous movements of the extremities, or a failure to nurse properly may one or all suggest the occurrence of cerebral damage by this mechanism. These signs are usually transitory, often minimal, so much so that they may be overlooked entirely.

The treatment of this acute phase is to be considered as (a) preventive and (b) curative, of which the first is to be most earnestly sought for. Avoidance of oversedation and overanesthetization of the mother during labor, careful evaluation of the time and measurement of any mechanical interference, and its undertaking only by those skilled in the art are most important. When the babe fails to breathe, prompt clearance of the air passages of any mucus or meconium and the utilization of effective but gentle methods of resuscitation such as intratracheal insufflation (Crotty [1942]) are important. The accoucheur must be prepared in mind and in facilities against the event, for when it occurs there is no time for uncertainty or delay.

The *interval picture*, namely, the period between the asphyxial episode and the immediate postasphyxial state, on the one side, and the delayed appearance of residuals, on the other, may be entirely symptom free. Many a perfectly "normal" baby during this interval has turned out to be completely otherwise. At times, however, one very important symptom is present. In such cases more or less constant crying occurs, so much so that a large portion of the child's waking hours is so consumed, to the considerable disturbance of the parents' peace of mind. This occurrence should forewarn the physician of troubles to come, giving him opportunity at this early period to review critically the details of delivery which might have played a part in producing asphyxia, as well as an occasion to prepare the parents for the possible unpleasant sequel.

The residual picture of neonatal asphyxia

varies within wide limits. Nevertheless, out of the apparent confusion a group of variable neurologic syndromes can be distinguished. This is not to say that all such clinical pictures are the result of asphyxia, for these syndromes are simply those of the localization of the predominant lesion. Moreover, in these cases more than one group of symptoms is often found, so that composite pictures are commonly encountered. The symptom-complexes are: (1) mental deficiency, (2) the spastic states, (3) the choreiform-athetoid complex, (4) the epileptic states, (5) the visual syndromes—usually a homonymous hemianopia, (6) speech disturbances, and (7) the ataxic states.

We are prepared for this variety of end-results by the preview of the physical changes in the brain already pointed out. The variations in extent, location, and degree of the cortical atrophies, cerebral and cerebellar, with the not-infrequent decadent changes in the lenticular nucleus and the focal scarring and cyst formation, small and large (porencephaly), are found months and years after the asphyxial episode at birth. Long confused with the effects of physical trauma incident to birth, these lesions are now recognized to be anoxial in nature because of their characteristic acellular foci.

Therefore, the evidence of retarded mental development and the associated slowness in sitting, walking, or learning to talk, with the aimless rolling of the head from one side to another, the vacant look, the drooling, head-beating and allied phenomena, are frequently residuals of asphyxia neonatorum, recognized or not. This state is often complicated by convulsive seizures. In this group will also have to be included a considerable number of instances of "behavior problems" in children with normal or almost normal intelligence (Preston [1945]). These patients, who had an asphyxial episode at birth, experience sub-

total recovery which leaves them with hyperkinetic activity, emotional aberrations, and disordered personality development.

Another group of the motor syndromes—the spastics, the choreoathetoids, and the ataxics—may or may not be complicated by mental retardation. Often such is not the case, and the crippled child may be bright and alert, capable of much intellectual development. Under such circumstances efforts at rehabilitation are eminently worth while. However, convulsions may serve to complicate the management of these cases.

There is also a group in which convulsions seem to be the outstanding manifestation (Nielsen [1946]), the child showing little or no disturbance in the other realms of encephalic function.

As a rule, speech disorders are but part and parcel of one of the other symptom-complexes, but in a few cases imperfections in motor speech or difficulty in learning to read may be isolated symptoms. Here again specialized training often corrects such deficiencies.

The outstanding defect in the sensory realm (aside from the highly specialized visual verbal agnosia [alexia] just referred to) is that of homonymous field defects. These defects are not infrequently found in older individuals with mild mental deficiency and persistent convulsive seizures, at times with some spasticity of hemiplegic distribution. The underlying lesion often proves to be a large porencephalic cyst in the contralateral parieto-occipital region. Uncapping of the cyst by surgical removal of the membranous covering may at times relieve the convulsions, but, of course, cannot restore vision in the defective field.

The *diagnosis* of the underlying lesion of the brain responsible for these clinical syndromes is usually not difficult, although the history of neonatal anoxia is not always very clear. Neurologically, the findings vary con-

siderably, depending upon the focalization of the atrophic process, and the precise delineation of objective findings is particularly difficult in young infants. At this age the electroencephalogram is not especially helpful and actually may be confusing, because the brain waves of children are normally large and of slow frequency. The most valuable diagnostic measure, therefore, is the pneumo-encephalogram, by which means the amount and localization of atrophy can usually be determined. Where dehydration, inanition, or other physical disease does not contraindicate, this procedure is usually indicated to establish once and for all the exact nature and degree of cerebral atrophy.

The *treatment* of the residuals of neonatal asphyxia must be directed toward correction of physical deformities of the extremities (or reinforcement of motor deficits), the lessening of the disability of ataxia by muscle training, the utilization of proved methods in the development of speech, et cetera. It must be kept in mind that all these must fail when there is not an associated adequate mental equipment, and that such measures will also fall short of their goal without the full cooperation of the parents. A study of the problem makes it evident that medical centers, properly manned and equipped, are the only complete solution to the problem.

ANOXIA INCIDENT TO EXPOSURE TO CARBON MONOXIDE

If one excludes neonatal asphyxia, anoxia due to excessive inhalation of carbon monoxide is the most common cause of death from oxygen want. Its effects have been known for centuries (Raskin and Mullaney [1940]), being described fairly completely by Portal in 1776 (Greidenberg [1900]). Claude Bernard (1865) is credited with a correct interpretation of asphyxia caused by this gas, and

Klebs (1865) for evaluation of the pathologic findings. At this period its victims were chiefly coal miners and those asphyxiated by the inhalation of fumes from coal stoves, the smoke of burning buildings, or illuminating gas. Today, however, the gases resulting from the combustion of motors of automobiles contribute in no small degree to the number of fatal cases and further add the problem of chronic poisoning with minor symptoms in those sufficiently exposed.

This gas is particularly treacherous because it is inert and nonirritating, its victims being entirely unaware of its presence. The amount of the gas in respired air need be relatively small, the issue being fatal if a concentration of only 0.4 per cent is breathed for an hour or 0.2 per cent for as little as four hours (Henderson and Haggard [1921]). If the concentration reaches from 2 to 5 per cent, death ensues within a few minutes. With low concentrations over a long period of time, minor untoward symptoms may result, with partial compensation due to the development of polycythemia. Although the outcome in any individual case must depend upon the concentration of the gas in the respired air and the length of time of exposure, more than half the patients recover fully. The series of 43 cases of carbon monoxide poisoning in the New York Metropolitan Area surveyed by Shillito, Drinker, and Shaughnessy (1936) may be taken as representative of the mortality and morbidity of the condition. In this group of patients 11 died, 9 survived with permanent residuals, and 23 fully recovered.

The clinical course varies widely. Exposed individuals may be dead when found or may die after a period of coma, short or prolonged. The outlook is grave if coma lasts more than 36 hours. When consciousness is regained, the patient may go on to prompt and full recovery or may have disturbing residuals over a variable interval of time. The immediate residuals

appear usually in the form of psychic aberrations, the more prolonged ones occurring more commonly either in the form of a psychosis or as pyramidal or extrapyramidal disability. The transitory character of many of these symptoms and the fact that progressive recovery may occur over a long period measured by weeks, months, or even years give one continued hope. Of course, the outcome of any given case depends specifically upon the amount of primary cortical and subcortical damage and on the extent of secondary changes incident to arterial occlusion.*

It is necessary to outline briefly the various clinical pictures which may result from exposure to carbon monoxide gas. Among these possible syndromes may be distinguished (1) acute poisoning; (2) the residual manifestations in the form of (a) visual disturbances, (b) motor symptoms, (c) the ganglionic symptom-complexes (lenticular syndrome and parkinsonism), (d) disturbances in speech, (e) peripheral neuritis, (f) psychoneurotic states, and (g) frank psychoses; and (3) chronic intoxication. Each of these clinical pictures will be briefly outlined in the light of recent contributions to the subject.

The symptoms of *acute poisoning* are well known; headaches, usually severe and throbbing, dizziness, nausea, and vomiting may be present before stupor supervenes. In many cases, however, the patient drifts off into coma from a normal sleep without any distressing symptoms. Motor manifestations in the form of muscular twitchings or even generalized

convulsions may occur. The respiratory movements are slow, deep, and labored; the pulse, at first slow, later becomes accelerated; the temperature becomes elevated, particularly before death, when hyperthermia may be present. The skin, and especially the mucous membranes, assumes a flushed, bright-red color, due to the presence of carboxyhemoglobin. Coma may persist for an interval varying between a few minutes and a number of days. Death usually follows respiratory failure. Even after apparent recovery death may occur from pulmonary edema or pneumonia, which frequently develops.

The *treatment* of acute anoxemia consists of removal of the patient from the foul atmosphere into fresh air, the utilization of artificial respiration when indicated and the administration of oxygen-carbon dioxide (carbogen), the application of heat when necessary, and the use of stimulants if the respiratory and cardiac action is feeble.

Residual symptoms often follow restoration of consciousness. Recovery may be progressive and complete or incomplete and marked with residuals which may be transitory, persistent for some time, or permanent. In any case, the symptoms frequently group themselves into complexes, although sometimes they present conjointly or serially a mixture of syndromes. These will be reviewed briefly.

Visual symptoms constitute a not uncommon residual, due to a primary anoxic effect upon the optic nerves or the visual cortex, or by secondary changes in the occipital lobe resulting from vascular occlusion.* The cases of cortical blindness may be transitory (Baumler [1933]), with normal optic fundi (Fejer [1935]; Grimsdale [1934]); partial, with preservation of color vision (Wechsler [1933]); or total and permanent (Abt and Witt [1922]). Transitory visual agnosia has also been reported (Adler [1944]). Homonymous hemianopia may also be present when gross occipital lesions are unilateral (Francois [1942]).

* These changes in the cerebral tissues have been described briefly in the section dealing with structural changes, but an additional word on alterations in the white substance is in order. While such changes have been recognized in the past, recent contributions have emphasized the extent of such involvement. Hsü and Ch'eng (1938) reported their findings in two cases in which degenerative changes attributed to the direct effects of anoxia were found in the deeper portions of the white matter of the brain. On the other hand, Eros and Priestman (1942) are inclined to attribute the changes to vascular spasms. While vascular change (thrombosis) does occur, the spotty or diffuse patches of demyelination speak against their being the result of occlusion of any large vessels. They well may be due to relative anoxemia caused by some impairment of circulation. The recent opinion of Morrison (1946), based on experimental evidence, is to the end that such changes are due to repeated episodes of anoxia.

* Perhaps no other recently acquired fact in the pathology of cerebral anoxia is more important than that of secondary arterial thrombosis with consequent softening. This explains the large areas of cortical softening in the case of carbon monoxide asphyxia and the small focal scars and cysts, as well as the large porencephalic cysts after neonatal asphyxia.

Xanthopsia has likewise been mentioned (Goodside [1939]).

Motor manifestations may occur either as defect phenomena (paralysis) or the hyperkinetic states (Stengel and Zeller Mayer [1937]). Such complications have been described in the form of hemiplegia (Balthazard [1919]; Vermeylen and Heernu [1935]; Lereboullet and Puech [1939-40]; Lhermitte, Monier-Vinard, and Ajuriaguerra [1939]); paraplegia (Goodside [1939]), apraxia and convulsions, either immediate (Longo and Barini [1945]) or delayed (Nichols and Keller [1937]; Schiersmann [1938]). These complexes are marked by increased deep reflexes and pathologic reflexes, bilateral, unilateral, or local, as the case may be. In minor cases altered reflexes may be the only abnormal finding. Tremor and choreo-athetoid movements, which may be unilateral (Nichols and Keller [1937]), will be described in the following paragraphs.

The *ganglionic syndromes* (particularly parkinsonism) have been described quite frequently as residual sequelae of carbon monoxide poisoning. This is not unexpected, because of the fairly high incidence (pathognomonic of carbon monoxide poisoning) of softening of the globus pallidus as found in fatal cases with prolonged survival interval. Yet, the *lenticular syndrome* is apparently quite rare in recognizable form, much more so than after anoxia from nitrous oxide. On the other hand, *parkinsonism* is much more common. In Grinker's case (1926) this syndrome appeared within two months. Other typical cases have been described by Mackay (1930), Boals (1934), Shillito, Drinker, and Shaughnessy (1936), and Goodside (1939). Strangely enough, complete recovery may occur after this syndrome develops. Sanger and Gilliland (1940) reported the recovery of a man from an incomplete parkinson's syndrome after about a month, and Nielsen (1943) after three years.

Speech disturbances (aphasia) have been observed as distinct features of several cases ("slow, incoherent speech," "slurred speech" [Dancey and Reed (1936)], sensory aphasia [Faure-Beaulieu (1936)], "slurred speech" [Hsü and Ch'eng (1938)], complete aphasia [Lhermitte, Monier-Vinard, and Ajuriaguerra (1939)], "marked speech defect," "speech halting and disconnected" [Rodgers (1940)], and perseveration [Wolf (1927); Cohen (1936)]). Evidently some degree of aphasia is not uncommon, judging from recently reported cases.

Peripheral neuritis is one of the complications which seems to be unique in instances of carbon monoxide poisoning in contrast to other forms of anoxia (Goodside [1939]). No doubt mild forms of neuritis are obscured in many cases by the other overshadowing symptoms, particularly the psychotic manifestations.

Minor disturbances reminiscent of *chronic psychoneurosis* are observed in many of the patients who recover. In some instances these symptoms persist for months or even years. Perhaps the most character-

istic features of this state are emotional flattening and change in personality (Nielsen and Ingham [1940]). Poor insight, indifference, obtuseness, anxiety, hazy memory, emotional depression, facetiousness, poor judgment, and deficiency in initiative have all been described, however. When such manifestations are alone present, the outlook seems to be good, recovery taking place after a prolonged interval (Nielsen [1943]).

It is the *psychotic manifestations* which seem to be the most constant, some aberrations being present in almost every patient who recovers, and being evident early in the course. At times the psychosis is permanent and even progressive to complete dementia. Psychosis after carbon monoxide asphyxia has been recognized for centuries (Cot and Guilleman [1935]; Raskin and Mullaney [1940]). Esquirol (1838) studied a case of complete dementia after carbon monoxide asphyxia, and Korsakoff (1889) is credited with recognizing the peculiar mental picture which he described as an effect of carbon monoxide poisoning, an observation which has been confirmed by many others since that time (Fracassi, Lambruschini, and Graziano [1935]; Daumezon [1936]; Ajuriaguerra and Daumezon [1937]; Goodside [1939]). The mental picture, however, may assume any one of a number of characters, such as hebephrenia or catatonia (Dancey and Reed [1936]), general paralysis (Dancey and Reed [1936]), dementia (Daday, Heuyer, and Mathon [1937]), manic-depressive psychosis (Stengel [1937]), agitated depression (Menninger [1936]), et cetera. Amnesia, confusion, irrationality, emotional depression, visual and auditory hallucinations, delusions of persecutory nature, resistiveness, and negativism are all commonly reported. As recovery occurs, irritability, imperfect memory, dullness or apathy, childishness, poor judgment, increased psychomotor activity, et cetera, replace the more profound manifestations.

The psychotic symptoms may be only transitory (Sanger and Gilliland [1940]), more enduring but still recoverable, persistent but nonprogressive, or they may pursue a progressively downhill course.

Fortunately, the incidence of serious psychosis is low (1 in approximately 2,000 cases of carbon monoxide poisoning, according to Rossiter [1928] and Shillito, Drinker, and Shaughnessy [1936], and 1 out of approximately 2,500 psychoses reported by Raskin and Mullaney [1940]).

Other *rare residuals* have been reported. The occurrence of anosmia has been noted (Roth and Herman [1938-39]), and marked nystagmus has also been described (Riedl [1941]).

From a study of these various residuals it is clear that cerebral damage is by no means uniform but scattered, and this is but a reflection of one's impressions from a review of the gross and microscopic alterations in the brain.

Therapy in this group of cases is essentially symptomatic.

Chronic poisoning occurs from a continuous exposure or from intermittent exposures to low concentrations of carbon monoxide gas. This may be so low that the patient may be unaware of any trouble until manifestations suggestive of a psychoneurosis appear. In other cases throbbing headaches, dizziness, and lack of strength and energy, at times associated with gastro-intestinal symptoms, may occur without any suspicion as to what the cause may be. These symptoms should be suspected as being the result of anoxemia in garage workers, traffic policemen, welders (especially those working in enclosed places), or people living in old, gas-heated or coal-heated homes. Polycythemia or the detection of carboxyhemoglobin in the blood is helpful in establishing the diagnosis. Treatment consists in correction of the cause.

THE SYNDROMES CONSEQUENT TO THE ANESTHETIC ASPHYXIAS

In previous sections attention has been called to the history, pathologic physiology, and the anatomy of the anoxial states resulting from anesthesia. It has been pointed out that nitrous oxide is the chief offender in this respect because of the advanced degree of anoxemia inherent upon deep anesthesia. However, no anesthetic capable of depression of the cardio-respiratory centers is entirely free from this danger. It is now recognized that cyclopropane (Gebauer and Coleman [1938]), sodium pentothal (Wilson [1946]), avertin (Nicolajev and Vitols [1938]), and even ether (Courville [1941]) are at times responsible for serious and even fatal anoxic episodes. The present writer has seen a number of patients who have had serious or lethal depression of the vital centers under spinal anesthesia with apparent residuals incident

to the resultant anoxia. There is good reason to believe that a multiplicity of agents is more likely to produce depression of the vital centers than one alone (Courville [1936]; Löwenberg, Wagonner, and Zbinden [1936]; Ford, Walsh, and Jarvis [1937]; O'Brien and Steegman [1938]; Stewart [1938]; Brown, Collins, and Vaughan [1938]; Van der Molen [1939]; Courville [1939]; McClure, Hartman, Schendorf, and Schilling [1939]; Behrend and Riggs [1940]; Gagel and Weese [1943]; Trier Morch [1943]; Madsen and Jorgensen [1943]; Barach and Rovenstine [1945]).

Further investigations have clearly shown, both clinically and experimentally, that the syndromes produced by anoxia incident to anesthesia are the result of physical changes in the cerebral tissues (see references cited above; also, Courville [1938]; Löwenberg and Zbinden [1938]; Steegman [1939]; Blume [1940]; Mehring [1942]; de Carvalho [1943]; Nesi [1944]). These postanesthetic syndromes, therefore, for the most part are produced by physical changes in the brain.

The syndromes which have been observed as a consequence of anesthesia are: (1) the acute psychoses; (2) hyperkinesias; (3) decerebrate states; (4) the residual psychoneurotic states, often chronic; (5) certain chronic psychotic states; (6) the parkinsonian syndrome; (7) the lenticular syndrome; (8) blindness; and (9) rare or atypical manifestations. As a rule these symptom-complexes are quite often "pure" (in contrast to the residuals of neonatal asphyxia), but this is not invariably the case.

The *acute psychotic states* are seen most characteristically after nitrous oxide (Courville [1936, 1939]; Batten and Courville [1940]). It has been pointed out that emotional instability, hysterical outbursts, acute delirium or mania, hallucinations, or cataleptic states may occur as an acute transitory residual after nitrous oxide-oxygen anesthesia. These more violent outbreaks, unaccompanied by decerebrate rigidity or convulsions, have a better prognosis as to life, but minor residuals in the form of psychoneurotic residuals may persist for some time.

The *hyperkinetic* states may be considered under several categories, namely, (a) muscular twitchings, (b) convulsive disorders, (c) increased psychomotor activity, (d) tremors, and (e) choreiform and athetoid movements. However, since most of these symptoms constitute but one manifestation among others in a given clinical picture, it is scarcely necessary to consider each one as a "state" by itself. For example, *muscle tremors* are often seen in the acute phase of anoxia incident to nitrous oxide, and *tremors at rest* and *choreiform* and *athetoid movements* occur as chronic residuals of anoxia of this origin. At times, however, *increased psychomotor activity* may be a very prominent symptom, constituting a clinical picture of its own (Nielsen and Friedman [1942]). The same is to be said at times for *convulsive seizures*, which for some reason or other are more apt to follow ether anesthesia.

The *decerebrate states*, associated as a rule with more or less profound *coma*, are also an immediate residual more often seen after nitrous oxide (Courville [1939]; Lenohan [1943]). The prognosis is much more grave under these circumstances but not necessarily hopeless. However, even with survival, serious and often crippling residuals persist. The patient is comatose, usually deeply so, and rigidity of the decerebrate type is present, often manifested by extensor spasms. Magnus-de-Kleijn phenomena may usually be elicited. The rigidity is usually generalized but may affect the members of one side or may alternate between the two sides. Between decerebrate episodes or "crises," which are characteristic of this state, this rigidity may not be so evident, although resistance of the individual members to flexion and extension may be elicited. Death usually occurs with hyperthermia (Courville [1936]; de Carvalho [1943]).

The residual *psychoneurotic states* are probably more common than has been supposed in the past. The present writer traced the experience of a professional woman who had an unfortunate experience under nitrous oxide and who thereafter became asocial, anxious, disinterested, and forgetful, and remained so for many months, with ultimate gradual recovery. Fletcher (1945) has also reported a similar and even more striking case. If the truth were fully known, it well might be that many instances of psychoneuroses are due to subclinical episodes of anoxia. This phase of the problem deserves more study.

Certain chronic *psychoses* are similarly to be accounted for. Savage (1887) reported a case of progressive mental deterioration after nitrous oxide anesthesia, and Batten and Courville (1940) reported their experiences with another case. In the latter some improvement was noted after the patient had spent a number of years in a mental institution. It is very likely that many examples of the so-called postoperative psychoses are in fact postanesthetic psychoses.

The *parkinsonian*, *athetoid*, or *lenticular syndromes* which follow the more profound postanesthetic anoxial states are quite rare but do occur (Courville [1936]; Lorentz de Haas [1941]). This is perhaps due to the fact that serious damage to the corpus striatum

and its substriatal connection must occur, yet with prolonged survival of the patient. In the present writer's experience these syndromes are usually associated with psychic changes of moderately advanced degree. Two subgroups have been delineated (Courville [1939]): (1) residual lenticular syndrome (with athetosis), and (2) residual parkinsonism.

Blindness as a residual of anesthetic anoxia must be extremely rare, and yet the present writer has had the opportunity to study three cases.* In one case (Case 19 [Courville (1939)]) blindness was found to be due to complete degeneration of the visual cortex, with death occurring 26 days after the anoxial episode. In another (Case 21 [Courville (1939)]) a patient with a residual lenticular syndrome was blind for three months after an anoxial episode under nitrous oxide-oxygen anesthesia. In the third case (Courville [1941]) blindness associated with primary optic atrophy followed ether anesthesia.

A few *rare* and *unusual manifestations* have been reported after the various types of anesthetics, but with ether again being indicted particularly. The case of hemiplegia reported by Pisetsky (1945) is an example of this situation. Deafness (Aagesen [1944]) and cranial nerve palsies (Humphrey and McClelland [1944]) have also been recently reported. There always remains the question, of course, whether it is the anesthetic or some coincident and unrelated vascular lesion (hemorrhage, embolism, or thrombosis) which lies at the bottom of the trouble.

As the problem becomes more widely understood, other variants of the chronic residuals after anesthetic anoxia may be added to this list.

The *treatment* of cerebral anoxia due to anesthetic agents is chiefly a matter of prevention. Once the episode has passed one can only hope. Energetic but intelligent efforts at restoration of cardiac and respiratory action are, of course, fundamental when a standstill of these functions occurs in the course of anesthesia. During the primary interval immediately following restoration of the circulation, the use of carbon dioxide-oxygen mixtures may help in quickly restoring tissue respirations, but it is very doubtful that prolonged administration of oxygen avails anything. Whether the immediate administration of ascorbic acid, presumed to be one of the inter-

* It is strange that visual defects have not been reported more often, when blindness is one of the early manifestations of anoxia. This is particularly true in altitude anoxia (see subsequent section).

mediary factors aiding in tissue respiration, would be of any help in borderline cases is uncertain, but it might be tried. Ultimately all treatment of those unfortunates who survive with crippling residuals is symptomatic.

ASPHYXIA DUE TO MECHANICAL OBSTRUCTION OF THE AIR PASSAGES

Anoxemia which is the result of mechanical interferences is much more prone to produce acute effects which leave no serious residuals. The etiologic factors are many and varied, and therefore are difficult to classify. Perhaps the simplest division of the clinical cases is on the basis of the location of the obstruction, viz., (1) internal, with interference in the upper or lower air passages, or in the lungs, and (2) interference with passage of air by external means. An internal obstruction block may be located in the upper air passages and may be transitory and incomplete, such as a relaxed tongue seen in the comatose patient or in one under anesthesia. Such an obstruction is rarely complete and ordinarily does not persist; it is manifested by coughing or gagging movements (in an effort to dislodge the object) and cyanosis. A foreign body, such as a bolus of food, on the other hand, may produce complete obstruction which results in death unless relieved very shortly. Swelling in the adjacent tissues due to a local abscess, phlegmon, or edema of the pharynx may also produce a relative anoxemia due to narrowing of the air passages. As has been pointed out elsewhere (Courville [1939]), such relative anoxemias may prove to be predisposing factors for serious anoxias of anesthesia.

The acute edemas of the lining membranes of the air passages due to irritant substances (war gases) or inflammation (particularly when the infection results in the formation of a false membrane, as in diphtheria) may produce an acute anoxemia of serious or

even fatal degree. The same mechanism applies in pulmonary edema, in a subacute phase in passive congestion, and in the pneumonias. Drowning occurs in much the same way, the air passages and pulmonary alveoli filling with water. Unless this fluid can be evacuated during a short time and respiration be restored, death will occur. However, when evacuation can be successfully accomplished, seldom do any serious persisting residuals occur.

In the relatively few cases in which the obstruction to ingress or egress of air is applied *externally*, on the other hand, residuals have been reported. Among the causes of this type of anoxia are smothering (as of infants by their bed clothing) and throttling (as by assault or hanging). As for the former, the accidental (or even purposeful) smothering of infants has been recognized since time out of mind (see section on history), and death is the unfortunate ending in the majority of these cases.

In throttling or hanging the possibility of severe but not sustained anoxemia not infrequently occurs. The present writer has had contact with one such case, that of a boy who had been throttled by an intoxicated man. As residuals the boy presented irregular choreiform movements which cleared up after several days. Nielsen and Friedman (1942) reported the case of accidental hanging in a lad of 16 who became cyanotic and unconscious within three minutes before he could be released. Maniacal outbursts and excessive motor activity continued for 16 hours; for another day jerking movements of the trunk and extremities were present; but within three days he had completely recovered.

In some instances the residuals are prolonged and permanent. Greidenberg (1900) reported a case of psychosis after hanging suggestive of that seen after carbon monoxide intoxication. Rotter's case developed psychotic

manifestations after throttling, surviving for a period of eight months. In those cases in which the patient does not survive but dies after an interval of several days, the histologic findings in the brain are those of mild anoxia (Rotter [1929]; Helwig [1937]; Tarsitano [1940]; Dublin and Brown [1942]).

The treatment in this group of cases consists in removal of the cause or alleviation of its effects and restoration of normal respiration. The latter is of paramount importance in instances of drowning, when drainage of excess water from the lungs and intelligent efforts at artificial respiration are indicated.

THE SYNDROMES OF ALTITUDE SICKNESS

We have learned that mountain sickness was man's introduction to the problems of anoxemia, and with high-altitude flying, it would seem as though it will likewise be the last of the frontiers of the subject to be explored. We learn from the history of mountain sickness that the Spanish conquistadores and their associates came to understand by experience the effects of the "too thin air" of the higher mountains. Ordaz, of Cortez's army, developed extreme fatigue and syncope on climbing the mountains about Mexico City. Acosta experienced dyspnea, fatigability, and nausea in the Andes. Later de Saussure (1803) defined more specifically the syndrome of acute mountain sickness, viz., dyspnea, palpitation, muscular weakness, and nausea at times followed by vomiting. An additional word was given by Glaisher (1871) in his experience in a balloon in which he and Coxwell had risen to an altitude of over 29,000 feet. Glaisher experienced difficulty in vision, extreme loss of motor power in the extremities, inability to speak soon followed by blindness, and loss of consciousness. These symptoms were later experienced by Tissandier when the disastrous flight of the *Zenith* on an experimental high-altitude flight at the re-

quest of Paul Bert caused the death of his two associates, Croce-Spinelli and Sivel.

A more recent report by McFarland (1937) indicates that the acute physiologic symptoms appearing in high altitudes are: (1) dyspnea on exertion and irregular, periodic respiration, (2) easy fatigability, (3) coldness of the extremities, (4) dry skin, (5) disturbed sleep, (6) flatulence, (7) headache, (8) sore throat, (9) irregular pulse rate, and (10) lassitude. Actual mountain sickness is characterized by cyanosis, dizziness, anoxia, nausea and vomiting, abdominal pain and diarrhea, and physical and mental depression. As a rule these symptoms are transitory and disappear as the patient becomes acclimated. However, cyanosis and mental obtuseness may persist.

Subacute and *chronic forms* of mountain sickness have also been recognized, a condition (*soroche*) which has been known by the native Indians of the Andes since time immemorial. In a study of high-altitude disease by Monge (1932) two types of the disease were disclosed, (1) the erythremic type, and (2) the emphysematous type.

In the *erythremic type* both subacute and chronic forms are described. The subacute form is characterized by fatigability, cyanosis, drowsiness, headache, respiratory irregularities, and digestive disturbances (to the extent of nausea and vomiting) followed by loss of weight. The red blood count is markedly elevated as a rule (approximately 7 million per cmm.). The symptoms may finally subside (if the patient can become acclimated) or may lapse into the chronic form.

Chronic mountain sickness is manifested by severe cyanosis, lethargy even to the extent of coma, marked dyspnea, epistaxis, and ultimately emphysema and cardiac failure. In addition, severe pains and paresthesias, mental confusion, apathy, and change in personality may be present. Death from hemorrhage, pulmonary complications, or cardiac failure may occur unless the patient seeks a lower altitude.

In the *emphysematous form* the predominant symptoms are pulmonary in character—chronic bronchial irritation, dyspnea, cyanosis, and hemoptysis. Objectively, the typical barrel-shaped thorax is evident, as is clubbing of the fingers. Cardiac insufficiency may also become apparent.

While the so-called *altitude sickness* of avi-

ators resembles closely acute mountain sickness, a special word on this clinical type of anoxemia is in order. In the *acute form* the first symptoms occur at about 9,000 feet (Armstrong [1939]), being increasingly prominent at higher elevations, with unconsciousness developing at 25,000 feet. Headaches, drowsiness, respiratory irregularities, increasing fatigability, and euphoria followed by mental obtuseness are characteristic.

The *chronic form* of altitude sickness results from repeated flights to high altitudes without adequate oxygen supply. Headaches, often persisting for some time after the flight, chronic fatigue, insomnia, mild psychic alterations (irritability, nervousness, lack of initiative, mental dullness), and at times lethargy are typical of this state. These symptoms tend to disappear in the course of time if the patient is not exposed to further anoxic episodes.

The indicated *therapeutic measures* in case of mountain sickness are absolute rest, administration of oxygen, and return to lower altitudes. In the case of high-altitude fliers with sudden deprivation of their oxygen supply, the immediate administration of oxygen from an auxiliary source is necessary to prevent a fatal issue. In chronic states cessation of flights is indicated unless an adequate supply of oxygen is available.

ANOXIA INCIDENT TO HEMOLYTIC ANEMIA, EXSANGUINATION, AND SHOCK

In previous sections mention has been made of a form of anoxemia attendant upon anemia. The *anemic form of anoxemia* results from a decrease in the amount of oxygen being carried in the blood for want of an adequate number of red cells, whose hemoglobin carries this gas in loose chemical combination. In most cases of anemia, particularly the chronic secondary types, this anoxemia is relative and not evident, except when the patient attempts

to carry out some physical effort beyond the limits set by the oxygen-carrying abilities of the blood. Then some degree of dyspnea, light-headedness, and fatigue soon becomes apparent. These effects are usually transitory, and no noteworthy residuals are known to occur.

A quarter of a century ago, before the present effective treatment of primary anemia was discovered, a common complication in the far-advanced cases was the occurrence of psychotic manifestations. Whether these symptoms were due alone to the profound anemia or to some associated toxin has never been established, but it is likely the defect in oxygen-carrying abilities of the blood was at least contributory.

In serious acute loss of blood to the point of *exsanguination* we have to do with the anemic form of anoxemia in its most serious form. Death in these instances is due to the effects of blood loss on the heart and brain, and ordinarily we do not have to deal with any residual problem of anoxia. In less severe forms of blood loss in which life is not lost there come to be evident some of the anoxic effects of this state. This situation was occasionally seen in the recent war (Church and Loeser [1944]). Maniacal outbursts, hyperkinetic and paralytic manifestations, and disturbances in speech similar to those found after other types of anoxia are seen in these cases of exsanguination. These residuals are usually transitory, and full recovery is to be expected in the majority of cases in which adequate and prompt replacement of blood has been accomplished. One can only guess the numbers of lives saved and the residuals prevented by effective preparative measures during the past war.

In cases of *shock* a somewhat different form of anoxemia occurs. It is allied to the stagnant type, in which anoxia of relative degree is due to partial oxygen depletion of the blood which circulates at too slow a rate. In most clinical

conditions stagnant anoxia plays no important role, and resultant symptoms are minor. However, in case of prolonged shock it is possible for structural changes to occur in the cerebral cortex which are probably to be attributed to anoxia (Rand and Courville [1936]). As far as has been reported, these alterations are not severe, and no late residuals have been noted. Just what might come to light with a continued study of patients who have had severe surgical shock is not known. The possibility of mild residual symptoms in the psychic realm is to be considered.

THE RELATIONSHIP OF ANOXIA TO CERTAIN FUNCTIONAL AND STRUCTURAL NERVOUS DISORDERS

A survey of the problems of anoxia results in certain impressions as to the possible relationship between episodes of oxygen want and certain nervous disorders of uncertain etiology with which we come in contact in clinical practice. We learn, for one thing, the effects of anoxia on the brain manifested by irregularly distributed areas of focal necrosis which fuse to form laminar degeneration of the more susceptible nerve cells. An ultimate result of such change is the shrunken, yet morphologically intact, convolutions (microgyria). When the process is more widespread, atrophy of a lobe or even of a hemisphere results. When the local destructive process is more complete, perhaps through the intervention of secondary vascular changes, local cortical scars or "cysts" (due to ultimate complete loss of all nervous substance), or even larger defect lesions designated as porencephaly are formed. Thus we have made clear the origin of a number of lesions of the brain found as a rule in young individuals, lesions, hitherto considered to be congenital or of unknown etiology. Ulegyria, or lobar sclerosis, of childhood (Friedman and Courville [1941]), hemispherical agenesis, local microgyria, and porencephalic cysts are now removed from these categories and can be

charged up to neonatal asphyxia. The same may be said for the source of the group of epileptogenic lesions described by Penfield and Erickson (1941) as focal cortical scars or cysts. Through this information we have a clearer insight into the cause of many instances of epilepsy, mental deficiency, spasticity, choreo-athetosis, ataxia, and other defect syndromes. But can we safely go further than this?

A study of the problem from the clinical side also has its rewards. When one views the residuals—acute, subacute, and chronic—of known anoxic episodes from various causes, he learns that hyperkinetic states, paralysis of variable extent, extrapyramidal syndromes, as well as disturbances in the psyche are characteristic effects of the cerebral insult. We have learned that parkinsonism as well as increased psychomotor activity, disturbances in vision and speech, apraxia, and psychotic episodes may be the transitory as well as permanent results of asphyxia.

More than this, we have learned that aberrations indistinguishable from neuroses or psychoneuroses of "psychogenic" nature can follow minor anoxemic episodes (Fletcher [1945]). It is now further believed that some instances of the hyperkinetic state associated with lack of amenability to disciplinary control in normally intelligent children and adolescents may be the ultimate residuals of neonatal asphyxia (Preston [1945]). With this in mind we can see some reason for the abnormal electro-encephalograms in so many of these children.

The question may now be fairly asked whether there are not many instances of psychoneuroses which are the result of some distant anoxemic episode or of a present one of long-continued want? May not some of our so-called "idiopathic" epileptic states have their genesis in birth anoxia, as Nielsen (1946) has suggested? Is it not possible that certain

examples of parkinsonism, of chorea, and of the primary pyramidal and cerebellar degenerative disorders of unknown cause may be the residuals of minor natal anoxia long since forgotten? May not the cortical or ganglionic nerve cells receive some minor but persistent damage which brings about their premature decadence? At least the similarity between the spastic diplegias of childhood of anoxial etiology and the "primary" paraplegias of later life suggests a possible connection.

Of course, it is possible to carry this analogy too far. Not all cases of idiopathic epilepsy (with evident inherited dysrhythmia), not all the behavior disorders (many obviously of traumatic etiology), not all the lenticular syndromes of childhood (kernicterus must also be considered), not all cases of mental deficiency or all spastic states are to be so classified. Neonatal anoxia is but one of several factors, albeit a very common one. But the fact remains that a more critical scrutiny of the birth history must be made in many of these diagnostic problems in which the etiology is obscure. We may, moreover, learn some-

thing of the etiologic factor by looking into the medical history in cases of some of our older patients with functional states in which no adequate psychic cause can be uncovered. At least, there is no harm in making the effort.

In our knowledge of anoxia and its effects on the human organism we have come a long way, medically speaking, since the days of Aristotle. We have found out that "air, otherwise too thin for respiration," can do many things besides make one light-headed when climbing Mount Olympus. But in spite of all that we have learned about anoxia and its residuals, there still remains a borderland to explore between those patients who are recognized as fully recovering from such an episode and those who survive with crippling or disabling effects. Let us further explore this new frontier of the minor residuals of anoxia, for our understanding of the cause of some of our clinical entities may thereby be considerably enhanced.

(NOTE.—The list of references used in this review was too long for inclusion in this journal. It is to be found in full in the author's reprints.)