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CEREBRAL ANOXIA AND ITS RESIDUALS*

III. THE STRUCTURAL CHANGES

CYRIL B. COURVILLE, M.D.

In a study of the structural alterations occurring in the central nervous system it is necessary to understand certain fundamentals of the pathogenesis of such changes. Some of the essentials of the pathologic physiology of anoxia have already been pointed out. There remains to be presented a brief summary of the steps leading to the residual lesions resulting from severe oxygen want which hitherto have often been misinterpreted. The stages in the development of the ultimate lesion, for all practical purposes, may be divided into the acute, subacute, and chronic phases. However, a few important facts need to be mentioned and briefly elucidated before we are prepared to investigate the end results of the process initiated by lowering the oxygen tension of the blood.

1. The principal and most important effects of anoxemia are to be found in the central nervous system. This is due to the sensitive character of these tissues. Changes are to be found also in the lungs (thickening and cellular infiltration of the alveolar walls), the kidneys (degeneration of the renal epithelium), the liver (perivenous necrosis), the spleen (cellular infiltration), the heart muscle (brown atrophy and focal necrosis [Figure 1]), and the adrenals (hemorrhages) (Courville [1939]).

2. The immediate effects of anoxemia, as far as one can judge from the anatomic appearances of the brain and other organs, are intensive congestion and vascular dilatation, presumably resulting in a considerable degree of stagnation.

3. It is not always possible to predict the outcome (hence the extent and degree of damage to the nervous tissues) by the immediate clinical reaction. When cardiac arrest as well as respiratory failure occurs, the prognosis is usually grave. On the other hand, a fatal issue may follow even transitory respiratory failure.

4. The full extent of ultimate damage is to be seen only after an interval of several days, and progressive changes occur for a period of several weeks.

5. Clinical manifestations do not necessarily parallel evidences of physical damage to the brain. Profound manifestations may be present in the early period when there is little to be seen, and considerable recovery may occur in the presence of grossly evident lesions.

6. While some selectivity is shown in the lesions produced by asphyxia (globus pallidus and visual cortex), there is considerable variability in the extent and distribution of damage to the cerebral gray matter.

7. The exact mechanism of asphyxia has something to do with the ultimate pathologic picture, for the residual lesions in the various clinical entities show a considerable latitude of physical changes in the nervous tissues.

These factors cover the important features of the clinical course of patients who have been subjected to oxygen want, and their enumeration will serve to maintain a clinical orientation while we delve into the problems which are essentially pathologic.

CEREBRAL CHANGES IN EXPERIMENTAL ASPHYXIA

The effects of experimental oxygen want on the brain have been known for many centuries, although, to be sure, the experimenters did not always know what it was that produced the ill effects. It is recorded that during the Middle Ages traveling magicians produced temporary paralysis in goats (whose cerebral blood supply is entirely dependent upon the carotids) by firmly grasping these animals about the neck. The animal would then fall completely paralyzed, ostensibly because of some powerful mumbo-jumbo pronounced by the magician. When the grip was released, the goat promptly jumped up and ran about as before.

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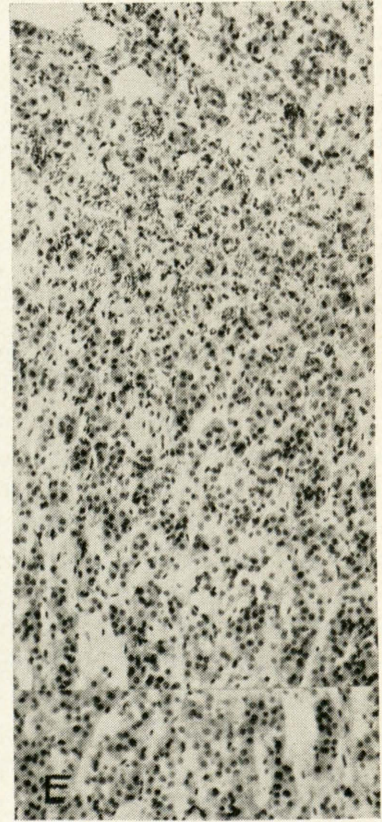
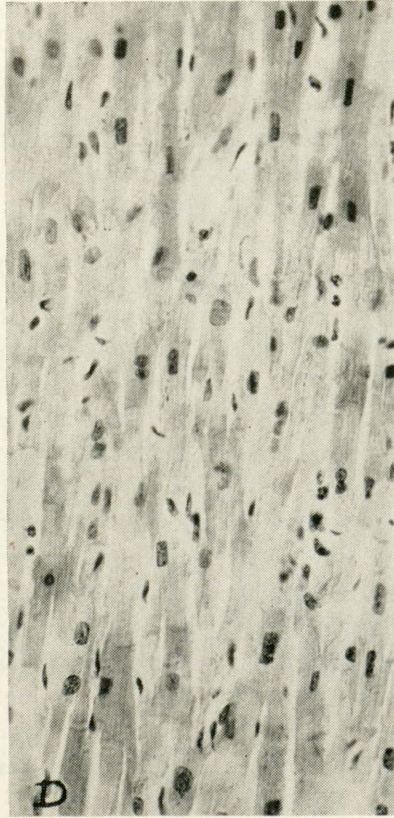
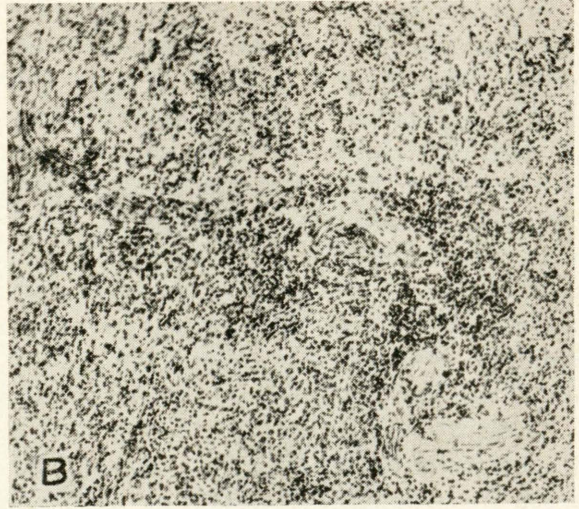
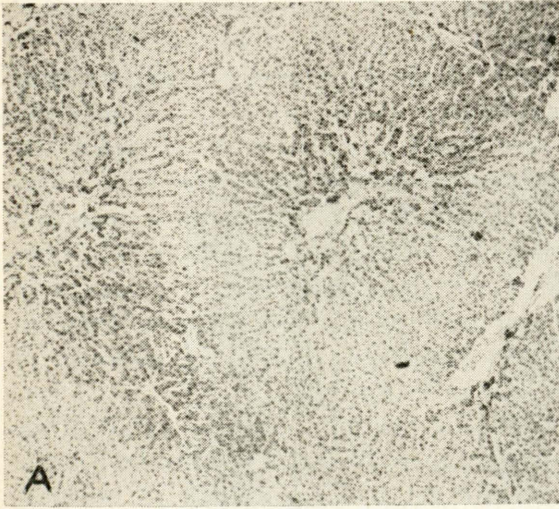


Figure 1. General pathology of anoxia. *A.* Perivenous necrosis of the liver. *B.* Cellular infiltration of the spleen (acute splenitis). *C.* Degenerative changes in the epithelium of the renal tubules. *D.* Minimal brown atrophy of cardiac muscle. *E.* Focal hemorrhages into adrenal cortex.

Sir Astley Cooper seems to have been the first to produce convulsions and other characteristic symptoms after ligation of the carotids in dogs, an experiment which was repeated by Leonard Hill (1896) over half a century later. Hill and Moot (1906) were among the first to study the alterations in the nerve cells under these circumstances. A more critical study of cerebral changes after temporary interruption of the cerebral circulation was made by Gildea and Cobb (1930), whose work remains a classic and a basic study of the effects of anoxemia.

These various experimenters have been able to demonstrate various effects on animals which are strikingly reminiscent of the effects of asphyxia on man. Convulsions—either immediate or delayed—spasticity, running fits, yowling spells, blindness, behavior peculiarities, and dementia have all been described. It is to be expected, therefore, that the changes in the brain found in animals after temporary ligation of the supplying arteries would be comparable to those found in man after profound asphyxia, since the immediate effects of ligation can be attributed only to the want of oxygen.

The histologic alterations in these animals were found to be characterized by areas of focal necrosis in the cerebral cortex, seen after a survival period of at least twenty-four hours. There was an associated dilatation of the perivascular or perineuronal spaces suggestive of some circulatory change (? edema). The nerve cells were predominantly affected, showing pyknotic change, acute swelling, ischemic change, liquefaction, vacuolization, or lipoidal degeneration. The interstitial cells were less affected, presenting evidence of reactive swelling and early proliferation. The leptomeninges were slightly thickened in some instances. In cases of death shortly after ligation the blood vessels were dilated. After an interval of time the walls of the blood vessels proved to be thickened and increased in number, and

their endothelial cells contained droplets of fat.

In an interesting study of experimental neonatal asphyxia in guinea pigs Windle and Becker (1943) found that fairly typical disorders in the affected animals were to be accounted for by an absence of, or regressive changes in, the nerve cells of the cerebral cortex. These alterations are very pertinent in view of the histologic findings, to be described in later paragraphs, in human examples of asphyxia neonatorum.

If these alterations are truly typical of the condition, then we may expect to find in the human subject (1) focal necrosis, (2) predominant structural alterations in the nerve cells, with (3) reactive changes in the interstitial elements and in (4) the leptomeninges, and (5) alterations in the blood vessels indicative of circulatory changes (edema and stagnation), as well as structural changes in the vessel walls. A study of human pathology is next in order.

THE ACUTE EFFECTS OF ASPHYXIA

The immediate effects of asphyxia are variable, particularly in degree, depending upon the means by which it is produced. The most profound changes in man have been observed in balloonists who have been exposed to rarefied atmospheres. In cases of death under these circumstances the skin is a livid bluish-purple color, and hemorrhage occurs from the lungs, less often from other body apertures. Internally, hemorrhages into the brain, viscera, and linings of the body cavities are also the rule, these being the result of an intense congestion.

In cases of carbon monoxide poisoning (illuminating gas, automobile exhausts) the manifestations are much less profound. The cherry-red color of the mucous membranes and viscera is characteristic and due to the formation of carboxyhemoglobin. Hemorrhages, when present, are usually small (petechial),

but occasionally may be of larger size. Intense congestion is still the most prominent feature at autopsy.

stances may be few or absent altogether, particularly as far as the brain substance is concerned. In one of the cases studied by the pres-

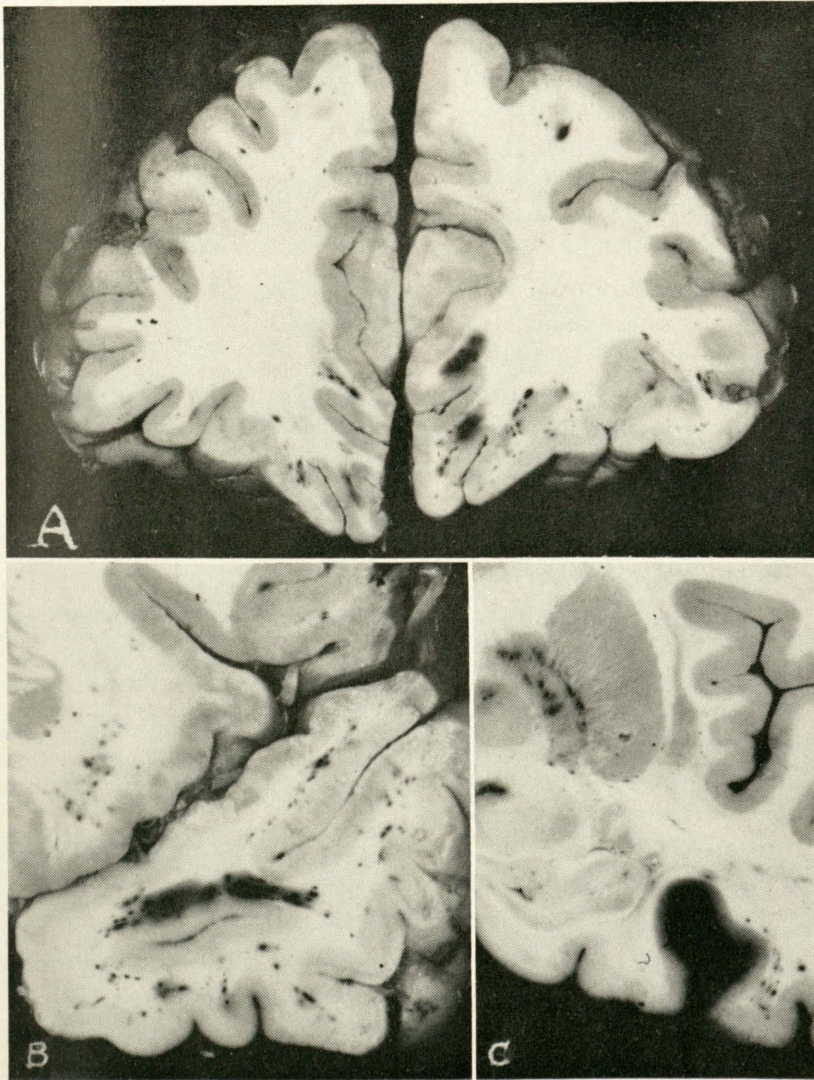


Figure 2. Hemorrhages into brain substance after asphyxia under nitrous oxide-oxygen anesthesia. Survival period six days, six hours. *A* and *B*, hemorrhages into cerebral centrum. Note tendency for hemorrhages to occur in white substance bordering gray matter. In *C* hemorrhages are found between divisions of lenticular nucleus.

Congestion is also the essential feature in cases of death after neonatal asphyxia and asphyxia after anesthesia, but it is much less profound. Hemorrhages under these circum-

stances may be few or absent altogether, particularly as far as the brain substance is concerned. In one of the cases studied by the pres- ent writer there was a predilection for localization of these hemorrhages, both large and small, in the white substance adjacent to the gray matter (Figure 2).

This congestion is also apparent histologically. Sections from the various visceral organs show the small blood vessels to be widely dilated and packed with red blood cells. Small hemorrhages, perivascular in location, are often found, particularly when death comes as a result of profound and acute asphyxia.

The brain and also the blood vessels of the pia mater, the cortex and basal ganglia (less so of the cerebral centrum), and of the choroid plexus are all considerably dilated and filled with red blood cells (if the body has not been fixed by embalming before autopsy). Hemorrhages into the nervous tissue may also be found. These are the typical ball, perivascular, or ring hemorrhages indicating focal rupture of small blood vessels. Not infrequently such hemorrhages are associated with focal infarctions in which the hemorrhagic pigment, free or phagocytized, is found in the necrotic area.

The changes in the cellular elements are not striking. Acute swelling of the nerve cells with loss of Nissl's substance and acute swelling of the oligodendroglia are most characteristic.

It may be said, then, that whatever be the underlying factors resulting in damage to cells and tissues, a more or less severe degree of congestion is the rule, and the more severe the congestion the greater the likelihood of the occurrence and increase in size of the hemorrhagic effusions.

SUBACUTE STRUCTURAL CHANGES

It is in the realm of the subacute course after asphyxia that there is so much misunderstanding, both as to the clinical findings and the effects on the brain. This has arisen from the previously accepted concept that deaths due to anesthesia are immediate. That individuals may survive for a varying interval before death, or partially or fully recover from what

appear to be profound insults to the brain, needs to be kept in mind.

The gross alterations in the brain in instances of subacute courses lasting a few hours to a few weeks vary considerably from one case to another; the changes are also somewhat dependent upon the means by which asphyxia was produced. In any case, it is the gray matter of the brain which is almost exclusively damaged by the process, if not entirely so.*

In instances of *carbon monoxide* (or illuminating gas) *poisoning* the resultants of asphyxia consist of areas of cortical softening and damage to the globus pallidus. The areas of softening in the cortex are sometimes of fairly large size and seem to be due to thrombosis of some of the terminal cortical arteries. The affected areas first undergo circumscribed softening, followed by depression of the area as phagocytosis of the decadent material proceeds. The subjacent white matter supplied by the vessel also undergoes softening with the overlying cerebral cortex. The globus pallidus may also undergo a type of central necrosis first manifested by a circumscribed granulation of the enclosed gray matter with subsequent liquefaction and absorption.

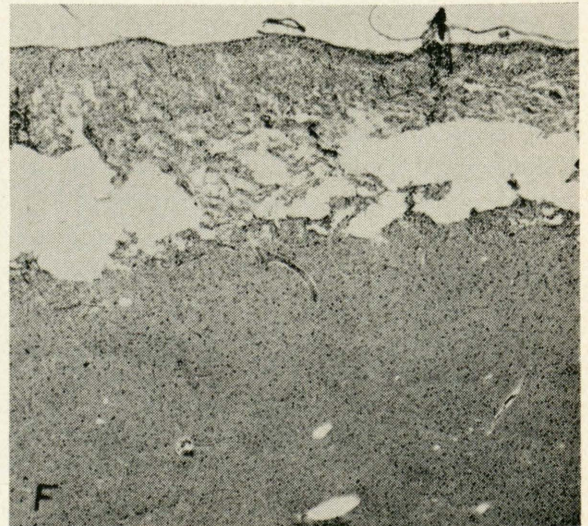
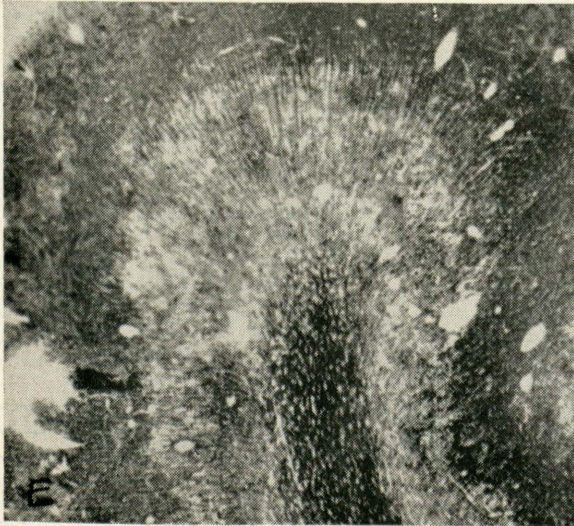
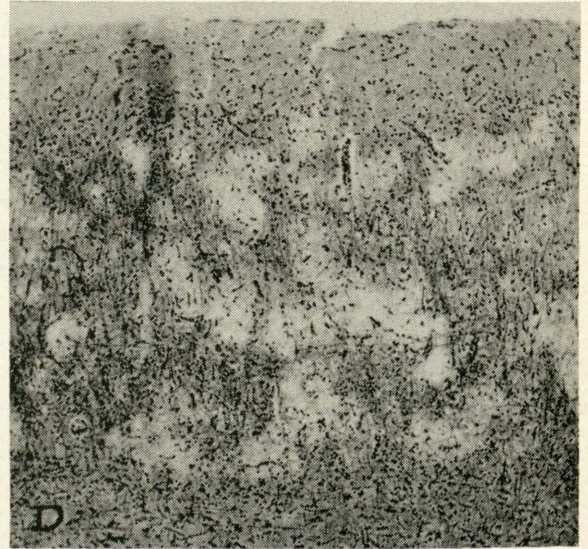
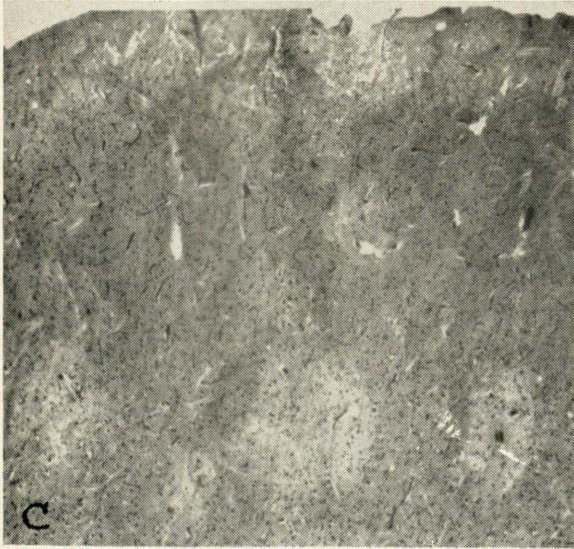
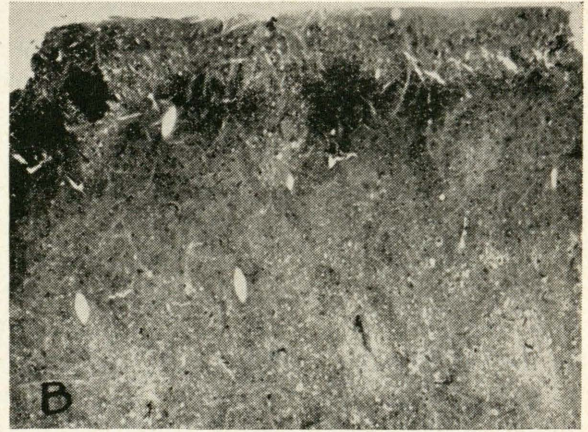
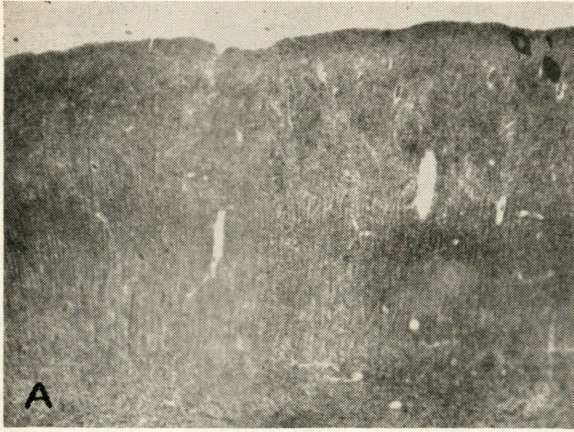
In cases of the *anesthetic asphyxias* the picture is somewhat different. No very large areas are affected, but within a few days after the episode there will be found by the palpating finger small spots of softening which suggest those following embolism. A modification of this pattern is a diffuse subtotal alteration in the visual cortex, which becomes evident grossly only on cut section. The changes in the globus pallidus are similar to those found after asphyxiation with carbon monoxide.

After *asphyxia neonatorum* as a rule death either occurs at once or else the patient survives for many months. The writer has not had the opportunity to study the brain of a case with a short survival period, nor does he know of reports of any so studied.

It is the histologic alterations within the cerebral gray matter which betray the course of the central lesions, and by following the sequence of events in the development of the cortical lesion we are able to learn something

* After experimental asphyxia in dogs, produced by exposure to carbon monoxide (Yant *et al* [1934]), degenerative changes in the white matter in the form of areas of demyelination resulting in the formation of small cysts were noted. Similar changes were also found in the peripheral nerves. These alterations have not been found by the writer in instances of asphyxial damage to the human brain; nor does he know of such changes as may have been observed by others.

Figure 3. Development of cerebral cortical lesions in cases of anoxia. A. Earliest evidence of focal cortical necrosis. B. Multiple foci of necrosis showing beginning limitation of margins. C. Well-defined foci involving several cortical layers. D. Early fusion of individual foci. E. Well-defined laminar necrosis affecting entire convolution. F. Subtotal cortical necrosis.



of the pathogenesis of this lesion. The various stages of development of the cortical lesion are shown in the accompanying series of photomicrographs (Figure 3).

As has been suggested in the previous section, the earliest lesion to be found in the brain in cases of postanesthetic (nitrous oxide-oxygen) anoxemia consists of early degeneration of small groups of cells with enlargement of the perivascular spaces and the formation of fluid spaces in the interstitial tissues. As the lesion progresses, areas of *focal necrosis* (*Herde*) develop which prove to be simply enlargements of the areas of degenerative changes affecting but a small group of cells. As Gildea and Cobb (1930) found experimentally, these areas of devastation appear to be the basic lesion, one which seems to be characteristic of the condition. Only when this is fully recognized is one in a position to evaluate critically the ultimate lesion.

Next in order in the line of development of the cortical lesion is *zonal necrosis*. In a survey of the distribution of these lesions it has been shown (Courville [1939]) that the cortical layer involved varies from one region to another in a given case and that no one layer is uniformly affected. It is also evident from a study of interval cases that zonal necrosis is but the result of fusion of multiple areas of focal necrosis.

In turn, the fusion of these multiple stratigraphically disposed laminae of zonal necrosis results in *subtotal cortical disintegration*. In the writer's experience this advanced degree of change resulting from asphyxia alone (without the intervention of vascular alterations) is found characteristically if not exclusively in the visual cortex in the region of the cal-

carine fissure after nitrous oxide anoxemia.

In the globus pallidus* only two types of degeneration have been found, viz., focal necrosis and subtotal necrosis. The absence of an intervening stage of zonal or laminar necrosis is obviously due to the lack of arrangement of cells in layers with their attendant characteristic blood supply.

The alterations in the cellular elements of the brain are of special interest to the pathologist. While injury to nerve cells and fibers is the earliest and most important change, destructive as well as reactive alterations are also found in the interstitial elements, in the leptomeninges, and in the blood vessels. These changes, some of the more important of which are shown in the accompanying figure (Figure 4), deserve brief mention.

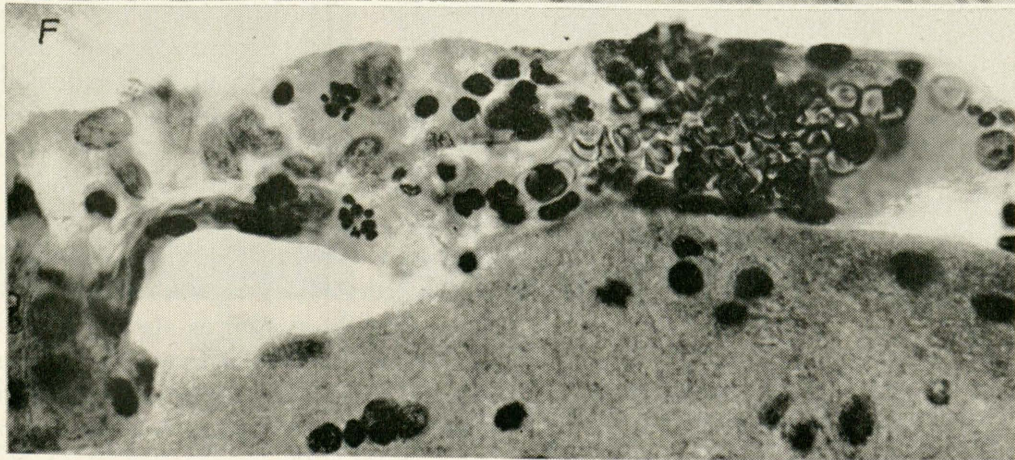
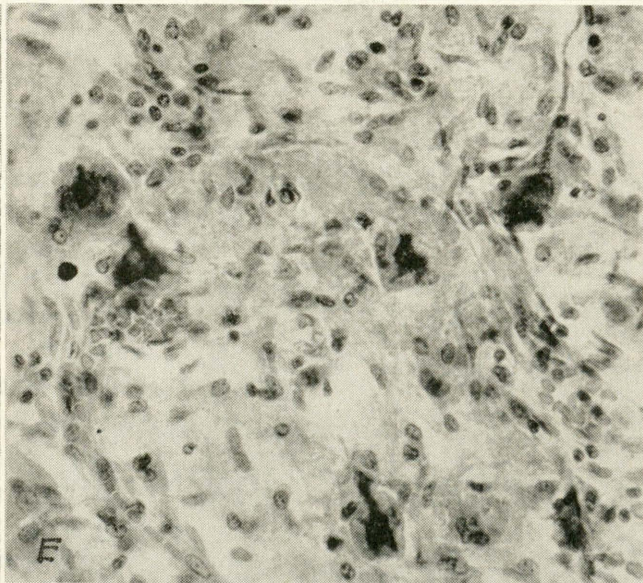
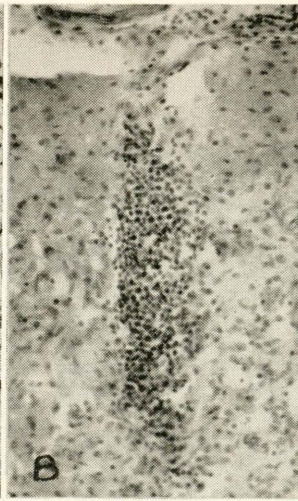
Alterations in the *nerve cells* consist in pyknotic change (sclerosis, *Zellschrumpfungen*), ischemic alteration, acute swelling, acute necrosis, pigmentary atrophy and ferrugination ("calcification"), depending upon the time interval after the asphyxial episode and the proximity of the cell areas of necrosis. These alterations in the parenchymatous elements are, after all, the most important, for they account for the clinical manifestations of the patient, whether these be acute, subacute, or chronic. A study of these changes in the parenchyma sheds considerable light on the etiology and pathogenesis of such changes as observed under other circumstances.

The *nerve fibers* are also damaged either directly (when adjacent to, or enclosed within, an area of focal necrosis) or indirectly, due to destruction of the parent cell. These alterations, not specific for asphyxia, involve not only the axis cylinders but also the myelin sheaths (Courville [1939]).

The supporting *astrocytic* network also suffers. Destructive changes occur in these elements within the areas of degeneration, while the glia cells bordering these areas undergo active and advanced proliferation

* The deposit of iron (calcification) in the small blood vessels of the lenticular nucleus has long been recognized as a change resulting from asphyxia, being found characteristically in individuals who succumb after exposure to carbon monoxide. The writer has studied the brain specimen in one case in which such deposits were present sixteen hours after asphyxiation. In fact, in the cases with short survival periods these vascular changes in the lenticular nucleus may be the only demonstrable abnormal findings.

Figure 4. Essential features of recent histopathologic alterations in the cerebral cortex after anoxia. *A*. Acute reactive changes in microglia provoked by tissue destruction. *B*. Perivascular round-cell infiltration observed three and a half weeks after an asphyxial episode. *C*. Proliferation of subpial astrocytes over subtotal destruction of the occipital cortex (interval, three and a half weeks). *D*. Acute changes in nerve cells in a small area of focal necrosis. *E*. Chronic change (ferrugination) of nerve cells. *F*. Mitoses in endothelial cells of small blood vessel leading to new vessel formation.



to form a dense glial scar. Proliferation of astrocytes is found also in the subpial region in cases of extensive cortical necrosis.

The *microglia* likewise respond promptly to degenerative changes with swelling and structural alterations leading to the formation of compound granular corpuscles. Phagocytosis by these cells is prompt and energetic, and one finds in cases of survival of three weeks or more that the debris has been cleared away to a remarkable extent.

As for the *oligodendroglia*, acute swelling of generalized distribution is the rule, with regressive changes taking place in those elements within areas of necrosis.

The *arachnoid* is found to be proliferated (chiefly the cap cells) and often adherent to the underlying *pia mater* in subacute cases. These changes appear to be the most prominent over areas of severe cortical injury.

Alterations in the *blood vessels* are important not only because of histologic interest but also because of the significance of such changes in the production of secondary lesions in the brain. Within three weeks after an asphyxial episode one finds evidence of proliferation (mitosis) of the intima of the small cortical and ganglionic vessels leading to proliferation of new-formed channels. This leads to the formation of a highly vascularized scar, with secondary loss of parenchymatous elements incident to interference on a different basis from that of simple anoxemia.

In addition to the evidences of proliferation observed in the smaller vessels, there occurs a similar change which affects specifically the intima of larger ones. This results in obstruction of these larger vessels with secondary softening of larger areas of the cortex. These changes are especially characteristic of later residuals of carbon monoxide asphyxiation. It has been suspected that similar changes occur in many cases of neonatal asphyxia, leading to the formation of small cortical cysts or the larger porencephalic cysts (Courville and Marsh [1944]).

It is clearly evident that while these asphyxial alterations of cells and tissues (only outlined in this connection) may be quite technical in their aspects, it is these changes which explain the ultimate pathologic picture as well as the intercurrent clinical picture. This will be shown to be true from a pathologic viewpoint in the succeeding section of this paper, and also more fully from its clinical aspects in the one to follow.

THE ULTIMATE PHYSICAL RESIDUALS OF CEREBRAL ANOXIA

Because some patients survive an asphyxial episode for many years, and because in some

instances this episode has not been correctly interpreted for what it really is (or perhaps has been entirely forgotten), the ultimate residuals in the form of physical changes in the brain have long gone misinterpreted. We still do not know what the ultimate changes in the brain are after asphyxia under anesthesia, for no known case has been followed over a period of years with final opportunity for a critical study of the cerebral tissues. The same is largely true of the carbon monoxide asphyxias. Even the residuals of neonatal asphyxia, common enough in clinical practice, have usually been mistaken for the results of traumatic lesions of the brain—assumed to be the effects of subdural, subarachnoid, or intracerebral hemorrhages. But we are now able to anticipate in some cases just what these changes may be, judging from the subacute lesions. In other instances of asphyxia of the newborn there is ample evidence of the ultimate changes, and these will now be briefly discussed.

As pointed out heretofore, the criterion for the establishment of the anoxic etiology of a given lesion of the brain is the discovery of histologic changes in the gray matter of focal character, in other words, residuals of focal necrosis. Simple recourse to a microscopic examination of blocks of atrophic cerebral cortex in many cases of spastics, idiotics, athetoids, ataxics and epileptics will serve to demonstrate these lesions. And, contrary to accepted concepts, these characteristic acellular areas will be found in cases of focal cortical scars ("microgyria"), lobar sclerosis of childhood (Friedman and Courville [1941], hemispherical (cerebral or cerebellar) agenesis (Courville and Marsh [1944]), as well as about focal cortical cysts (Penfield and Erickson [1941]) or porencephalic cysts. Many of these lesions, formerly considered to be due to imperfect morphogenesis or to birth trauma, can now be proved to be of asphyxial etiology.

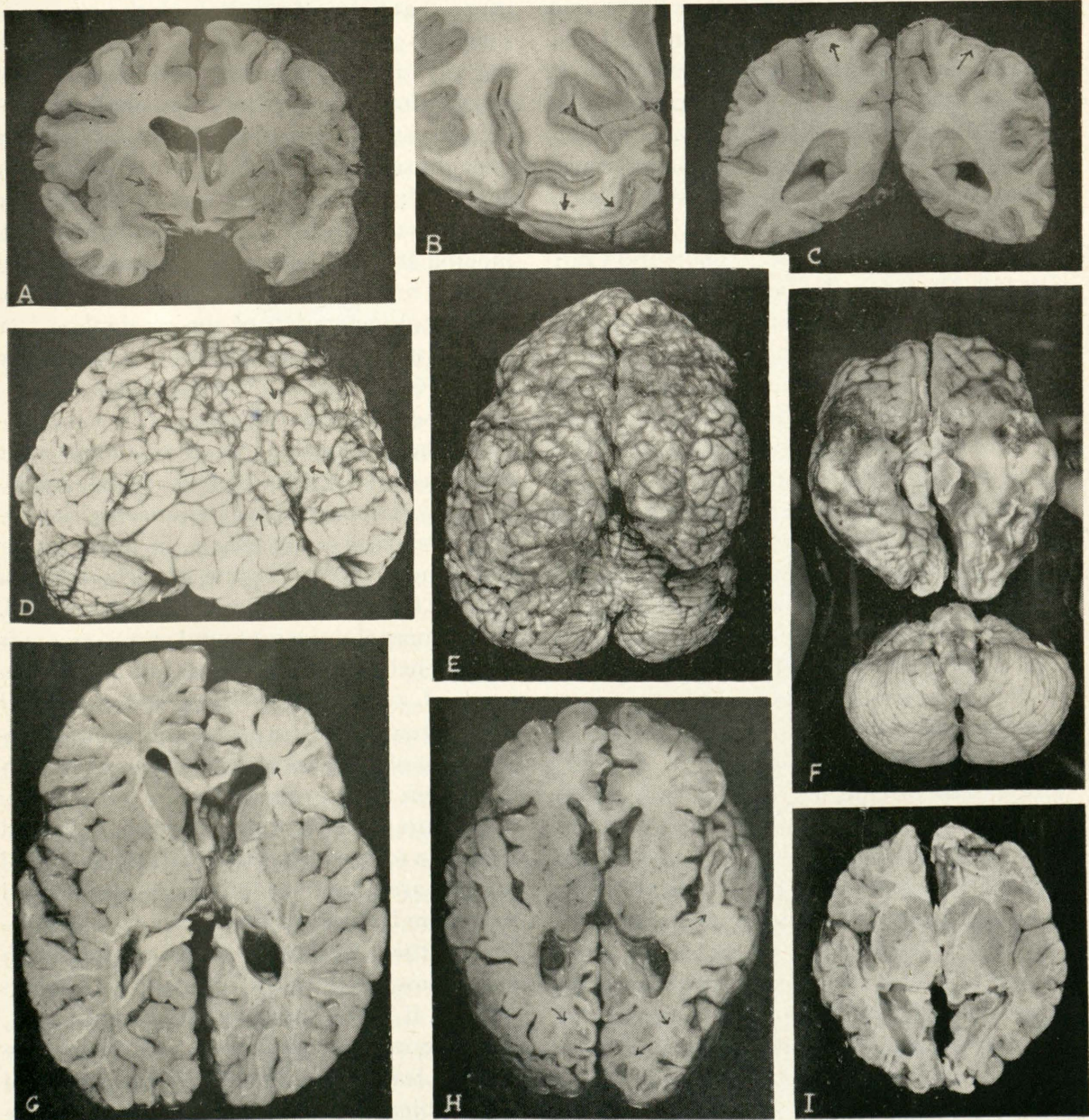


Figure 5. Residuals of asphyxial episodes of various etiologies. *A*. Degeneration of the globus pallidus after carbon monoxide "poisoning." *B*. Necrosis of the occipital cortex three and a half weeks after nitrous oxide anoxia. *C*. Softening of the parietal cortex bilaterally after carbon monoxide asphyxia. *D*. Focal cortical atrophy (lobar sclerosis, ulegyria), a residual of neonatal asphyxia. *E*. Marked hemiatrophy of the brain resulting from birth asphyxia. *F*. Profound changes in the brain of an idiotic, epileptic infant resulting from severe asphyxia at the time of delivery. *G*, *H*, *I*. Series of horizontal sections through brains showing variable degrees and distribution of changes following neonatal asphyxia.

This is but another way of saying that the ultimate residuals of neonatal asphyxia may be found in the brain in the form of focal cortical scars or cysts, atrophy of the cortex of a single lobe (ulegyria), a hemisphere, or of the entire brain with shrunken cortex (microgyria) of varying degrees as the characteristic change (Courville and Marsh [1944]). In some cases the globus pallidus of one or both hemispheres is likewise atrophic (Abbott and Courville [1938]). It has also been pointed out that instances of large porencephalic cysts are similarly to be accounted for as the result of vascular occlusion due to a proliferation of the cells of the vascular intima. These lesions have long been considered the residual of birth hemorrhage into the brain substance.

Histologically the typical finding is the loss of nerve cells in focal areas and laminae; in the extremely atrophic cortex no cells may be evident. These findings imply the selective destruction of nerve cells by oxygen want.

As for the residuals of other types of asphyxia, one cannot be so sure, for opportunities to study the brain after an interval of years is a relatively rare experience. One can only say that variable degrees of atrophy of the cortex and the globus pallidus are to be considered. This atrophy may be localized or generalized. Small vascular scars in cases of carbon monoxide asphyxia are also to be expected.

Some of the more characteristic gross changes following the anoxias of nitrous oxide-oxygen anesthesia, of carbon monoxide intoxication, and of neonatal asphyxia are shown in the accompanying illustration (Figure 5).

GENERAL CONSIDERATIONS

The story of the mechanism and effects of cerebral anoxia may now be considered to be fairly complete, at least in its larger outlines. In the case of nitrous oxide the pathogenesis

of degenerative changes in the cerebral gray matter has been traced through the acute and subacute phases (Courville [1938]). Although the case in the relatively rare instances of anoxia after ether anesthesia has not been completely settled, the residual clinical findings strongly suggest a similar picture (Courville [1941]). In instances of neonatal asphyxia we lack information as to the subacute phase, but, judging from the clear-cut picture presented in the chronic cases, one can only conclude that the degeneration of the cerebral and/or cerebellar gray matter is likewise a progressive lesion (Courville and Marsh [1944]).

In cases in which the anoxia is not too profound the nerve cells of the cortex or lenticular nuclei seem to be selectively damaged, and ultimately disappear. This accounts for the primary shrinkage of the cortex, the white matter becoming atrophic because of secondary loss of nerve fibers when their parent cells are dead. In instances of more profound anoxia not only the parenchymatous elements but also the interstitial cells undergo destruction. Under these circumstances we find the subtotal destruction of the cortex, as noted in cases of survival from three to six weeks.

In those cases in which survival is limited from two to seven days the characteristic focal necrotic areas are to be found either in isolated form or in laminar arrangements. It is the presence of these focal areas of destruction which makes possible the clear recognition of the lesion, be it acute, subacute, or chronic.

But much time and space have been occupied in leading up to the clinical aspects of the problem. Since it is these clinical symptoms upon which we are dependent for a diagnosis and whose course indicates the prognosis of a given case, these matters will next be given due attention.

NOTE.—The bibliography will appear at the end of the completed article.

(To be concluded)