Pathological-clinical correlations

I. Indirect trauma to the optic nerves and chiasm

II. Certain cerebral involvements associated with defective blood supply

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Much of this paper results directly from collaboration with Dr. Richard Lindenberg. His interest in neuropathology as it concerns the visual pathways has become an avocation; for this I share credit with Drs. William F. Hoyt, J. Lawton Smith, and others. That Dr. Lindenberg is on the staff of the Wilmer Institute exemplifies Dr. A. Edward Maumenee's vision and foresight. Through Dr. Lindenberg's position in the Maryland State Department of Mental Hygiene, his association with the Chief Medical Examiner's office, and the opportunities within The Johns Hopkins Hospital, we enjoy a remarkable opportunity in what might properly be termed "postmortem neuro-ophthalmology." What we have observed in the laboratory often suggests application in clinical evaluations.

I shall report on two of our studies which demonstrate the significance of our research on clinical-pathological correlations. The first study concerns indirect trauma to the optic nerve and chiasm. In 1962, a paper on the subject was presented in Hamburg. The second topic deals with systemic hypoxia; our 1961 paper concerned hypoxia occurring in infants and children. A third and last topic concerns the rate at which cerebral anoxia develops relative to anatomical sequelae and possible clinical application. Because I am reporting our own observations and their possible clinical applications, only a few references are made to the work of others.

Indirect trauma to the optic nerves and chiasm

Lacerations of the optic nerve and chiasm by foreign objects or fractures are not under consideration. The lesions with which we are concerned result mainly from falls on the head with the impact to the forehead, or frontal convexity, and anterior temporal regions.

Before presenting our classification of lesions associated with indirect trauma to the optic nerves and chiasm, I shall mention briefly an entity upon which little clinical information is available, and concerning which we do not have laboratory material. I refer to concussion of the optic nerve or nerves, and I propose that other parts of the cerebral visual pathways may be so affected. The question immediately arises as to whether or not concussion of

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the optic nerves is a valid concept. We believe it is.

There is lack of uniformity among observers as to a precise definition of concussion. Loss of consciousness, a common feature, is not invariably present. The usual definition, "loss of consciousness and associated traumatic amnesia as a result of trauma to the head in the absence of visible damage to the brain," usually, but not always, is adequate. Denny-Brown and Russell, on the basis of experimental studies on animals, concluded that cerebral concussion can be defined as "a direct traumatic paralysis of nervous function without vascular lesion, which persists for a varying period according to the type and severity of injury," and they concluded as follows: "The paralytic phenomena of concussion we have studied are due to a direct generalized physical injury to the neurons. This injury causes immediate loss of function, but is reversible." Induced vascular spasm has been suggested as having a role in the production of concussion. Denny-Brown and Russell questioned this possibility on the basis of not having observed it, and on an experiment performed in 1877 by Witkowski. After its heart was removed, a frog continued making spontaneous movements, including righting itself; a sharp blow to the head would stun the frog so that it remained motionless for many seconds before the movements reappeared.

With cerebral concussion and surgical shock the symptomatology is essentially the same: pallor, rapid feeble pulse, shallow respirations, fall in blood pressure, and subnormal temperature; when death occurs as a result of concussion it is due to depression of the respiratory and cardiac centers. Prominent investigators, including Denny-Brown, Spatz, and Lindenberg, believe that with "pure cerebral concussion" there are no demonstrable morphological changes. If such changes are present, more has happened than cerebral concussion. Changes not visible with light microscopy or localized chemical alterations ultimately may be found to exist in such cases, but that is for the future.

That cerebral concussion does not interfere with function of all the cerebral neurons is immediately established by the persistence, even enhancement, in some such cases of photic driving, also, after a concussive blow strychnine spikes, induced in one hemisphere by the application of strychnine to the opposite cerebral cortex, persist. There is plentiful clinical evidence that trauma to the head may modify or abolish vision briefly, followed by complete recovery. A sharp blow to the forehead or temporal regions may produce a sensation of "seeing stars" for a few seconds, after which normalcy returns. A blow to the back of the head, without producing unconsciousness, has caused loss of vision persisting for only a few moments. Recently Bodian described a total bilateral loss of vision in five of six children as a result of trauma, and a unilateral loss in one child; in all instances there was pupillary dilatation. Recovery was complete in all within 12 hours, which included a period of several hours' sleep. In all, the retinas appeared normal. Whether in some of these children there was more than "pure concussion" cannot be determined.

**Table I. Classification of lesions of the optic nerves and chiasm associated with indirect trauma**

<table>
<thead>
<tr>
<th>Primary lesions:</th>
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<tr>
<td>1. Hemorrhages in the nerve, dura, and sheath spaces</td>
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<td>2. Tears in the nerve or chiasm</td>
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<td>3. Contusion necrosis of the optic nerves and chiasm</td>
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<th>Secondary lesions:</th>
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<tr>
<td>1. Edema and swelling of the optic nerves and chiasm</td>
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<tr>
<td>2. Necrosis from systemic circulatory failure or local compression of vessels</td>
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<tr>
<td>3. Softening (infarction) in the optic nerve or chiasm related to vascular obstruction from thrombosis, possibly from arterial spasm</td>
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*Based upon microscopic studies of 140 specimens (70 subjects). Posterior segments of the globe and chiasm were studied in approximately half of the cases.*
but from a clinical standpoint they must be so classified. Lesions we have observed are shown in Table I.

**Primary lesions associated with indirect trauma to the optic nerves and chiasm.**

**Hemorrhages.** Hemorrhages in the optic nerve sheath spaces within the nerve and within the dura occurred most frequently in the posterior orbit, within the optic canal, and the intracranial nerve (see Fig. 1). In a majority of cases there is a fall with anteriorly situated head trauma.

We have concluded as follows: (1) Movement of the optic nerves and of the cerebral structures is an important factor in indirect trauma, and often accompanied by ruptured aneurysm, which leads to the death of the patient. (2) We are unable to evaluate visual loss on the basis of the probability of there being hemorrhage within the optic nerve or nerve-sheaths. (3) The constancy of the site of intradural bleeding supports a previous contention that sheath-space blood does not in the main represent a forward passage of blood from the intracranial cavity. Until recently, experience made me skeptical concerning a diagnosis of subdural hematoma of the optic nerve sheaths as an isolated entity accounting for visual loss. However, recently I have had notes on a case in which such a diagnosis seemed to have been proved. An incision through the dura released a blood clot, and the visual acuity returned to normal.

It seemed interesting to compare the situation regarding hemorrhages in indirect trauma to what occurs when there is rupture of an intracranial aneurysm (Figs. 2 and 3). We examined the optic nerves and sheath spaces in ten cases (20 specimens) in which death was due to rupture of a "berry" aneurysm. The site for bleeding into the nerve and dura was the same as was observed in cases of indirect trauma and it occurred in 9 of 10 cases. In the cases of ruptured aneurysm, movement undoubtedly is a factor, but the movement is slow as compared with what happens in trauma.

**Tears.** Tears of the optic nerve, as a result of indirect trauma, occur infrequently. In only one optic nerve did we find such a tear of the nerve as it entered the cranial cavity (Fig. 4). Seitz explored the region of the optic canal in six persons who had suffered acute loss of vision as a result of blunt trauma; in four the blindness was unilateral, in two, bilateral. In a single instance he observed an optic nerve torn across, as in our case. We did not assess incomplete tears in our material because of the difficulty of identifying them with certainty. If there is hemorrhage within an optic nerve, obviously there has been disruption of capillaries. The force of the trauma must have been stronger than the cohesive forces of the capillary walls. If hemorrhages are found in an optic nerve, and there are no evidences of other lesions, the nerve must have been concussed.

**Necrosis.** Contusion necrosis is a primary lesion of infrequent occurrence, but it is of real significance because recovery from
Fig. 2. Intraneural hemorrhage in the usual situation with indirect trauma. The hemorrhage is seen in the upper half of the optic nerve. There is intradural hemorrhage below the nerve in the vicinity of the canal.

Fig. 3. Intraneural “plasma bleeding.” Dilated capillary. From Walsh, F. B., and Lindenberg, R.: Entwicklung und Fortschritt in der Augenheilkunde, 1963, Ferdinand Enke Verlag.

It cannot occur. Such a necrosis, with a characteristic triangular shape as shown in Fig. 5 in which the chiasm was affected, develops within a fraction of a millisecond. It is the result of shearing forces producing disruption of cellular constituents visible at the microscopic or submicroscopic level. Ultrasound has the same necrotizing effect on tissues.5

Years ago, Turner described loss of vision that developed immediately from indirect trauma to the optic nerve. In brief, with or without loss of consciousness, a blow to the temporal region led to loss of vision.

Fig. 4. Complete tear through optic nerve as it entered cranial cavity as a result of indirect trauma. There was no evidence of fracture. The intracranial nerve is on the right side of the figure. From Walsh, F. B., and Lindenberg, R.: Entwicklung und Fortschritt in der Augenheilkunde, 1963, Ferdinand Enke Verlag.
Fig. 5. Primary contusion necrosis of the chiasm which resulted from a blow to the vertex. The lesion has a characteristic triangular shape with the apex internal to the base. From Walsh, F. B., and Lindenberg, R.: Entwicklung und Fortschritt in der Augenheilkunde, 1963, Ferdinand Enke Verlag.

in the homolateral eye, usually absolute. If recovery in any degree was to develop, it began within 3 or 4 days after the injury and reached its highest degree in 3 weeks, at about which time the optic nerve commenced to show progressive pallor. Turner concluded that the responsible lesion was in the optic canal region (and we agreed). He surmised that the basic etiology was vascular (we do not agree). We suggest that in cases where there is immediate total loss of vision there are three possible explanations: (1) concussion of the nerve with or without hemorrhage into it, (2) a primary contusion necrosis, (3) a tear across the nerve, or a partial tear. If there is recovery of vision there has been concussion of the nerve with or without hemorrhage into it, or the area of primary necrosis or tear has not involved the entire nerve. The situation is quite different when there is delay in the onset of visual loss, as is subsequently described (Fig. 6).

Case 1. A 10-year-old girl fell off her bicycle and struck the left temporal region. She was not unconscious. The pupil was dilated and fixed to light. The fundus appeared normal. The unilateral blindness persisted. Three weeks after the injury the optic disk became pale. The eye has remained blind and the optic disk now is entirely white.

We propose that the same mechanism explains many cases of traumatic bitemporal hemianopsia. In all such cases I have encountered there was loss of consciousness, usually associated with a blow to the vertex. In the absence of fracture of the base, it would seem reasonable that a median line primary contusion necrosis would account for the hemianopsia. Traquair and associates, in surgically investigating such cases, concluded that "vascular involvement" explained them because they did not observe in any instance an actual division of the chiasm. Subsequently, I shall present a case history illustrating such bitemporal hemianopsia and what must have resulted from a secondary lesion.

Secondary lesions of the optic nerves and chiasm associated with trauma. Swelling of the brain and of the optic nerves and chiasm is a frequent finding in persons who have suffered trauma to the skull sufficiently severe to cause death (Fig. 7). It is also observed under other circum-
Fig. 6. Contusion necroses in individual who survived a blow to the vertex of the skull for 30 days. On the left side of the figure there is an area of contusion necrosis in the gyrus rectus of the frontal lobe, another on the dorsal surface of the chiasm and a third such area on the ventral surface of the chiasm. Also there is such an area on the lateral aspect of the chiasm (right side of figure). From Walsh, F. B., and Lindenberg, R.: Entwicklung und Fortschritt in der Augenheilkunde, 1963, Ferdinand Enke Verlag.

stances, including hypoxemia from any cause. Regarding the rapidity with which it may develop, Lindenberg has observed pronounced brain swelling within 15 min. after a fatal accident. It would be reasonable to anticipate that swelling of the optic nerves would make them particularly liable to damage in the bony optic canal region (Fig. 7). In cases in which there is necrosis of the optic nerves it is regularly present in the nerve of the posterior orbit, optic canal, and intracranial nerve. In severe necrosis the entire cross section of the nerve is affected. In less severe cases the necrosis is first seen centrally. That necrosis may be dependent upon circulatory failure or compression of nutrient vessels seems entirely reasonable.

From the clinician’s viewpoint it is not yet known what amount of swelling is necessary to interfere with functioning of the optic nerve. It seems certain that minor degrees of swelling may not interfere with functioning, and that profound degrees of swelling are likely to result in failure of function. It would seem obvious that in Case 2, cited subsequently, extreme vascular hypotension accounted for swelling but not necrosis, making possible the return of vision. The regularity with which central scotomas are observed in cases of orbital tumor corresponds to what we have observed as the usual site of traumatic necrosis.

In Fig. 8, the necrosis of the left optic nerve is in the usual position, but in the right optic nerve there is necrosis of the anterior portion of the nerve. It seemed possible in this case that with the right optic nerve there was a particular reason for the anterior involvement. The trauma had resulted in the entire right side of the face and head showing extensive lesions. Probably there was interference with the cross circulation between the external carotid system and the right ophthalmic artery. We are aware that in some instances trauma is followed by necrosis of the anterior portion of the optic nerve, but this is rare as compared with posterior involvement according to our experience, for we have only this one example of anterior nerve necrosis. Fig. 9 shows a necrosis involving the central nerve most severely; there was thrombosis of the ophthalmic artery associated with trauma.
Fig. 7. A, swelling of the optic nerve, a secondary lesion. On the right side of the figure the nerve appears glistening. The dura is cutting into it. B, the dura has been reflected and the indentation in the upper surface of the nerve is visible.

Case 2 exemplifies the responses to a primary lesion, contusion necrosis, and a secondary lesion, swelling of the optic nerves and chiasm without necrosis developing as a result of swelling.

Case 2. A 50-year-old man suffered severe trauma to the head and face from being thrown to the ocean floor while bathing in heavy surf. He was immediately unconscious and remained so for about two weeks. During the first few days he had extremely low blood pressure. The pupils were wide and fixed to light. When he regained consciousness he was bilaterally blind, but after a few days vision gradually improved to almost normal. The disks became white. There was bilateral hemianopsia.

It seems probable that at the moment of impact (Case 2) there was an immediate development of a primary contusion necrosis which accounted for the permanent total bitemporal hemianopsia. With the low blood pressure he must have had cerebral oligemia, particularly severe in the parieto-occipital areas, and swelling of the brain, including the optic nerves and chiasm, which we have seen frequently when there has been a history of defective blood supply. It is reasonable to assume that his temporary visual loss resulted from marked swelling of the optic nerves and chiasm, or was related to insufficient blood supply to the calcarine cortex.

Fig. 7C. A myelin sheath preparation shows the damage done to the nerve. The injured individual died within a few days of the trauma and was unconscious. From Walsh, F. B., and Lindenberg, R.: Entwicklung und Fortschritt in der Augenhilfekunde, 1963, Ferdinand Enke Verlag.
Fig. 8. The optic nerve necrosis occurred in an individual who suffered a severe trauma to the right side of the face and skull with multiple fractures of facial bones. The left optic nerve is seen below. In this nerve the necrosis is observed in the usual site. Here it is most marked in the intracanalicular nerve but is present in a short segment of the posterior orbital nerve and also in the intracranial segment. The right nerve, above, shows necrosis in its anterior orbital segment. Presumably cross circulation from the external carotid system to the ophthalmic artery was interrupted but this was not proven. From Walsh, F. B., and Lindenberg, R.: Entwicklung und Fortschritt in der Augenheilkunde, 1963, Ferdinand Enke Verlag.

Fig. 9. Thrombosis ophthalmic artery in association with necrosis of nerve particularly pronounced in intracanalicular segment. From Walsh, F. B., and Lindenberg, R.: Entwicklung und Fortschritt in der Augenheilkunde, 1963, Ferdinand Enke Verlag.

Relative to our classification of lesions (Table I) there is a single important consideration: its possible value relative to therapy. Unfortunately, I am unable to cite cases that indicate its value, but I believe such cases exist.

Before commenting further on the possible indications or contraindications for surgical intervention in cases of indirect trauma to the optic nerves, let me mention briefly the problems the examiner faces in cases of trauma to the head. The diffi-
cultivates in diagnosis are greatly increased if the patient is unconscious. Immediate concern relates to procedures that might afford relief and return to consciousness. Attention must be given to shock, low blood pressure, elevation of depressed fractures, removal of extradural hematoma, and the like. Evaluations of the pupils and their responses are important in all such cases, including those we are now considering.

If it can be established beyond question that the loss of vision, whether in one or both eyes, occurred at the moment of impact, it is unlikely that recovery of vision would be enhanced by therapy. If recovery occurs in such cases, there has been concussion to the nerves, or nerves and chiasm, with or without hemorrhage into these structures. The possibility of there being an incomplete tear or an incomplete primary contusion necrosis is exceedingly less likely. However, if it can be established that there has been a period during which the injured person has retained vision, even though it may have been for only a few minutes, the situation is entirely different. The lesion or lesions responsible for the loss of vision have been secondary. It is in these cases that operative removal of the roof of the optic canal, theoretically at least, might have a beneficial effect. If such a procedure is to be undertaken, the earlier the better.

In many cases of trauma to the skull the injured person is unconscious when first seen and it is impossible to test visual acuity. In such cases the pupillary state is important. If the pupil (or pupils) that have reacted to light fail to do so, the possibility of a secondary type of optic nerve involvement should come to mind. Unfortunately, in many cases of head injury where there is loss of vision and absent pupillary light responses, it is impossible to determine whether the loss of vision occurred at the moment of impact or later. The examiner faces a dilemma if he believes that operation (decompression of the canal) ever has value.

What has been stated above is in largest part based upon our small and unproductive experience with decompression of the optic canal, and, according to unofficial information, in a few other centers in this country the experience has been similar. Our laboratory findings strongly suggest that in some cases unroofing the optic canal might provide help. Possibly we have not had sufficient experience with this procedure to pass judgment on it. Our selection of cases for operation may have been defective. I am not here concerned with possible medical therapy. Cortisone and Mannitol may be helpful where optic nerve swelling is a feature.

The following general principles which might add to our knowledge of unroofing the optic canal are now stated: (1) It should never be undertaken as a selective procedure on an unconscious patient. (2) If the loss of vision is associated with a nonreactive pupil, and the loss occurred at the moment of impact, the procedure probably is contraindicated. (3) If the loss of vision or loss of pupillary response to light developed after the moment of impact the possibility of the operation improving the situation should be considered. (4) If it cannot be determined that the loss of vision or of pupillary response to light was delayed, it should be sound judgment to wait and watch for 4 to 6 days, because spontaneous improvement occurs in some such cases. If improvement does not occur, it might be reasonable to undertake the procedure.

Although I do not have a case indicating that removal of the roof of the optic canal may have helped in recovery of vision, two cases are cited; they exemplify secondary involvements of an intracranial optic nerve in which operation was successful.

Case 3 (courtesy of Dr. Lindenberg). A middle-aged man suffered a trauma to the right frontal vertex region. He developed loss of vision in the eye homolateral to the principal area of trauma. At operation a large blood clot, extending from an area of contusion on the inferior surface of the frontal lobe, pressed upon the optic nerve (see Fig. 9). The nerve was swollen and had a dark
appearance. Removal of the blood clot was followed by recovery of vision in the affected eye.

Case 4. In a 40-year-old woman there had been progressive loss of vision in the left eye. X-rays suggested a parasellar mass. At operation the tumor, a grape-sized meningioma which arose from the tuberculum sella, was removed without incident. There was some bleeding and the cavity was packed with oxycel gauze. When the patient awakened from the anesthesia the vision seemed unchanged, normal in the right and low in the left eye as had been found prior to operation. Several hours later there was complaint of dimming of vision in both eyes and the pupils ceased responding to light stimulation. A return visit was made to the operating room. The neurosurgeon removed a swollen mass of oxycel that was pressing upon the right nerve. The nerve had become swollen and had a dusky color, whereas at the time of the first operation it appeared normal. Within a day there was a slight return of the pupillary response in the right eye soon followed by a similar response in the left eye. The ultimate result promises to be excellent. The vision in the right eye is 20/20, in the left 20/40 (2/200 before operation). There is a residual temporal defect in the right upper field; the scotoma is not dense and further recovery is anticipated.

The remainder of this paper is based on observations made by Dr. Lindenberg. I am responsible for the clinical correlations. Two topics are selected for comment: (1) the significance of the cerebrovascular pattern relative to lesions involving the higher visual pathways, and (2) the significance of the rapidity of development of stagnant anoxia.

Certain cerebral cortical involvements associated with defective blood supply

It is established that, with insufficiency of the basilar-vertebral system, visual failure is a predominant feature in some instances and is the sole disability in others. This is accepted as the result of oligemia. It is generally well known that, with an acute fall in blood pressure, vision may be lowered or lost, and that "blackout spells" may be the principal feature of such episodes. It has been suggested that under such a circumstance the visual cortex is particularly vulnerable to oxygen deficiency relative to other cortical areas. The question arises as to whether such a particular feature of the visual cortex exists. Lindenberg believes that the anatomy of the blood supply satisfactorily explains the frequent involvements of the visual cortex by oligemia and that proof of "particular vulnerability" is wanting.

Fig. 10 shows that the terminal branches of the three large arteries that supply the cerebrum—the anterior, middle and posterior cerebral—terminate posteriorly and in the parieto-occipital region of each hemisphere. Here the terminal twigs derive from branches only slightly larger than themselves. These arteries supply the cerebral cortex and the white matter of the hemispheres. Our particular interest here is the visual cortical areas.

If we visualize for a moment the three arteries as garden hoses each supplying a sprinkler, the situation as regards terminal blood supply is illuminated. With adequate and normal blood pressure in the three-part water system, there is overlapping of water supply in the terminal areas served. If there is a drop in water pressure below the critical level the border areas served by the sprinklers are the first to suffer. If there is a further drop in pressure the arid areas increase in size until finally the only areas receiving water are close to the main trunks of the water supply. This analogy between a watering system and the cerebral vascular supply introduces the border-zone concept of blood supply as described by Lindenberg.

If the blood pressure drops to 40 systolic or below, the border-zones of insufficient supply first appear in the parieto-occipital area. If the blood pressure is further reduced, the border-zone areas extend forward and toward the arterial stems, and from thence expand to ultimately include the entire cortical areas, basal nuclei, and cerebellum. According to the severity and duration of the stagnant hypoxia, the cellular changes are reversible or irreversible. It is probable that insufficiency of the left heart is principally responsible for cerebral cortical involvement associated with defective blood supply. Cerebral cor-
Fig. 10. The cerebral vascular supply. It is observed that the terminal branches of the anterior, middle and posterior cerebral arteries are situated posteriorly. Quite obviously the terminal branches of the middle and posterior cerebral arteries farthest from the main stems are directed toward the parieto-occipital areas. From Lindenberg, R.: Die Gefassversorgung und ihre Bedeutung für Art und Ort von kreislaufbedingten Gewebsschäden und Gefäßprozessen. Handbuch de speziellen pathologischen Anatomie und Histologie, Bd. 13, T. 1 B, S. 1071–1164. Berlin-Göttingen-Heidelberg, 1957, Springer Verlag.

tical damage occurs much more often than white matter involvement.

The cerebral cortical blood supply and the border-zone concept is particularly significant as regards involvement of the higher visual pathways. It is important that the parieto-occipital border-zone area is a potential emergency area of first order; in consequence, visual field loss and visual failure are frequently observed in association with defective blood pressure and it is the higher visual pathways that are particularly likely to be affected. An example of border-zone involvement by hemorrhagic necrosis of the cerebral cortex shown in Fig. 11 and Case 5 illustrates what has been stated.

Case 5. A 78-year-old woman died in a nursing home after having been in and out of coma for two weeks. There was a history of blackout
spells and falls some three years before her admission to the nursing home, which followed a fall with fracture of a hip. Autopsy revealed arteriosclerotic heart disease (Fig. 11).

Application of this concept is important in cases diagnosed as having cortical blindness and bilateral homonymous hemianopsia. With the last-named affection, if the homonymous field defects develop concurrently the diagnosis is obvious. In those cases that have sudden loss of visual fields in their entirety as a result of visual cortical involvement, the terms are interchangeable. In a great majority of cases of cortical blindness and bilateral homonymous hemianopsia, when recovery commences it is the central fields and vision which first reappear. The pattern of recovery seems different in some cases of cardiac arrest.

Hoyt and Walsh reported on cortical blindness associated with cardiac arrest. In our patient there was unawareness of blindness for several days (Anton’s syndrome). Recovery commenced with some return of peripheral fields. It was possible to identify from the field the cortical areas least severely affected; there was persistent loss of central vision, indicating that the most

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Fig. 11a. Hemorrhagic cortical necrosis along arterial border zones. Dorsum of cerebral hemispheres. At bottom of figure there is extensive involvement of the occipital and posterior parietal lobes symmetrically bilateral. Note the narrow dark areas extending forward. The dark areas are along the border zones.

Fig. 11b. Cross sections of brain. Upper left section anterior half of brain shows no lesion affecting anterior frontal lobes while lower left section, more posterior, shows bilateral areas of involvement (between anterior and middle cerebral arterial circulation). Figures upper and lower right, still more posterior, show slight increase in the size of the affected areas.
severe damage was in the occipital poles. In our studies on this patient we remarked upon brain swelling and herniation having a possible role in the damage to the visual cortex (and both these phenomena have been remarked upon relative to indirect trauma to the optic nerves and chiasm). Hypothermia was thought possibly to have been an aid to recovery in our case.

With recovery of central vision and central fields as first evidence of improvement in cases of cortical blindness and bilateral homonymous hemianopsia, a collateral supply to the occipital poles from the carotid system via the terminal branches of the middle cerebral arteries, which anastomose with terminal branches from the posterior cerebals, is significant. Many such cases of blindness are associated with vertebral-basilar insufficiency, and here the middle cerebral artery remains intact. With cardiac arrest all cerebral arteries are involved in the oligemia; the anastomoses via the middle cerebral artery have no value and in consequence the posterior poles are liable to the most severe damage.

Cerebral white matter involvement. The cerebral arteries not only supply the cortex but pass through it to supply the white matter by arterial filaments or branches running toward the walls of the ventricles. These arterial twigs supplying the white matter of the parieto-occipital region are the longest arteries in the brain. The drainage of the white matter is via veins which start close to the cortex and pass toward the ventricle wall from whence they join larger collecting veins that finally drain into the internal cerebral veins and the vein of Galen and into the straight sinus. The drainage of the white matter is more complex than that of the cerebral cortex from which the venous blood almost immediately reaches the external cerebral veins. It can be logically assumed that in failure of systemic venous drainage the resultant venous back pressure must be of greater intensity in the white matter than in the cerebral cortex. Failure of the right heart is predominant in white matter involvement. If with such failure there is only a slight drop in arterial pressure (function of the left side of the heart), capillary flow in the white matter cannot be maintained because of venous counterpressure. Thus
it is possible that with failure of the right side of the heart and only a slight lowering of the arterial blood pressure, the white matter may be the sole area of brain damage. Again the first region affected is the parieto-occipital area. A more pronounced loss of arterial pressure under such circumstances will provide in addition cortical damage along the arterial border zones. Selective white-matter involvement occurs much less often than cortical damage from cardiac failure or cardiac arrest.

Almost isolated damage to white matter may occur in carbon monoxide poisoning in which the right side of the heart is, for some unknown reason, more severely damaged than the left. Lindenberg has observed in severe cases pronounced fatty degenerative changes in the right heart. With his co-workers he has shown that in experimental carbon monoxide poisoning in dogs white matter damage occurred repeatedly (Fig. 12). Such necrosis developed when the arterial pressure fell temporarily to a third or a half of normal and simultaneously the venous pressure increased five- or sixfold.

It is characteristic for such white matter damage as has been described (anoxic leukoencephalopathy) to be bilaterally symmetrical. The largest lesions are found in the occipital regions; the lesions become smaller as they progress forward to the frontal regions.

We have observed extensive destruction of cerebral white matter most frequently in infants and children. Our 1961 paper contains several figures depicting such involvements. Here two cases are cited. In Case 6 undoubtedly the cerebral damage occurred in early childhood; in Case 7 it occurred in an adult.

Case 6. A woman who resembled a pituitary dwarf died at 47 years of age. According to the obtainable history she developed normally until 3 years of age, at which time she contracted diphtheria. From that time she behaved abnormally, with irritability a prominent feature. It was suggested that she had "diphtheritic encephalitis."

Fig. 12. A, white matter damage occurring in a dog subjected to carbon monoxide. Affected area marked by ink line; there is a similar area in opposite hemisphere. B, normal appearing section same region for comparison. (Courtesy of Dr. R. Lindenberg.)

Fig. 13. Case 6. There is ancient demyelination symmetrically situated in centrum ovale region both hemispheres (lateral to corpus callosum).
Some time later she was said to exhibit congenital diplegia. When she was 32 years old she was mentally defective. Tendon reflexes were brisk, particularly in the legs; there was ataxia, more pronounced in the lower limbs; the plantar response was said to be flexor; the Romberg sign was positive; there was an alternating internal strabismus; there was mild bilateral clubfoot.

At autopsy evidence of congestive heart failure was found. The aorta was atheromatous. There was ancient demyelination in the centrum ovale region of both hemispheres not reaching the frontal lobes or the ventricles. Also there was demyelination of the peduncles and internal capsules (Fig. 13).

Case 7. A Negro man, 34 years old at the time of death, had been treated for pulmonary tuberculosis and discharged as cured. He continued working for more than a year, when he was re-examined. There was evidence of reactivation of the pulmonary lesions, and he was readmitted to a hospital.

Two days after admission he awakened quite blind in both eyes. The pupils responded actively to light. Information on the optic fundi is not available, but no mention was made of abnormality. He had difficulty in moving the left arm and leg.

Two days later he had an epileptiform seizure and became unresponsive. He died 11 days after admission.

Autopsy revealed pulmonary embolism as a cause of death, also active pulmonary tuberculosis. There was extensive and severe cortical necrosis and subcortical white matter damage of variable extent in the border zones between the anterior and middle and between the middle and posterior cerebral arteries. There was pronounced white-matter involvement in the end-artery distribution of the middle and posterior cerebral arteries (Fig. 14).

Rapid versus slow development of stagnant anoxia

From time to time an individual who for weeks or months has exhibited signs of severe and extensive cerebral involvement makes a dramatic and complete recovery. Such occurrences excite reader interest and consequently are featured by newspapers and magazines. Fairly recently, the story of a famous actress was recounted. She had prolonged unconsciousness, with cardiac and respiratory difficulties, and on regaining consciousness was blind. Because she later recovered completely, her case history became newsworthy. Relative to recovery or failure to recover from some cerebral involvements, Lindenberg's studies on morphotropic and morphostatic behavior of cerebral cells in response to stagnant anoxia, are vitally important. The subject is one of great complexity. Here, I barely outline the principal feature of his studies, and cite a case which seems to substantiate that feature.

Lindenberg found from his work on experimental animals that, with a rapidly developing stagnant anoxia, irreversible cerebral damage developed rapidly. He was able to identify cellular changes within 20 to 30 minutes after the onset of the anoxia. However, when the onset of anoxia was preceded by a period of severe and critical hypoxemia lasting for 45 to 60 minutes, no cellular changes could be identified in the unfixed brain during a period up to 24 hours after the animal was put to death.

An explanation for the difference in the behavior of the cells would seem to be as follows: With a sudden onset of anoxia the cerebral cells are actively taking part in the cerebral metabolism. With good reasoning we may visualize the accumulation of metabolites from the activity of
the cells playing a role in their own destruction. However, if there is a period of hypoxemia preceding the anoxia, the cellular metabolism has been gradually diminished and the cells are protected by their inactivity.

It must be obvious that I have eliminated almost all of the complexities of the situation, particularly as regards the chemistry of what happens in rapid and slow development of stagnant anoxia. However, the following case history with autopsy findings supports the concept just stated.

**Case 8.** A 25-year-old man was admitted to hospital following a fall at home. There was a history of his having had seizures. His physician considered him psychotic, but remarked that examinations showed him to be normal physically.

At the time of admission it was found there was a fracture of the left parietal bone. On the day he was admitted an epidural hematoma was evacuated from the left parieto-occipital region. He remained unconscious during his survival time of 5 months.

Autopsy revealed extensive softening of the cerebral cortex in its entirety excepting for much of the cortex of the left occipital lobe where the extradural hematoma was located (Fig. 15, lower right). All other cortex is unidentifiable.

In Case 8 the relative survival of the parieto-occipital cortex immediately directly available to pressure from the epidural hematoma supports the viewpoint that has been stated. Through early pressure this isolated area of cortex was subjected to hypoxemia prior to the onset of widespread cerebral damage from subsequent shock.

The next, and last, case report further exemplifies the concept that critical hypoxemia preceding stagnant anoxia protects cerebral tissues from structural change.

**Case 9** (courtesy of Dr. Lindenberg). A middle-aged woman was hospitalized for fracture of the femur. Suddenly she went into shock as a result of pulmonary embolism. The shock deepened over a period of 40 minutes when she developed cardiac arrest. Artificial respiration and cardiac massage were started immediately. She remained almost pulseless for 35 minutes and was uncons-

![Fig. 15. An extradural hematoma was removed from the left parieto-occipital area. There is complete softening of the cerebral cortex from shock excepting in the left occipital lobe pressed upon and deformed by the hematoma (see lower right figure). The white matter also was extensively necrotic. (Courtesy of Dr. R. Lindenberg.)](image-url)
scious for 2 days. A neurological examination a day after she had become conscious revealed nothing remarkable. She conversed intelligently. Ten days later she died suddenly as the result of another embolus.

Examination of the brain revealed no loss of neurons other than for loss of a few neurons in both Ammon’s horns. The white matter showed some diffuse gliosis but no significant tissue damage.

That severe hypoxemia preceding stagnant anoxia protects the cerebral tissue from structural change seems established on the basis of Lindenberg’s experimental work. The concept is strengthened by clinical-pathological evidence as has been given here. The clinical value of such observations would seem to merit attention.

This paper was designed only to acquaint you with one of the activities of the Wilmer Institute. My ideas concerning university teaching hospital practice and teaching relative to research I inflicted upon you, and for this I ask your indulgence—and thoughtful consideration. Please accept my thanks for your careful attention to my comments concerning Dr. Lindenberg’s and my autopsy studies and clinical correlations.

REFERENCES